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

Siegfried N, van der Merwe L, Brocklehurst P, Sint TT

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 7

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

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

Nandi Siegfried[1], Lize van der Merwe[2], Peter Brocklehurst[3], Tin Tin Sint[4]

[1]Department of Public Health and Primary Health Care, University of Cape Town, Cape Town, South Africa. [2]Biostatistics Unit, Medical Research Council, Cape Town, South Africa. [3]National Perinatal Epidemiology Unit, University of Oxford, Headington, UK. [4]Department of HIV/AIDS, World Health Organization, Geneva, Switzerland

Contact address: Nandi Siegfried, Department of Public Health and Primary Health Care, University of Cape Town, Cape Town, South Africa. nandi.siegfried@gmail.com.

Editorial group: Cochrane HIV/AIDS Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 7, 2011.
Review content assessed as up-to-date: 17 January 2011.

Citation: Siegfried N, van der Merwe L, Brocklehurst P, Sint TT. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No.: CD003510. DOI: 10.1002/14651858.CD003510.pub3.

ABSTRACT

Background

Antiretroviral drugs reduce viral replication and can reduce mother-to-child transmission of HIV either by lowering plasma viral load in pregnant women or through post-exposure prophylaxis in their newborns. In rich countries, highly active antiretroviral therapy (HAART) which usually comprises three drugs, has reduced the mother-to-child transmission rates to around 1-2%, but HAART is not always 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 methods

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 conducted in 2002 and updated in 2006 and again in 2009.

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, or compared with another antiretroviral regimen.

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 identical drug regimens.

Main results

Twenty-five trials including 18,901 participants with a median trial sample size of 627 ranging from 50 to 1,844 participants were included in this update. Twenty-two trials randomised mothers (18 pre-natally and four in labour) and followed up their infants, and three trials randomised infants. 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. We present the results stratified by regimen and type of feeding.

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 1.50 to 62.50), 3 to 4 months (Efficacy 33.07%; 95% CI 5.57 to 60.57), 6 months (Efficacy 34.55%; 95% CI 9.05 to 60.05), 12 months (Efficacy 34.31%; 95% CI 9.30 to 59.32) and 18 months (Efficacy 29.74%; 95% CI 2.73 to 56.75).

ZDV given to mothers from 36 weeks gestation and during labour significantly reduced HIV infection at 4 to 8 weeks (Efficacy 43.78%; 95% CI 8.78 to 78.78) and 3 to 4 months (Efficacy 36.95%; 95% CI 2.94 to 70.96) 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 after birth (PETRA 'regimen A') significantly reduced HIV infection (Efficacy 62.75%; 95% CI 40.76 to 84.74) and a combined endpoint of HIV infection or death (Efficacy 62.75 [,]61.00%; 95% CI 40.76 to 84.74) 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 after birth (PETRA 'regimen B') significantly reduced HIV infection (Efficacy 41.83%; 95% CI 12.82 to 70.84) and HIV infection or death at 4 to 8 weeks (Efficacy 35.91%; 95% CI 8.41 to 63.41) 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 after birth significantly reduced HIV infection in babies at 18 months (Efficacy 66.22%; 95% CI 33.94 to 98.50).

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 50.26%; 95% CI 13.80 to 86.72) 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 after birth 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 45.35 %; 95% CI 1.39 to 89.31) 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 11.84 to 70.16), 3-4 months (Efficacy 38.91%; 95% CI 11.24 to 66.58), 12 months (Efficacy 35.98 [9.25, 62.71]36.00%; 95% CI 8.56 to 63.44) and 18 months (Efficacy 39.15%; 95% CI 13.81 to 64.49). In addition, the NVP regimen significantly reduced the risk of HIV infection or death at 4-8 weeks (Efficacy 41.74%; 95% CI 14.30 to 69.18), 3 to 4 months (Efficacy 40.00%; 95% CI 14.34 to 65.66), 12 months (Efficacy 32.17%; 95% CI 8.51 to 55.83) and 18 months (Efficacy 32.57 [9.93, 55.21]33.00%; 95% CI 9.93 to 55.21).

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 36.79%; 95% CI 3.57 to 70.01).

Five trials in non-breastfeeding populations found that:

In a population in which mothers were receiving 'standard' antiretroviral 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 after birth 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 antiretroviral 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.

TRIPLE regimens versus other

Two trials compared a regimen of three antiretrovirals given to the mother, which we refer to as TRIPLE, with other regimens.

In a breastfeeding population, a trial of TRIPLE regimen commenced at 34 weeks compared with only ZDV for the same period until labour when sdNVP was added found no babies infected with HIV at birth in either group and at 6 months post delivery there was no statistically significant difference in HIV infection between groups (Efficacy -84.62%, 95%CI: -490.35 to 321.11). The infants in the TRIPLE group did not receive any drugs while those in the ZDV group received sdNVP at birth.

In a non-breastfeeding population, a trial compared a protease inhibitor-based TRIPLE regimen combination of lopinavir/ritonavir, ZDV and lamivudine from 26 to 34 weeks gestation through 6 months post-partum with a shorter regimen of ZDV from 28 to 36 weeks, then ZDV and 3TC and sdNVP at onset of labour, followed by ZDV and 3TC for one week after delivery. Infants in both groups received sdNVP within 72 hours of delivery and ZDV for one week. There was no statistically significant difference between groups in HIV infection at birth (Efficacy 18.18%, 95%CI -83.48 to 119.84) or at four to eight weeks (Efficacy 31.25%, 95%CI -29.29 to 91.79). At six months, HIV infection was higher but not statistically significantly so in the non-TRIPLE group (Efficacy 42.35%, 95%CI -0.57 to 85.27). At 12 months HIV infection was statistically significantly higher in the non-TRIPLE group (Efficacy = 42.11%, 95%CI 0.66 to 83.56). At 6 months, the HIV infection or death incidence remained higher in the non-TRIPLE group (RR 34.13, 95%CI [-0.29 to 68.55) and at 12 months this difference was statistically significant (RR 36.20, 95%CI 5.92 to 66.48).

TRIPLE regimen versus TRIPLE regimen

In a breastfeeding population, one trial compared two triple combination antiretroviral regimens with each other, viz abacavir, lamivudine and ZDV with lopinavir/ritonavir and ZDV and lamivudine in the mother from 26 to 34 weeks and continued for six months post-partum. Infants in both groups received sdNVP and one month of ZDV. This trial found no significant difference in HIV infection rates at birth (Efficacy -189.47%; 95%CI -715.29 to 336.35) with incidence at six months remaining non-significant with transmission rates being very low (< 1%).

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

A regimen combining triple antiretrovirals is most effective for preventing transmission of HIV from mothers to babies. The risk of adverse events to both mother and baby appears low in the short-term but the optimal antiretroviral combination and the optimal time to initiate this to maximise prevention efficacy without compromising the health of either mother or baby remains unclear.

Short courses of antiretroviral drugs are also effective for reducing mother-to-child transmission of HIV and are not associated with any safety concerns in the short-term. ZDV given to mothers during the antenatal period, followed by ZDV+3TC intrapartum and postpartum for one week, and sd-NVP given to infants within 72 hours of delivery and ZDV for one week, may be most effective when considering short antiretroviral courses. 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 after birth is beneficial. The long term implications of the emergence of resistant mutations following the use of these regimens, especially those containing Nevirapine, require further study.

PLAIN LANGUAGE SUMMARY

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

At the end of 2009, 2.5 million children under the age of 15 years were estimated to be living with HIV/AIDS (WHO 2011). The majority of these children acquired their infections as a result of mother-to-child transmission during pregnancy, labor, or breastfeeding. Antiretroviral drugs administered to the HIV-infected mother and/or to her child during pregnancy, labor, or breastfeeding can reduce mother-to-child transmission of HIV. The objective of this review is to determine whether a regimen of antiretroviral drugs leads to a significant reduction in HIV transmission during pregnancy and labor without serious side-effects.

The 25 trials found eligible for this review included 18,901 participants.The included trials compared the use of antiretrovirals versus placebo, longer regimens versus shorter regimens using the same antiretrovirals, and antiretroviral regimens using different drugs and drug combinations. This review of trials found that short courses of certain antiretroviral drugs are effective in reducing mother-to-child transmission of HIV, but are not associated with any safety concerns in the short term.

BACKGROUND

The World Health Organization estimated that 2.7 million people were newly infected with HIV in 2008 (WHO 2010a). Of the 1.4 million HIV-positive pregnant women, more than 628 000 received antiretroviral drugs to prevent the transmission of HIV to their children. Although this represents a global increase of 10% compared with 2007, there are vast regional differences in coverage, for example only 45% of African pregnant women received treatment (WHO 2010a). Babies born of HIV-infected mothers who are not on antiretrovirals for treatment or for prevention of transmission of HIV to their babies, can acquire infection during three time periods: 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 an independent determinant of the risk of mother-to-child transmission (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).

Despite improvements in childhood survival globally over the past decade (You 2010), HIV infection continues to contribute to infant and child mortality and in many African countries this effect is reversing gains in child survival (UNICEF 2010). UNICEF reports that in Namibia, the under-five mortality rate for 2001-2006 from the 2006 Demographic and Health Survey had to be increased from 69 deaths per 1,000 live births to 78 deaths to account for the impact of AIDS. Similar adjustments were made for 17 other countries in sub-Saharan Africa. 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 and based on the best available evidence (Chinnock 2005).

The aims of antiretroviral drugs are to suppress the replication of HIV and thereby result in improvements in the immune system and clinical status of adults and children living with HIV/AIDS (Volberding 2010). Antiretroviral drugs can reduce mother-to-child transmission of HIV in one or more of 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; and 4) through reducing transmission via breast-feeding. In resource-rich countries, antiretroviral regimens usually comprising at least three different drugs, has reduced the vertical transmission rates to around 1-2% but antiretrovirals are 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 and/or their newborn babies.

Antiretroviral drugs can be grouped into the following classes:

1. Nucleoside analogue reverse transcriptase inhibitors:

i) 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.

i) This class of drugs includes nevirapine (NVP), delavirdine and efavirenz.

3. Protease inhibitors.

i) 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

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; Volberding 2010). 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.

Development of resistance to antiretroviral drugs continues to be an important consideration when choosing the most appropriate preventive drug, or combination of drugs, for prevention of mother-to-child transmission (pMTCT). As stated above, use of NVP as a monotherapy can result in selection for HIV resistance mutations that may negatively affect the future efficacy of NVP-based therapies for those mothers who require treatment for their own health and for those of their children to whom the virus is transmitted (Lallemant 2010). Trials with sufficiently long follow-up periods are required to determine how long resistance is sustained and the effects of such resistance on not only possible future treatment, but also prevention requirements during future pregnancies.

A Cochrane systematic review of all currently trialed interventions for preventing MTCT was conducted initially in 2002. The review was then updated in 2006 to focus only on antiretrovirals. This is the third update to provide timely evidence to assist policymakers, clinicians and consumers in choosing the most effective drug regimen. The review was done as one of a series of reviews prepared at the request of the World Health Organization (WHO) to inform the development of the 2010 guidelines on preventing MTCT (WHO 2009). Treatment of the HIV-infected mother is addressed in a partner review (Sturt 2010). In addition to informing the WHO guidelines, this 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.

METHODS

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 are included in another Cochrane review (Horvath 2009).

Types of participants

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

Types of interventions

- 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 (Division of AIDS, NIAID 1992; Division of AIDS, NIAID 1994a; Division of AIDS, NIAID 1994b). 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. In addition if trials report on development of HIV resistance we will record this.

Search methods for identification of studies

See: HIV/AIDS Collaborative Review Group search strategy.

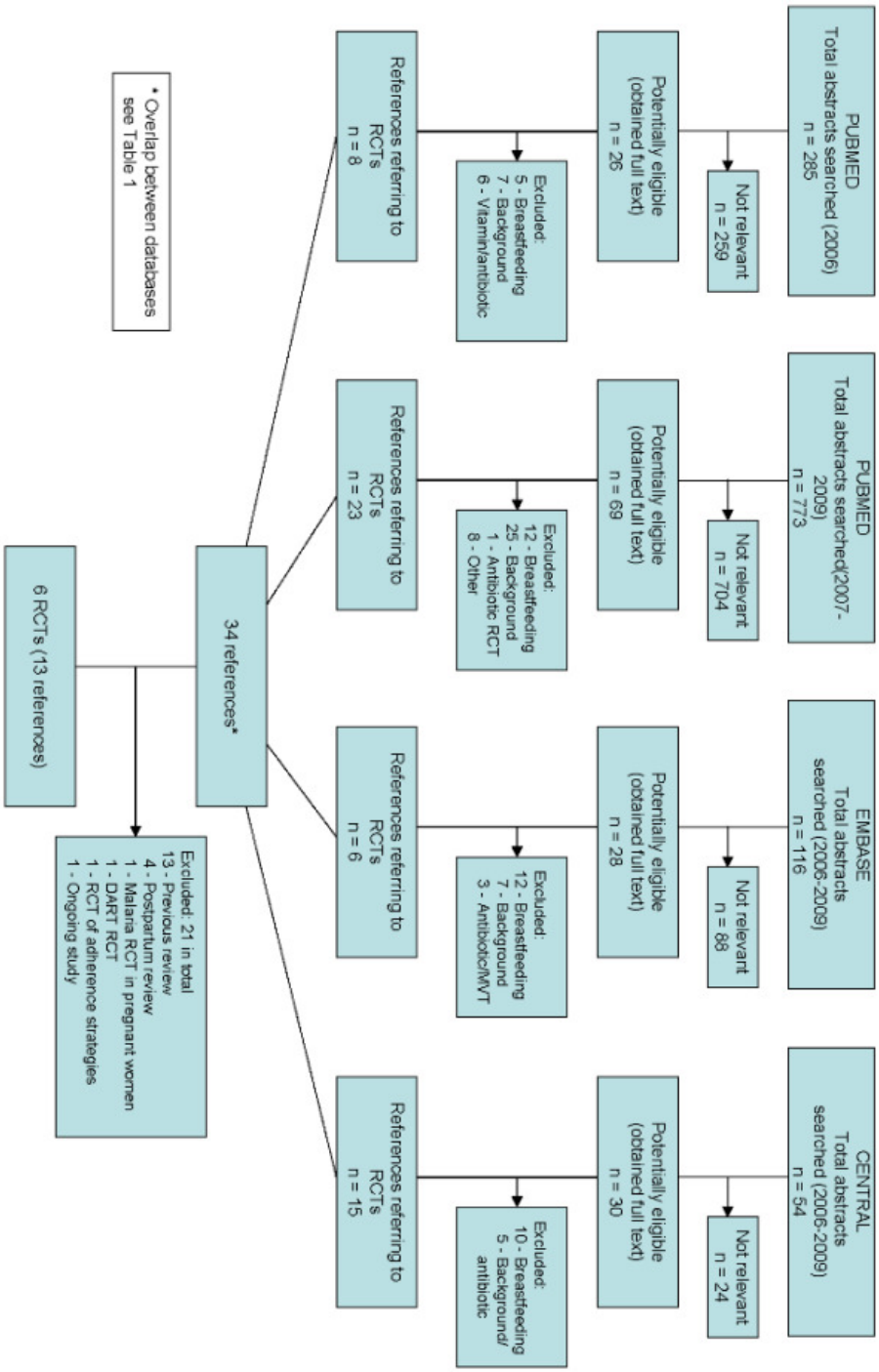
The original review, published in 2002, used a search strategy developed for the Pregnancy and Childbirth Group as a whole. Relevant trials were identified in the Group's Specialized Register of Controlled Trials. In addition, the Cochrane Controlled Trials Register was searched with each new edition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

The review was updated in 2006 after refining the search strategy 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 1. 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.)

For this update we searched MEDLINE via PubMed on 17 April 2009 using the strategy documented in Table 1 for the years 2007 to date.This search yielded 773 records of which we selected 23 records for full article retrieval. We also updated the 2006 search as the previous search had been done up until February 2006. This yielded 285 records of which we selected 8 for full article retrieval. See Figure 1 for flow diagram details.

Figure 1. Flow diagram search results for PubMed, EMBASE and CENTRAL for 2009 update



(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 2.

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.)

For this 2009 update we searched EMBASE again using the strategy documented in Table 2 for the years 2006 to date. This search yielded 116 records of which we selected 7 for full article retrieval. See Figure 1.

(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 3 for the full search strategy.

For this 2009 update, we searched NLM Gateway instead of AIDSearch as this database is no longer operational. NLM Gateway covers some relevant AIDS conferences and meetings and we used the strategy outlined in Table 4 but no meeting abstracts were found.

As we needed to identify other means of searching conference abstracts, we searched the AEGIS database (www.aegis.org). A research specialist searched all the abstract records from the following major related conferences: 1st-5th IAS Pathogenesis (2001-2009); 10th-17th IAC (1994-2008); 1st-16th CROI (1994-2009); US National HIV Prevention Conference ('99, '03, '05); 7th-14th BHIVA (2001-2008); and 8th-9th European AIDS Society Conference (2001, 2003), using the search terms:

3TC, ABC, AZT, ZDV, d4T, TDF, FTC, NRTI, NNRTI, nucleoside, nucleotide, protease, DLV, EFV, ETR, NVP, APV, ATV, DRV, IDV, LPV, RTV, NFV, TPV, T-20, MVC, Atripla, lamivudine, abacavir, zidovudine, stavudine, zalcitabine, didanosine, emtricitabine, epzicom, kivexa, trizivir, combivir, truvada, delavirdine, efavirenz, nevirapine, amprenavir, fosamprenavir, atazanavir, darunavir, indinavir, lopinavir, ritonavir, saquinavir, tipranavir, enfurvitide, maraviroc, raltegravir, tenofovir, breast, mother, infant, baby, pregnant, pregnancy, perinatal, postnatal, feeding, breastfeeding, vertical, mtct, pmtct.

This yielded 6099 results. Results relevant to animal research, behavioural research, etc. (e.g. simian, feline, monkey, baboon, chimpanzee, rhesus, macaque, msm, condom, behavio/ural, couples, husband, wife, boyfriend, girlfriend, violent, violence, cocaine, heroin, methamphetamine, in vitro, murine, mouse), were then excluded leaving 607 net results. No trials that had not been identified previously were identified through this process.

(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 5 for search strategy.

For the 2009 update we searched CENTRAL of Issue 2 of *The Cochrane Library* on 11 May 2009 using the same strategy as before in Table 5 and yielded 54 records of which we identified 17 for full article retrieval.

[Table 4 contains the search strategy for NLM Gateway used in the previous update in 2005].

We also checked the reference lists of all the articles retrieved by the search strategy for relevant studies.

One of us (NS) attended the International AIDS Society Conference held in Cape Town, South Africa, from 20 to 22 July 2009 and identified additional trials first presented at the conference. Three trials were identified in this way.

Finally, we contacted research organizations and experts in the field for unpublished and ongoing studies and have included these as studies for future assessment.

Data collection and analysis

The methods detailed below refer to the process used in the 2009 update.

Selection of studies

NS and a hand-searcher trained in identification of trials 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.

NS and LvdM 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.

Data extraction and management

NS and LvdM 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 measures** 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 consultation.

Assessment of risk of bias in included studies

NS and LvdM independently examined the components of each included trial for risk of bias using a standard form using the Cochrane guidelines below:
Sequence generation
- Adequate: investigators described a random component in the sequence generation process such as the use of random number table, coin tossing, cards or envelops shuffling etc
- Inadequate: investigators described a non-random component in the sequence generation process such as the use of odd or even date of birth, algorithm based on the day/date of birth, hospital or clinic record number
- Unclear: insufficient information to permit judgement of the sequence generation process

Allocation concealment
- Adequate: participants and the investigators enrolling participants cannot foresee assignment, e.g. central allocation; or sequentially numbered, opaque, sealed envelopes.
- Inadequate: participants and investigators enrolling participants can foresee upcoming assignment, e.g. an open random allocation schedule (e.g. a list of random numbers); or envelopes were unsealed or nonopaque or not sequentially numbered
- Unclear: insufficient information to permit judgement of the allocation concealment or the method not described

Blinding
- Adequate: blinding of the participants, key study personnel and outcome assessor, and unlikely that the blinding could have been broken. Or lack of blinding unlikely to introduce bias. No blinding in the situation where non-blinding is not likely to introduce bias.
- Inadequate: no blinding, incomplete blinding and the outcome is likely to be influenced by lack of blinding
- Unclear: insufficient information to permit judgement of adequacy or otherwise of the blinding.

NOTE a study may not have blinded the personnel and participants but reported clearly that the assessor was blinded. In this case, we assessed blinding as Inadequate. Similarly if a study was placebo-controlled and participants and providers were blinded but the assessors were not, then we assessed blinding as inadequate.
Incomplete outcome data
- Adequate: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome, or missing outcome data balanced in number across groups
- Inadequate: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data
- Unclear: insufficient reporting of attrition or exclusions

We did not assess *Selective Reporting* or *Other forms of bias* for each trial. Given that many trials were conducted prior to prospective trial registration becoming mandatory, it would not have been feasible to collect the protocols for each trial to make the judgment on *Selective Reporting*. Similarly we did not think it was feasible to provide a judgment on *Other forms of Bias* and therefore only report on the first four recommended criteria in the **Risk of Bias** Tables.

Data synthesis

The primary outcome is the estimated transmission rate of HIV (the observed proportion) at various specific time-points. Our choice was between analysing the crude proportions or the rates as reported by the authors using different survival analytic methods to estimate transmission rates of HIV (these included Cox regression, Kaplan-Meier, Turnbull and life-tables). Survival analysis methods 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 preven-

tive 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 randomised, not the number analysed, and report the 95% confidence intervals as calculated by REVMAN.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

For the 2009 update, from the searches described above, we identified an additional seven relevant trials (Mashi; Thistle 2007; Chung 2005; Chung 2008; Chi 2007; Kesho Bora; Mma Bana) and one ongoing trial (BAN 2005) (also identified in the previous review) since the review was published in 2007. In total, 25 trials met our inclusion criteria. Overall the 25 trials included 18,901 participants with a median trial sample size of 627 ranging from 50 (Bhoopat 2005) to 1,844 participants (PHPT-2). Twenty-two trials randomised mothers (18 pre-natally and four in labour) and followed up their infants, and three trials (Taha 2004; Gray 2005; Taha 2003) randomised infants.

Location of trials

Most trials (N=20) were conducted in a single country, all in poor regions of the world: Thailand (N=5), South Africa (N=3), Kenya (N=3), Botswana (N=2), Zimbabwe (N=2), Malawi (N=2), Cote d'Ivoire (N=1), Uganda (N=1) and Zambia (N=1). Of the five multinational trials, three 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; and the Kesho Bora trial was conducted in five sites in Burkina Faso, Kenya and South Africa. 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.

Feeding mode

Twelve trials, all conducted in Africa, included mothers who were breastfeeding (DITRAME; HIVNET 012; PETRA; RETRO-CI; Taha 2003; Taha 2004; Thistle 2004; Chi 2007; Chung 2005; Chung 2008; Mma Bana; Thistle 2007). 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. Five trials included mixed feeding: 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; and in the Mashi and the Kesho Bora mode of feeding was mixed.

Dates

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 randomised 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 have been modified in each subsequent trial. No two trials in this review compare identical interventions (see Characteristics 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 2). Trials in the breastfeeding populations continue for a longer period than those in non-breastfeeding in order to assess any additional benefit of antiretrovirals in reducing breast-milk transmission.

Figure 2. Trial characteristics and time-points for HIV or HIV and Death

Ages with HIV efficacy (X) and HIV or death efficacy (XM) data available																			
								Number of months											
NAME	BF	Period	Comparison	Randomized	0	0.25	0.5	1	1.5	2	3	4	6	9	12	18	Points
DITRAME	yes	1995-1998	1	Prenatal		X			X		X		X	X	X	X	7
RETRO-CI	yes	1996-1998	1	Prenatal	X			X			X	X					4
PETRA*	yes	1996-2000	1	Prenatal					XM							XM	2
HIVNET 012	yes	1997-1999	3	Prenatal		XM				XM		XM			XM	XM	5
Thistle 2004	yes	1999-2000	2	Prenatal	X	X	X		X		X		X		X		7
Taha 2003	yes	2000-2002	3	Labour						X							1
Taha 2004	yes	2000-2003	3	Infants						X							1
Thistle 2007	yes	2002-2004	3	Labour	X				X								2
Chung 2005	yes	2003	3	Prenatal					X								1
Chung 2008	yes	2003-2006	4	Prenatal	X								X				2
Chi 2007	yes	2005-2007	3	Prenatal	X				XM								2
Mma Bana	yes	2006-2008	5	Prenatal	X								X				2
PACTG 076	no	1991-1993	1	Prenatal											X		1
Limpongsanurak 2001	no	1995-1996	1	Prenatal									X				1
Thai-CDC	no	1996-1997	1	Prenatal						X							1
PACTG 316	no	1997-2000	2	Labour						X							1
PHPT-1*	no	1997-1999	2	Prenatal									XM				1
SAINT	no	1999-2000	3	Labour					XM								1
Gray 2006*	no	1999-2000	3	Prenatal	X			X		X		X					4
Kiarie 2003	no	1999-2001	3	Prenatal				X									1
Gray 2005	no	2000-2002	3	Infants				X		X							2
PHPT-2	no	2001-2003	2	Labour	X								XM				2
Bhoopat 2005	no	not reported	2	Prenatal	X						X						2
Mashi	no	2002-2003	4	Prenatal	X												1
Kesho Bora	no	2005+	4	Prenatal	X			XM				XM		XM	XM		4
					11	3	1	1	10	6	5	3	9	1	4	4	25

Risk of bias in included studies

Please see Figure 3 and Figure 4 for a graphical description of the risk of bias.

Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies. Note the blank spaces are to accommodate sub-groups within trials and are not included as this would be double-counting.

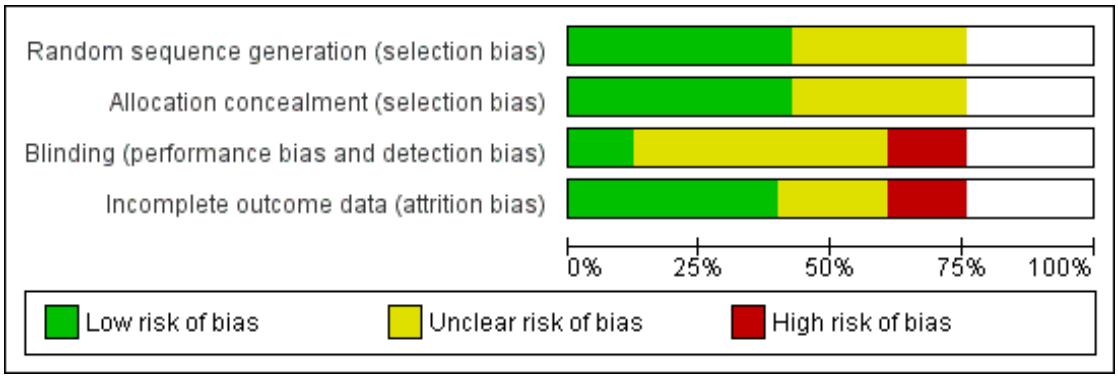
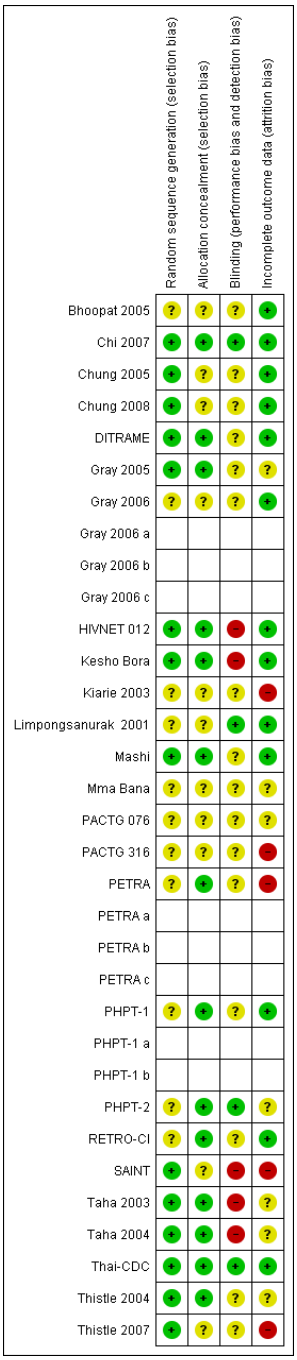


Figure 4. Methodological quality summary: review authors' judgements about each methodological quality item for each included study. Note the blank spaces are to accommodate sub-groups within trials and are not included as this would be double-counting.



Allocation

GENERATION OF RANDOM SEQUENCE

Fourteen trials reported adequate generation of the random sequence (Chi 2007; Chung 2005; Chung 2008; DITRAME; Gray 2005; HIVNET 012; Kesho Bora; Mashi; SAINT; Taha 2003; Taha 2004; Thai-CDC; Thistle 2004; Thistle 2007) and the other twelve trials either did not report how this was done or the report was unclear. All trials reporting adequate generation used computerised methods for generating the sequence.

ALLOCATION CONCEALMENT

Fourteen trials reported adequate allocation concealment (Chi 2007; DITRAME; Gray 2005; HIVNET 012; Kesho Bora; Mashi; PETRA; PHPT-1;PHPT-2; RETRO-CI; Taha 2003; Taha 2004; Thai-CDC; Thistle 2004), and eleven trials failed to report on allocation concealment or were not sufficiently specific. Of those trials with adequate allocation concealment, six trials reported providing the allocation schedule in sequentially ordered, opaque envelopes (Chi 2007; Gray 2005; Kesho Bora; Taha 2003; Taha 2004; Thistle 2004); one trial reported randomisation as being done centrally (Mashi) and the remaining trials reported concealing allocation by providing sequentially numbered sealed treatment packs prepared off-site.

Blinding

Clear information on who was masked was reported or obtained from authors in eight trials; three of these clearly reported masking the providers, participants and assessors (Limpongsanurak 2001; PHPT-2; Thai-CDC), and five of these clearly reported on masking the assessor but not the provider or participant (HIVNET 012; SAINT; Taha 2003; Taha 2004; Chi 2007). Fourteen trials did not clearly report masking at every stage: nine 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; Mashi; Mma Bana; Thistle 2007); five 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; Chung 2005; Chung 2008); one trial clearly reported masking the provider but was unclear about the other stages (PACTG 076); one trial report was unclear about every stage of masking (Bhoopat 2005) and one trial (Kesho Bora) reported that neither participants nor study investigators were masked.

Incomplete outcome data

In order to standardise the reporting of attrition in each trial we calculated a percentage of the number of participants randomised 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.

The attrition rate ranged from 0% in the Bhoopat 2005 trial to 53.4% in the Thistle 2007 trial. The latter attrition was reportedly due to a lack of fuel in Zimbabwe at the time of the trial severely hampering the ability of participants to attend follow-up clinics. Eight 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.

Effects of interventions

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 trials ordered chronologically on the date of the start of the trial rather than the date when the report was published.

For the 2009 update, no new trials were identified evaluating antiretrovirals compared with placebo or longer regimens with shorter regimens of the same antiretrovirals. We classified three of the trials identified in the 2009 update as regimens using different antiretrovirals and different durations of treatment. Three trials included evaluations of a regimen of three antiretrovirals given to the mother which we refer to as TRIPLE (also known as Highly Active Antiretroviral Treatment [HAART]) compared with other shorter regimens, and one compared two different TRIPLE regimens with each other.

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 1.50 to 62.50), 3 to 4 months (Efficacy 33.07%; 95% CI 5.57 to 60.57), 6 months (Efficacy 34.55%; 95% CI 9.05 to 60.05), 12 months (Efficacy 34.31%; 95% CI 9.30 to 59.32) and 18 months (Efficacy 29.74%; 95% CI 2.73 to 56.75). The treatment did not influence risk of infant death in the first week after

birth (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 risk 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 43.78%; 95% CI 8.78 to 78.78) and 3 to 4 months (Efficacy 36.95%; 95% CI 2.94 to 70.96) but not at birth (Efficacy -13.95%; 95% CI -163.75 to 135.85). Treatment also reduced the risk of infant death in the first week after birth (RR 0.13; 95% CI 0.02 to 0.99) and during the first 3 to 4 months after birth (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 after birth significantly reduced HIV infection at 4 to 8 weeks (Efficacy 62.75%; 95% CI 40.76 to 84.74) but not at 18 months (Efficacy 32.88%; 95% CI -11.75 to 77.51). The incidence of a combined endpoint of HIV infection or death was also significantly reduced (Efficacy 61.33%; 95% CI 41.34 to 81.32) at 4 to 8 weeks but not at 18 months (Efficacy 26.17%; 95% CI -13.62 to 65.96). 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 after birth significantly reduced HIV infection at 4 to 8 weeks (Efficacy 41.83%; 95% CI 12.82 to 70.84) but not at 18 months (Efficacy 18.47%; 95% CI -27.16 to 64.10). The risk of HIV infection or death was significantly reduced at 4 to 8 weeks (Efficacy 35.91%; 95% CI 8.41 to 63.41) but not at 18 months (Efficacy 7.03%; 95% CI -39.17 to 53.23). 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 significantly reduce HIV infection at either 4 to 8 weeks (Efficacy 7.19%; 95% CI -31.81 to 46.19) or 18 months (Efficacy 9.91%; 95% CI -40.99 to 60.81). There was also no significant difference in the combined outcome of HIV infection or death at 4 to 8 weeks (Efficacy 3.31%; 95% CI -31.69 to 38.31) and at 18 months (Efficacy 1.56%; 95% CI -44.60 to 47.72). 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 after birth significantly reduced HIV infection in babies at 18 months (Efficacy 66.22%; 95% CI 33.94 to 98.50). The treatment did not significantly reduce the risk of infant death in the first 18 months (RR 1.33; 95% CI 0.30 to 5.87) or the risks of premature delivery (RR 1.23; 95 CI 0.60 to 2.49) and low birth weight (RR 0.75; 95% CI 0.48 to 1.19). No significant 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 after birth 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.

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 8.59%; 95% CI -26.63 to 43.81). There was also no significant difference in the risk 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 50.26%; 95% CI 13.80 to 86.72) but not at birth (Efficacy 29.71%, 95% CI -43.48 to 102.90). 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 after birth (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 after birth) was compared to a 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 -15.10%, 95% CI -152.08 to 121.88), 4-8 weeks (Efficacy 16.72% 95% CI -42.43 to 75.87), 3 to 4 months (Efficacy 13.95%, 95% CI -38.50 to 66.40), 6 months (Efficacy 8.28%, 95% CI -41.76 to 58.32) and 12 months (Efficacy 8.62%, 95% CI -33.93 to 51.17). 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 'ultrashort' 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-1; PHPT-2; Bhoopat 2005)

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 24.42%; 95% CI -20.25 to 69.09) and in the risk of HIV infection or death at 6 months (Efficacy

14.61%; 95% CI -30.80 to 60.02). 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 45.33%; 95% CI 1.39 to 89.31). While the risk of HIV infection or death at 6 months was also reduced this was not statistically significant (Efficacy 37.08%; 95% CI -6.88 to 81.04). 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 postpartum 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.

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 37.50%; 95% CI -40.94 to 115.94) and at 6 months (Efficacy 28.57%; 95% CI -26.09 to 83.23) 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.

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 -294.36 to 494.36) 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 -16.50 to 216.50).

Adverse events:

- Not reported

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

This section describes those trials which compared regimens comprising different drugs either in a mono- or dual therapy manner and for varying periods of time. Trials which evaluate antiretrovirals comprising triple therapy are described in the following sections and Comparisons 04 and 05.

BREASTFEEDING

Six trials assessed this comparison (HIVNET 012; Taha 2003; Taha 2004; Thistle 2007; Chung 2005; Chi 2007). Three of these trials were identified in the most recent 2009/10 update (Thistle 2007; Chung 2005; Chi 2007).

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 significantly lower HIV infection rates at 4-8 weeks (Efficacy 41.00%; 95% CI 11.84 to 70.16), 3-4 months (Efficacy 38.91%; 95% CI 11.24 to 66.58), 12 months (Efficacy 35.98%; 95% CI 9.25 to 62.71) and 18 months (Efficacy 39.15%; 95% CI 13.81 to 64.49). In addition, the NVP regimen significantly reduced the risk of HIV infection or death at 4-8 weeks (Efficacy 41.74%; 95% CI 14.30 to 69.18), 3 to 4 months (Efficacy 40.00%; 95% CI 14.34 to 65.66), 12 months (Efficacy 32.17%; 95% CI 8.51 to 55.83) and 18 months (Efficacy 32.57%; 95% CI 9.93 to 55.21). There

was no significant difference between the two groups for infant mortality in the first week after birth (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 after birth compared to a regimen consisting of a single dose of NVP to babies only significantly reduced HIV infection at 4 to 8 weeks (Efficacy 36.79%; 95% CI 3.57 to 70.01). 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 -15.60%; 95% CI -50.21 to 19.01) 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).

Thistle 2007

This Zimbabwean trial compared the ultra-short ZDV regimen given to mothers at the onset of labour and 3 hourly during labour, combined with a single 200mg dose of NVP during labour; infants received ZDV four times daily for 72 hours post delivery and a single dose of NVP. Mothers in the placebo group received a placebo rather than ZDV and the single dose of NVP in labour; their infants received placebo for ZDV and the single dose of NVP within 72 hours of delivery. There was no difference in HIV infection rates at birth between the groups (Efficacy -5.45%; 95%CI -79.95 to 69.05) and at four to six weeks, HIV infection efficacy remained statistically non-significant with an efficacy of 9.21% (95%CI -27.56 to 45.8). For HIV infection or death at four to six weeks, there was no statistically significant difference between the groups (Efficacy 3.97%,95%CI -26.14 to 34.08). Infant deaths during the first four to six weeks was similar in both groups (RR = 1.08; 95% CI 0.61 to 1.92).

Adverse events

Mothers:There were 9 maternal deaths in the ultra-short ZDV regimen and 13 in the NVP group.

Infants: No cases of severe drug toxicity were observed in the infants in both groups.

Chung 2005

In this trial the so-called Thai-CDC regimen of ZDV given to mothers from 34 weeks until onset of labour and during labour was compared with the HIVNET 012 regimen of NVP given to mothers at onset of labour and to infants within 72 hours of delivery. There was no statistically significant difference between HIV infection at 2 weeks in infants (Efficacy -100%, 95%CI -536.39 to 336.39). At 4 to 8 weeks HIV infection in infants of the mothers receiving the NVP regimen was statistically significantly lower than those in the ZDV group (Efficacy -345.59%; 95%CI -630.00 to -61.18). The risk of infant death at 6 weeks was lower in the NVP group compared with the ZDV group (RR 5; 95%CI 0.25 to 99.95) but not statistically significant. As there were no events in the NVP group the RR must be treated with caution. The RR for infants weighing less than 2.5kg in the ZDV group was half that in the NVP group (RR 0.50; 95%CI 0.10 to 2.53), which was not statistically significant.

Adverse events:

- There were no adverse events or side effects reported in either intervention group in the mothers or babies.

Chi 2007

In this Zambian trial all mothers received the standard of care at the time, which was ZDV 300mg twice daily from 32 weeks

until labour, sdNVP 200mg at onset of labour and all infants received the standard of care of NVP 2mg/kg once within 72 hours of delivery and ZDV 4mg/kg orally twice daily for 7 days post delivery. Mothers were randomised to either receive the addition of Tenofovir 300mg and Emtricitabine 200mg (co-formulated as Truvada) orally in labour in addition to standard of care or only standard of care. The primary aim of this trial was to evaluate maternal resistance to non-nucleoside reverse transcriptase inhibitor drugs at 6 weeks post-partum.

HIV infection at birth was not statistically different between groups (Efficacy 20.40%, 95%CI -66.86 to 107.66) or at four to eight weeks (Efficacy 28.93%, 95%CI -40.84 to 98.70). The risk of death in the first four to eight weeks after birth was not statistically different between the groups (RR 1.26; 95%CI 0.34 to 4.61), nor was the risk of stillbirth (RR 1.99, 95%CI 0.18 to 21.77).

Adverse events:

- Mothers: The primary aim of this trial was to evaluate maternal resistance to non-nucleoside reverse transcriptase inhibitor drugs at 6 weeks post-partum. Women assigned to the intervention were reported to be statistically significantly less likely to develop resistance to NNTRI at 2 weeks (RR 0.27; 95%CI 0.11 to 0.66) and 6 weeks (RR 0.47; 95%CI 0.29 to 0.76) post childbirth.
- Seven of 198 mothers receiving the intervention and nine of 199 in the control group experience serious adverse events, four each group had postpartum anaemia. There was no statistically significant difference between the groups.
- Infants: Ten percent (20/198) of infants in the intervention group and 12% (23/199) in the control group experienced serious adverse events, including septicaemia (22) and pneumonia (8). There was no statistically significant difference between the groups and the authors report that none of the events were judged to be due to the study intervention.

NON-BREASTFEEDING

Five trials assessed this comparison (PACTG 316; SAINT; Gray 2006; Kiarie 2003; Gray 2005) with one additional trial (Mashi) identified in the 2009/10 update.

PACTG 316

In a population in which mothers were receiving 'standard' antiretrovirals 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 2.22%, 95% CI -140.39 to 144.83) and 4 to 8 weeks (Efficacy 12.50%, 95% CI -82.89 to 107.89) 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 the risks of stillbirth (RR 2.99; 95% CI 0.12 to 73.33), low birth weight (RR 1.14; 95% CI 0.85 to 1.53) or prematurity (RR 1.05, 95% CI 0.83 to 1.32).

Adverse events:

- Mothers: The risks 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 24.39%; 95% CI -4.15 to 52.93), 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 risk 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 risks 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 antiretroviral 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 risks of HIV infection at birth (Efficacy 26.65%; 95% CI -122.44 to 175.74), 4 to 8 weeks (Efficacy -120.05%; 95% CI -301.07 to 60.97), 3 to 4 months (Efficacy -144.51%; 95% CI -329.90 to 40.88) and 6 months (Efficacy -116.07%; 95% CI -280.57 to 48.43). 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 52.66%; 95% CI -88.01 to 193.33), 4 to 8 weeks (Efficacy -42.02%; 95% CI -205.79 to 121.75), 3 to 4 months (Efficacy -113.03%; 95% CI -290.84 to 64.78) and 6 months (Efficacy -89.29%; 95% CI -247.73 to 69.15). 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 risks of HIV infection were found at birth (Efficacy 49.43%; 95% CI -94.88 to 193.74), 4 to 8 weeks (Efficacy 24.15%; 95% CI -127.10 to 175.40), 3 to 4 months (Efficacy -1.14%; 95% CI -158.84 to 156.56) and 6 months (Efficacy 17.86%; 95% CI -118.79 to 154.51). 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 59.09%; 95% CI -3.90 to 122.08). 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 after birth did not result in a statistically significant difference in HIV infection rates at 4-8 weeks (Efficacy 35.37%; 95% CI -10.00 to 80.74) and 3 to 4 months (Efficacy 39.69%; 95% CI -1.08 to 80.46). 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 risk 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.

Mashi

This trial was conducted in Botswana and compared sdNVP with placebo in mothers receiving ZDV from 34 weeks and in labour and infants receiving ZDV twice daily for one month post delivery. Initially the trial aimed to compare sdNVP with placebo in both mothers and infants but this was terminated in August 2002 after the results from the PHPT-2 trial showed the superiority of sdNVP in infants. The trial continued to evaluate sdNVP versus placebo in mothers only. Infants in both groups then received sdNVP.

For HIV infection at birth, there were no differences between the groups (Efficacy -64.38%, 95%CI -183.72 to 54.96). At one month post-partum HIV infection rates were not statistically significantly different between the groups (Efficacy -16.22%; 95%CI -102.24 to 69.80). Infant deaths in the first month were not statistically different between groups (RR 0.54, 95%CI 0.22 to 1.35). Stillbirth rates were similar in both groups (RR 1.50, 95%CI 0.43 to 5.28) and there was no difference in the incidence of premature delivery (RR = 1.00, 95%CI 0.40 to 2.50).

In October 2002, TRIPLE became available in Botswana and so all participating women with CD4 < 200 cells/μL or with an AIDS-defining illness were offered TRIPLE and did not receive sdNVP or placebo at onset of labour.

Adverse events:

- Mothers: Twenty women experienced life-threatening or serious events between study entry and three months after delivery. Of these, the report states that one event of anaemia was possibly related to sdNVP and two events of rash and abnormal liver function tests were possibly related to sdNVP or placebo as both of these were in the placebo arm.
- Infants: Twelve stopped ZDV before one month due to toxicity (mainly due to anaemia or neutropaenia); there were five serious or life-threatening events possibly related to sdNVP. Four were serious rashes and one was raised bilirubin levels and jaundice. Two were hospitalised but did not die due to adverse events.

TRIPLE REGIMENS VERSUS OTHER (See Comparison 04)

Two trials evaluated TRIPLE antiretroviral regimens compared with previously used regimens which did not include triple antiretrovirals (Chung 2008; Kesho Bora).

BREASTFEEDING

Chung 2008

This single-centre Kenyan trial compared TRIPLE (ZDV 300mg twice daily, Lamivudine 150mg twice daily, NVP 200mg twice daily from 34 weeks until 6 months post delivery) with mothers receiving ZDV 300mg twice daily from 34 weeks until labour and sdNVP 200mg at onset of labour. Infants in the TRIPLE group received no additional drugs while those in the ZDV/sdNVP group received sdNVP 2mg/kg within 72 hours of delivery. No babies were infected with HIV at birth in either group; at 6 months post delivery there was no statistically significant difference in HIV infection between groups (Efficacy -84.62%, 95%CI: -490.35 to 321.11). There was no statistically significant differ-

ence for the outcome of HIV infection or death at two weeks (Efficacy -84.62%, 95%CI: -490.35 to 321.11), or at 12 months (Efficacy 35.90%; 95%CI: -118.33 to 190.13). There were two stillbirths in the TRIPLE group and one in the ZDV/sdNVP group (RR 1.87, 95%CI 0.18 to 19.47). There were no infant deaths in the TRIPLE arm and one at 2 weeks from sepsis (RR 0.31, 95%CI 0.01 to 7.30). There were five infants weighing less than 2.5kg in the TRIPLE group and none in the ZDV/sdNVP group (RR 10.29, 95%CI 0.59 to 177.97) but this was not statistically significant.

Adverse events:

- Mothers: Two adverse events were reported in women receiving TRIPLE. These were not graded in the report but one was a diffuse rash pre-delivery ascribed to NVP and the other was anaemia arising two months post-partum resolving after blood transfusion.
- Infants: None reported.

MIXED FEEDING

Kesho Bora

This trial was conducted in five sites in three countries. TRIPLE (Lopinivar 200mg /ritonavir 50mg and ZDV 300mg and lamivudine 150mg from 26 to 34 weeks gestation through 6 months post-partum) given to the mother was compared with ZDV given to the mother from 28 to 36 weeks, ZDV and lamivudine and sdNVP given at onset of labour and ZDV and lamivudine for one week after delivery. Infants in both groups received sdNVP within 72 hours of delivery and ZDV for one week.

There was no statistically significant difference between groups in HIV infection at birth (Efficacy 18.18%, 95%CI -83.48 to 119.84) or at four to eight weeks (Efficacy 31.25%, 95%CI -29.29 to 91.79). At six months, HIV infection was higher but not statistically significantly so in the non-TRIPLE group (Efficacy 42.35%, 95%CI -0.57 to 85.27). At 12 months HIV infection was statistically significantly higher in the non-TRIPLE group (Efficacy = 42.11%, 95%CI 0.66 to 83.56). The incidence of HIV infection or death at four to eight weeks was higher in the non-TRIPLE group (RR 20.00, 95%CI -34.13 to 74.13) but this was not statistically significant. At 6 months, the HIV infection or death incidence remained higher in the non-TRIPLE group (RR 34.13, 95%CI [-0.29 to 68.55) and at 12 months this difference was statistically significant (RR 36.20, 95%CI 5.92 to 66.48).

The number of infants dying in the first week after birth was not statistically significantly different between groups (RR 2.00, 95%CI 0.37 to 10.88), nor in the first 4 to 8 weeks (RR 0.86, 95%CI 0.29 to 2.53), or first 6 months (RR 0.78, 95%CI 0.43 to 1.43). In the first 12 months, more babies died in the non-TRIPLE group although this difference was not statistically significant (RR 0.65, 95%CI 0.40 to 1.07).

There was no statistically significant difference between groups for prematurity as defined by the authors (RR 1.44, 95%CI 0.93 to 2.24) or in those weighing less than 2.5kg (RR 1.25, 95%CI 0.86 to 1.82). The risks of stillbirth were the same between groups (RR 1.00, 95%CI 0.25 to 3.95).

Adverse events:

- Mothers: There were four maternal deaths in both groups. Other adverse events are reported as percentages only which we calculated backwards to determine numbers. In the TRIPLE group, 11 (2.7%) of mothers developed anaemia at delivery with 7 (1.8%) in the non-TRIPLE group. In the TRIPLE group. one mother developed Grade 3 neutropaenia and two mothers had ALT level raised five times above the upper limit of normal at delivery . Five deaths were attributed to serious adverse events in both groups.
- Infants: Adverse events are reported as percentages only. In the TRIPLE group 14.6% of infants developed a grade 3 anaemia and 12% in the non-TRIPLE group. In the TRIPLE group, 7.8% of infants developed a grade 3 or 4 neutropaenia and 8.4% in the non-TRIPLE group. Fatalities attributed to serious adverse events were 6.7% in the TRIPLE group and 10.2% in the non-TRIPLE group.

TRIPLE ANTIRETROVIRAL REGIMENS VERSUS TRIPLE ANTIRETROVIRAL REGIMENS (See Comparison 05)

To date, one trial (Mma Bana) has evaluated the superiority of the drug composition of two different types of triple antiretroviral regimens given to mothers.

BREASTFEEDING

Mma Bana

This trial was conducted in the same centres in Botswana as the Mashi trial. Mothers either received Abacavir 300mg, lamivudine 150mg, and ZDV 300mg (co-formulated as Trizivir (TZV)) one tablet taken twice daily from 26 to 34 weeks gestation or Lopinivar 400mg /ritonavir 100mg tablet and ZDV 300mg and Lamivudine 150mg (co-formulated as Combivir (CBV)) taken orally twice daily from 26 to 34 weeks gestation through 6 months post-partum. Infants in both groups received sdNVP within 72 hours of delivery and one month of ZDV following birth.

There was no significant difference in HIV infection rates at birth (Efficacy -189.47%; 95%CI -715.29 to 336.35) with three babies infected in the TZV group and one in the CBV group. At three months the incidence in infant HIV was still not significantly different (5 versus 1) between groups (Efficacy -390.88%; 95%CI -981.63 to 199.87). The differences between groups in the number of infants dying in the first eight days after birth (RR 1.96; 95%CI 0.18 to 21.53) and in the first six months after birth (RR 0.98; 95%CI 0.35 to 2.76) were not significantly different. Incidence of prematurity defined as gestational age < 37 weeks was higher in the CBV group (RR 0.66; 95%CI 0.47 to 0.95) but not statistically significant. Low birthweight less than 2.5kg was also higher in the CBV group but was not statistically significant (RR 0.79; 95%CI 0.53 to 1.19). Stillbirth rates did not differ statistically significantly between the groups (RR 1.54; 95%CI 0.51 to 4.66).

Adverse events:

- Mothers: Six percent (17) of mothers in the TZV group and six percent (16) in the CBV group had a new grade 3+ diagnosis

after initiating antiretrovirals. Of these, four mothers in the TZV group and five in the CBV group experienced eclampsia or pre-eclampsia with two and one intra-uterine death following respectively. The site investigators judged the death in the CBV group 'probably not' due to the study drug but that the deaths in the TZV group were 'possibly' related to the study drug.

- Infants: There were 28 (10%) diagnoses of grade 3 or more severity in the TZV group and 17 (6%) in the CBV group.

DISCUSSION

Summary of main results

This update of the review shows that a combination of antiretroviral drugs is the most effective antiretroviral regimen for decreasing mother-to-child transmission of HIV. It builds on the findings from our previous review that antiretroviral treatment administered in the perinatal period lowers the risk of mother-to-child transmission of HIV. This information is relevant to the care of pregnant women who are HIV-infected in both resource-rich and resource-constrained settings. The choice of which combination of triple antiretrovirals, and the optimal time to initiate antiretrovirals in pregnancy, remains unclear. None of the trials in this review follow-up the infants for longer than 24 months and the long-term adverse effects of in-utero or early neonatal exposure to antiretrovirals is not known. Importantly, data on the emergence and duration of resistance is currently limited.

Summary of main results from this update

In this update, the most noteworthy addition to the evidence base is the inclusion of results from trials which compare antiretroviral regimens comprising three drugs either with other regimens (Kesho Bora;Chung 2008) or with another triple antiretroviral combination as in the case of the Mma Bana trial. In the Kesho Bora trial TRIPLE ART including a protease-based inhibitor was given from 26 to 34 weeks gestation through six months post-partum and compared with a ZDV-based regimen starting later at 28 to 36 weeks with no post-partum component. Infants in the TRIPLE antiretrovirals group were significantly less likely to have the virus at 12 months. The trial population was classified as mixed feeding and the results are likely to indicate the importance of mothers continuing with antiretrovirals should they choose to breastfeed. The Chung 2008 trial was conducted in a breastfeeding population, with a TRIPLE antiretroviral regimen commenced at 34 weeks compared with only ZDV for the same period until labour when sdNVP was added found no babies were infected with HIV at birth in either group and at 6 months post delivery there was no statistically significant difference in HIV infection between groups. Although the lack of events rates does not allow inferences regarding superiority of the TRIPLE regimen over the ZDV regimen, it does confirm the efficacy of providing antiretrovirals, even if monotherapy ZDV, to mothers earlier in pregnancy. In Mma Bana transmission rates are again gratifyingly low both at birth and later at six months, suggesting that either choice of triple combination antiretroviral is effective. Our results concur with those of the Sturt 2010 Cochrane review which evaluated the efficacy of treatment for HIV-infected pregnant women and considered transmission as a secondary outcome. Adverse event rates both for mothers and babies were low in all three trials with the exception of a significant difference seen in stillbirths in the Kesho Bora trial.

The results from the additional four trials identified in this update contributed to the evidence base for the category of antiretroviral regimens using different drugs and durations of treatment. None of the trial results provided significantly different results to those previously documented.

Summary of main results from previous versions of the review

ZDV has been the most extensively studied drug and forms a component of treatment in all 25 trials included in this review. In a non-breastfeeding population a long course of ZDV monotherapy 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 after birth 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 after birth reduced the risk of mother-to-child transmission at 4 to 8 weeks by about 40% with the benefit persisting at 18 months (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 after birth, 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

For TRIPLE antiretroviral regimens, there are no trials evaluating provision of antiretrovirals before 26 weeks gestation. However, the World Health Organisation has now suggested that ARV can be started as early as 14 weeks of pregnancy once the period of major teratogenicity is passed (WHO 2009) because of the paucity of evidence to suggest any harmful effects after 14 weeks. This evidence of lack of harm, however, is limited to the immediate effect on the fetus and the child up until the end of follow-up, which is often short. The experience with other drugs in pregnancy, particularly diethylstilboestrol is that the toxic effects of in-utero exposure (vaginal cancers in the female offspring and sub-fertility in the male offspring) only became apparent when the offspring were young adults (Giusti 1995). Although this exposure was in the first trimester of pregnancy, there are more recent examples where erythromycin given to women in threatened preterm labour lead to an increase in the risk of cerebral palsy at age 7 (Kenyon 2008) and dexamethasone given to preterm neonates resulted in a excess of cerebral palsy with only limited beneficial effects in the neonatal period ([3]. These examples illustrate that long term effects of drug exposures in pregnancy may not be realised until many years, and perhaps decades, after exposure. These later effects are unlikely to prevent the use of antiretrovirals to prevent mother-to-child transmission, but as more regimens of similar efficacy become available, and as the majority of exposed children will remain free of HIV and survive into adulthood, the relative safety (both short term and long term) of different drugs will be important in guiding treatment choices. The importance of long-term follow-up of these cohorts of exposed children is therefore essential.

With ZDV-based regimens, the length of treatment seems to influence transmission rates with a longer antenatal component being the most beneficial. 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 were 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 risk 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 after birth 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 risk 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 2005 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. Of note, is that the Mma Bana trial provided TRIPLE antiretrovirals to breastfeeding mothers and the low transmission rates in both the protease-inhibitor-based and the nucleoside reverse transcriptase inhibitor arms confirm that either TRIPLE an-

tiretroviral combination was effective in maintaining maternal virologic suppression throughout breastfeeding.

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 between intervention groups. 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, although follow-up was not sufficiently long in most of the trials to assess these later outcomes.

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 2005c). 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).

In this update, the completeness of the evidence is again limited by the lack of information pertaining to the emergence and duration of resistance. In a trial of ritonavir-boosted lopinavir compared with NVP-based therapy for treating HIV, 241 HIV-infected mothers who had previously been exposed to single dose NVP six months or more before randomisation, were followed up for two years (Lockman 2010). In the group receiving NVP, women with resistance mutations to NVP detectable at treatment initiation had a 73% failure rates compared with 19% of those without resistance mutations. Findings were similar in a trial of 164 HIV-infected children (Palumbo 2010) . GIven the high costs of antiretrovirals and the fact that in resource-constrained settings many women present late to antenatal care, NVP will continue to play an important role in preventing mother-to-child transmission (Lallemant 2010). This will continue to have implications for clinicians determining which treatment to provide to HIV-infected women and children. Lallemant and Jourdain question whether there is a role for resistance screening to identify individuals who would require non-NVP based treatment (Lallemant 2010) but the costs of this are likely to limit its usefulness.

Overall completeness and applicability of evidence

This 2010 update added evidence from seven new trials to that of the previous 18 trials reported in the update in 2006. None of the new trials compared the same interventions with each other or comprised identical comparisons to those comparisons reported in the previous update.

Four of the new trials contributed data to the comparisons between different antiretroviral regimens of different durations first described in the previous review (Chi 2007; Thistle 2007; Chung 2005; Mashi). Three trials evaluated interventions in breast-feeding populations and one in a non-breastfeeding population. None of the new included data changed our previous results or interpretations significantly.

Two new trials contributed data to a new comparison between TRIPLE and other regimens (Chung 2008; Kesho Bora), both conducted in breast-feeding populations. The remaining new trial, Mma Bana, provided data on comparing two types of TRIPLE regimens aimed at treating both the mother and preventing transmission to the infant and was conducted in a mixed-feeding population.

The addition of these seven trials to previous evidence, raised a number of questions including the most effective combination of TRIPLE antiretrovirals and the optimal time to initiate TRIPLE antiretrovirals during pregnancy for both the mother and her baby. Future trials may provide clearer guidance but much of this information is likely to be derived from cohort studies, particularly in the light of the World Health Organization guidelines to commence prevention antiretrovirals at 14 weeks gestation (WHO 2009).

As almost all trials were conducted in African countries in populations of women representative of the general population, the level of applicability of the data from these trials can be viewed as high. However, the decision regarding which combination of antiretrovirals to use will likely be determined by resource availability, setting and costs and it may not always be possible to implement optimal recommendations from guidelines. In such situations results from our previous versions of this review remain pertinent.

Quality of the evidence

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; Bartlett 2009). As a result of these differences, any indirect comparisons between regimens across trials must 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 of the trials using meta-analytic techniques. Given that many 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. However, the increasing consistency in reduction of transmission rates using combined antiretrovirals over time provides good evidence in our opinion, to provide triple combination antiretrovirals to all HIV-infected pregnant mothers.

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 of 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. Although we made this observation in our previous update, none of the included trials used the recommended standardised testing schedules which would allow for better comparisons to 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.

Potential biases in the review process

As recommended for all Cochrane reviews we conducted an extensive and comprehensive search of multiple electronic bibliographic databases and searched conference abstracts and conducted handsearching of relevant medical journals to identify eligible trials for inclusion. Where possible, we also engaged directly with trialists to obtain missing data or for clarification where this was required. Completed but as yet unpublished trial data, such as that of the trial reported in Characteristics of ongoing studies will be included in the following update of this review. Our ongoing interaction with investigators of trials and our regular communication with global policymakers at WHO, ensured we were aware of all trial activity in this field. Furthermore, given the high profile nature of the intervention, it is unlikely that our search strategy failed to detect existing current trial evidence.

Potential bias in the conduct of our review was also minimised by having two independent researchers extracting data and assessing the methodological quality of each study. This detailed process allows for a thorough assessment of trial conduct and an exploration of the possible biases that may be present in each trial. In this update we re-evaluated the possible risk of bias in four domains for not only the new trials, but also for all of the previously included 18 trials, ensuring that newer methods were incorporated into the overall assessment. For many of the trials reported in earlier years, quality of reporting of these domains is poor and, as such, we were compelled to judge many of the risks as unclear. Empirical evidence has found that poor quality of reporting is not always associated with actual poor conduct and our judgments must be viewed in this light.

The review is of aggregate trial data. Published aggregate data from trials can be variable in the completeness of outcome reporting and in definitions of both the intervention and outcomes used between trials. This is particularly relevant where survival analysis has been used for outcome reporting and individuals have been censored at different endpoints during a trial, as occurred in many of the included trials. Ideally we would have obtained the individual patient data (IPD) from each trial allowing us to calculate efficacy measures using identical methods across each trial. Differences in analytical methodology does and can make a difference. For instance our results for transmission rates from those trials included in both this review and the Sturt 2010 Cochrane review

differ slightly. This is because the Sturt 2010 review calculated relative risks from the presented data rather than incorporating the reported survival curves into the analysis as was done in our review. While the latter is arguably desirable given that the time-to-event data is accounted for, the differences in methods to calculate the curves across trials means that greater variation may have been introduced into the final calculations. Obtaining IPD would eliminate this potential source of bias.

The relative effect and harms of perinatal antiretroviral regimens in babies who are breast fed versus those who are formula fed will continue to require further study. This research should focus on all the outcomes of breastfeeding versus formula feeding in women taking antiretrovirals and include the impact of bottle feeding on mortality and morbidity from other infectious diseases in less-resourced settings.

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.

AUTHORS' CONCLUSIONS

Implications for practice

Ideally, HIV-infected pregnant women should be provided with a combination of antiretroviral drugs to prevent PMTCT. A regimen combining TRIPLE antiretrovirals is most effective in the long term.

In countries where TRIPLE antiretroviral drug regimens are 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 yet clear which regimen is best but a combination of antepartum ZDV, and intrapartum and postpartum ZDV and 3TC given to mothers and to babies for one 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 after birth is beneficial.

Implications for research

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.

Follow-up of cohorts of infants into adulthood is required to establish the long term safety of provision of antiretrovirals during pregnancy and lactation.

ACKNOWLEDGEMENTS

This update of the review was done to inform the World Health Organization guidelines on Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants, first published as Rapid Advice (WHO 2009), with the full guidelines published in July 2010 (WHO 2010b). We are very grateful to Joy Oliver who provided invaluable administrative assistance during completion of the update. The assistance of Tara Horvath in conducting searches of conference abstracts databases is gratefully acknowledged. Liesl Grobler conducted a duplicate eligibility process and we thank her for her willingness to do this. Alfred Musekiwa kindly assisted with checking the accuracy of extracted numerical data.

The 2005 update of this review was made possible by a grant received from the Cochrane Child Health Field, which contributed towards travel costs for Lize van der Merwe and to the MRC Biostatistics Unit for supporting the review analysis. The United Kingdom Cochrane Centre kindly provided office space for Lize van der Merwe. Jayne Tierney and Lesley Stewart kindly provided their time and expertise regarding survival analysis for the 2005 update.

Mapping in previous versions of the review was done as part of the Cochrane HIV/AIDS Trial Mapping Project based at the South African Cochrane Centre.

With many thanks to the trial authors who provided additional information: Dr L Mofenson from the Pediatric AIDS Clinical Trials Group Protocol 185 Trial; Dr F Dabis from the DITRAME Study Group and Dr G Jourdain from the Perinatal HIV Prevention Trial (Thailand) Investigators.

REFERENCES

References to studies included in this review

Bhoopat 2005 *{published data only}*

* Bhoopat L, Khunamornpong S, Lerdsrimongkol P, Sirivatanapa P, Sethavanich S, Limtrakul A, et al.Effectiveness of short-term and long-term zidovudine prophylaxis on detection of HIV-1 subtype E in human placenta and vertical transmission. *Journal of Acquired Immune Deficiency Syndromes* 2005;**40**:545–50.

Chi 2007 *{published data only}*

* Chi BH, Chintu N, Cantrell RA, Kankasa C, Kruse G, Mbewe F, et al.Addition of single-dose tenofovir and emtricitabine to intrapartum nevirapine to reduce perinatal HIV transmission. *Journal of acquired immune deficiency syndromes (1999)* 2008;**48**(2):220–3. [PUBMED: 18520682]

Chung 2005 *{published data only}*

* Chung MH, Kiarie JN, Richardson BA, Lehman DA, Overbaugh J, John-Stewart GC. Breast milk HIV-1 suppression and decreased transmission: a randomized trial comparing HIVNET 012 nevirapine versus short-course zidovudine. *AIDS (London, England)* 2005;**19**(13): 1415–22. [PUBMED: 16103773]

Chung MH, Kiarie JN, Richardson BA, Lehman DA, Overbaugh J, Njiri F, et al.Independent effects of nevirapine prophylaxis and HIV-1 RNA suppression in breast milk on early perinatal HIV-1 transmission. *Journal of acquired immune deficiency syndromes (1999)* 2007;**46**(4):472–8. [PUBMED: 18077838]

Lehman DA, Chung MH, John-Stewart GC, Richardson BA, Kiarie J, Kinuthia J, et al.HIV-1 persists in breast milk cells despite antiretroviral treatment to prevent mother-to-child transmission. *AIDS (London, England)* 2008;**22**(12): 1475–85. [PUBMED: 18614871]

Chung 2008 *{published data only}*

* Chung MH, Kiarie JN, Richardson BA, Lehman DA, Overbaugh J, Kinuthia J, et al.Highly active antiretroviral therapy versus zidovudine/nevirapine effects on early breast milk HIV type-1 Rna: a phase II randomized clinical trial. *Antiviral therapy* 2008;**13**(6):799–807. [PUBMED: 18839781]

DITRAME *{published data only}*

Dabis F, Elenga N, Meda N, Leroy V, Viho I, Manigart O, Dequae-Merchadou L, et al.18-Month mortality and perinatal exposure to zidovudine in West Africa. *AIDS* 2001;**15**:2204–5.

Dabis F, Msellati P, Meda N, Leroy V, Van De Perre P, Merchadou L, et al.Infant mortality and perinatal exposure to zidovudine in Africa. *XIII International AIDS Conference, Durban* 2000;**Abstract MoPpB1024**.

* Dabis F, Msellati P, Meda N, Welffens-Ekra C, You B, Manigart O, et al.6-month efficacy, tolerance and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. *Lancet* 1999;**353**:786–92.

Dabis F, Msellati P, Newell ML, Halsey N, Van de Perre P, Peckham C, et al.Methodology of intervention trials to reduce mother to child transmission of HIV with special reference to developing countries. International Working Group on Mother to Child Transmission of HIV. *AIDS* 1995;**9**:Suppl A:S67-74.

DITRAME ANRS 049 Study Group. 15-month efficacy of maternal oral zidovudine to decrease vertical transmission of HIV-1 in breastfed African children. *Lancet* 1999;**354**: 2050–1.

Msellati P, Ramon R, Viho I, et al.Prevention of mother-to-child transmission of HIV in Africa: uptake of pregnant women in a clinical trial in Abidjan, Cote d'Ivoire. *AIDS* 1998;**12**:1257–8.

Gray 2005 *{published data only}*

Gray GE, Urban M, Chersich MF, Bolton C, van Niekerk R, Violari A, et al.A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. *AIDS* 2005; **19**:1289–97.

Gray 2006 *{published data only}*

* Gray G, Violari A, McIntyre J, Jivkov B, Schnittman S, Reynolds L, et al.Antiviral activity of nucleoside analogues during short-course monotherapy or dual therapy: Its role in preventing HIV infection in infants. *Journal of Acquired Immune Deficiency Syndromes* 2006;**42**.

Gray 2006 a *{published data only}*

* See Gray 2006.

Gray 2006 b *{published data only}*

See Gray 2006.

Gray 2006 c *{published data only}*

See Gray 2006.

HIVNET 012 *{published data only}*

Eshleman SH, Guay LA, Mwatha A, Brown E, Musoke P, Mmiro F, et al.Comparison of mother-to-child transmission rates in Ugandan women with subtype A versus D HIV-1 who received single-dose nevirapine prophylaxis: HIV Network For Prevention Trials 012. *Journal of Acquired Immune Deficiency Syndromes* 2005;**39**:593–7.

Eshleman SH, Guay LA, Wang J, Mwatha A, Brown ER, Musoke P, et al.Distinct patterns of emergence and fading of K103N and Y181C in women with subtype A vs. D after single-dose nevirapine: HIVNET 012. *Journal of Acquired Immune Deficiency Syndromes* 2005;**40**:24–9.

Eshleman SH, Hoover DR, Chen S, Hudelson SE, Guay LA, Mwatha A, et al.Nevirapine (NVP) resistance in women with HIV-1 subtype C, compared with subtypes A and D, after the administration of single-dose NVP. *The Journal of Infectious Diseases* 2005;**192**:30–6.

Flys T, Nissley DV, Claasen CW, Jones D, Shi C, Guay LA, et al.Sensitive drug-resistance assays reveal long-term persistence of HIV-1 variants with the K103N nevirapine

(NVP) resistance mutation in some women and infants after the administration of single-dose NVP: HIVNET 012. *The Journal of Infectious Diseases* 2005;**192**:1–3.
* Guay L, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, et al.Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 1999;**354**: 795–802.
Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, et al.Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 2003;**362**:859–68.
James JS. IOM: nevirapine study is reliable. AIDS Treatment News 2005 March 25:411.
Owor M, Desyve M, Duefield C, et al.The one year safety and efficacy data of HIVNET 012 trial. XIII International AIDS Conference, Durban. 2000; Vol. LbOr1.

Kesho Bora ***{published and unpublished data}***
Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *The Lancet infectious diseases* 2011;**11**(3): 171–80. [PUBMED: 21237718]

Kiarie 2003 ***{published data only}***
* Kiarie JN, Kreiss JK, Richardson BA, John-Stewart GC. Compliance with antiretroviral regimens to prevent perinatal HIV-1 transmission in Kenya. *AIDS* 2003;**17**: 65–71.

Limpongsanurak 2001 ***{published data only}***
Limpongsanurak S, Thaithumyanon P, Chaithongwongwatthana S, Thisyakorn U, Ruxrungtham K, Kongsin P, et al.Short course zidovudine maternal treatment in HIV-1 vertical transmission: randomized controlled multicenter trial. *Journal of the Medical Association of Thailand* 2001;**84**:Suppl 1:S338-45.

Mashi ***{published data only}***
Bae WH, Wester C, Smeaton LM, Shapiro RL, Lockman S, Onyait K, et al.Hematologic and hepatic toxicities associated with antenatal and postnatal exposure to maternal highly active antiretroviral therapy among infants. *AIDS (London, England)* 2008;**22**(13):1633–40. [PUBMED: 18670224]
Lockman S, Shapiro RL, Smeaton LM, Wester C, Thior I, Stevens L, et al.Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *The New England journal of medicine* 2007;**356**(2):135–47. [PUBMED: 17215531]
Shapiro RL, Smeaton L, Lockman S, Thior I, Rossenkhan R, Wester C, et al.Risk factors for early and late transmission of HIV via breast-feeding among infants born to HIV-infected women in a randomized clinical trial in Botswana. *The Journal of infectious diseases* 2009;**199**(3):414–8. [PUBMED: 19090775]
* Shapiro RL, Thior I, Gilbert PB, Lockman S, Wester C, Smeaton LM, et al.Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS (London, England)* 2006;**20**(9):1281–8. [PUBMED: 16816557]
Thior I, Lockman S, Smeaton LM, Shapiro RL, Wester C, Heymann SJ, et al.Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. *JAMA : the journal of the American Medical Association* 2006;**296**(7):794–805. [PUBMED: 16905785]

Mma Bana ***{published and unpublished data}***
Shapiro RL, Hughes MD, Ogwu A, Kitch D, Lockman S, Moffat C, et al.Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *The New England journal of medicine* 2010;**362**(24):2282–94. [PUBMED: 20554983]

PACTG 076 ***{published data only}***
Connor E, Mofenson L. Zidovudine for the reduction of perinatal human immunodeficiency virus transmission: Pediatric AIDS Clinical Trials Group Protocol 076 - results and treatment recommendations. *The Pediatric Infectious Disease Journal* 1995;**14**:536–41.
* Connor E, Sperling R, Gelber R, Kiselev P, Scott G, O'Sullivan M, et al.Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *The New England Journal of Medicine* 1994;**331**:1173–80.
Sperling R, Shapiro D, Coombs R, Todd J, Herman S, McSherry G, et al.Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. *The New England Journal of Medicine* 1996;**335**:1621–9.
Sperling R, Shapiro D, McSherry G, Britto P, Cunningham B, Culnane M, et al.Safety of the maternal-infant zidovudine regimen utilized in the Pediatric AIDS Clinical Trial Group 076 study. *AIDS* 1998;**12**:1805–1813.

PACTG 316 ***{published data only}***
* Dorenbaum A. Report of results of PACTG 316: An international phase III trial of standard antiretroviral (ARV) prophylaxis plus nevirapine (NVP) for prevention of perinatal HIV transmission. 8th Conference on Retroviruses and Opportunistic Infections, Chicago, Illinois, February 2001. 2001.
Dorenbaum A, Cunningham CK, Gelber RD, Culnane M, Mofenson L, Britto P, et al.Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *The Journal of the American Medical Association* 2002;**288**:189–98.

PETRA ***{published data only}***
* PETRA study team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a

randomised, double-blind, placebo-controlled trial. *Lancet* 2002;**359**:1178–86.

PETRA a *{published data only}*
See PETRA.

PETRA b *{published data only}*
See PETRA.

PETRA c *{published data only}*
See PETRA.

PHPT-1 *{published data only}*
* Lallemant M, Jourdain G, Le Couer S, Kim S, Koetsawang S, Comeau A, et al.A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. *NEJM* 2000;**343**:982–991.

PHPT-1 a *{published data only}*
* See PHPT-1.

PHPT-1 b *{published data only}*
See PHPT-1.

PHPT-2 *{published data only}*
Cressey TR, Jourdain G, Lallemant MJ, Kunkeaw S, Jackson JB, Musoke P, et al.Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *Journal of Acquired Immune Deficiency Syndromes* 2005;**38**: 283–8.
* Lallemant M, Jourdain G, Le Coeur S, Mary JY, Ngo-Giang-Huong N, Koetsawang S, Kanshana S, et al.Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *The New England Journal of Medicine* 2004;**351**:217–28.

RETRO-CI *{published data only}*
Sibailly T, Ekpini E, Boni-Ouattara E, Nkengasong J, Maurice C, Kouassi M, et al.Clinical course of HIV infection and surveillance for zidovudine resistance among HIV-infected women receiving short-course zidovudine therapy in Abidjan, Cote d'Ivoire. XIII International AIDS Conference, Durban. 2000; Vol. Abstract TuPeC3354.
* Wiktor S, Ekpini E, Karon J, Nkengasong J, Maurice C, Severin S, et al.Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial. *Lancet* 1999;**353**:781–5.

SAINT *{published data only}*
Moodley D, Moodley J, Coovadia H, Gray G, McIntyre J, Hofmyer J, et al.A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *The Journal of Infectious Diseases* 2003;**187**: 725–35.

Taha 2003 *{published data only}*
Eshleman SH, Hoover DR, Hudelson SE, Chen S, Fiscus SA, Piwowar-Manning E, et al.Development of nevirapine resistance in infants is reduced by use of infant-only single-dose nevirapine plus zidovudine postexposure prophylaxis for the prevention of mother-to-child transmission of HIV-1. *The Journal of Infectious Diseases* 2006;**193**:479–81.
Taha TE, Kumwenda N, Kafulafula G, Kumwenda J, Chitale R, Nkhoma C, et al.Haematological changes in African children who received short-term prophylaxis with nevirapine and zidovudine at birth. *Annals of Tropical Paediatrics* 2004;**24**:301–9.
Taha TE, Kumwenda NI, Gibbons A, Broadhead RL. Fiscus S, Lema V, et al.Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet* 2003;**362**: 1171–77.

Taha 2004 *{published data only}*
Eshleman SH, Hoover DR, Hudelson SE, Chen S, Fiscus SA, Piwowar-Manning, et al.Development of nevirapine resistance in infants is reduced by use of infant-only single-dose nevirapine plus zidovudine postexposure prophylaxis for the prevention of mother-to-child transmission of HIV-1. *The Journal of Infectious Diseases* 2006;**193**:479–81.
Taha TE, Kumwenda N, Kafulafula G, Kumwenda J, Chitale R, Nkhoma C, et al.Haematological changes in African children who received short-term prophylaxis with nevirapine and zidovudine at birth. *Annals of Tropical Paediatrics* 2004;**24**:301–9.
Taha TE, Kumwenda NI, Hoover DR, Fiscus SA, Kafulafula G, Nkhoma C, et al.Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. *The Journal of the American Medical Association* 2004;**292**:202–9.

Thai-CDC *{published data only}*
Bhadrakom C, Simonds R, Mei J, Asavapiriyanont S, Sangtaweesin V, Vanprapar N, et al.Oral zidovudine during labour to prevent perinatal HIV transmission, Bangkok: tolerance and zidovudine concentration in cord blood. *AIDS* 2000;**14**:509–516.
Chotpitaysaunondh T, Vanprapar N, Simonds R, Chokephaibulkit K, Waranawat N, Mock P, et al.Safety of late in utero exposure to zidovudine in infants born to human immunodeficiency virus-infected mothers: Bangkok. *Pediatrics* 2001;**107**:E5.
Roongpisuthipong A, Siriwasin W, Asavapiriyanont S, Chaisilwattana P, Schaffer N, Mock P, et al.Predictors of mortality in 18-month postpartum period among HIV-infected women enrolled in a trial of short-course antenatal zidovudine, Bangkok, Thailand. XIII International AIDS Conferecce, Durban. 2000; Vol. Abstract TuPeB3253.
* Shaffer N, Chuachoowong R, Mock P, Bhadrakom C, Siriwasin W, Young NL, et al.Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. *Lancet* 1999;**353**:773–80.
Vuthipongse P, Bhadrakom C, Chasisiiwattana P, Roongpisuthipong A, Chalermchokcharoenkit A, Chearskul S, et al.Administration of zidovudine during late pregnancy and delivery to prevent perinatal HIV transmission - Thailand 1996-1998. *MMWR* 1998;**47**(8):151–4.

Thistle 2004 *{published data only}*
Thistle P, Gottesman M, Pilon R, Glazier RH, Arbess G,

Phillips E, et al.A randomized control trial of an Ultra-Short zidovudine regimen in the prevention of perinatal HIV transmission in rural Zimbabwe. *The Central African Journal of Medicine* 2004;**50**:79–84.

Thistle 2007 ***{published data only}***

* Thistle P, Spitzer RF, Glazier RH, Pilon R, Arbess G, Simor A, et al.A randomized, double-blind, placebo-controlled trial of combined nevirapine and zidovudine compared with nevirapine alone in the prevention of perinatal transmission of HIV in Zimbabwe. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2007; **44**(1):111–9. [PUBMED: 17143826]

References to studies excluded from this review

El Beitune 2005 ***{published data only}***

El Beitune P, Duarte G, Machado AA, Quintana SM, Figueiro-Filho EA, Abduch R. Effect of antiretroviral drugs on maternal CD4 lymphocyte counts, HIV-1 RNA levels, and anthropometric parameters of their neonates. *Clinics* 2005;**60**:207–12.

Leroy 2002 ***{published data only}***

Leroy V, Karon JM, Alioum A, Ekpini ER, Meda N, Greenberg AE, et al.Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. *AIDS* 2002;**16**:631–41.

Leroy 2005 ***{published data only}***

* Leroy V, Sakarovitch C, Cortina-Borja M, McIntyre J, Coovadia H, Dabis F, et al.Is there a difference in the efficacy of peripartum antiretroviral regimens in reducing mother-to-child transmission of HIV in Africa?. *AIDS* 2005;**19**:1865–75.

Shetty 2003 ***{published data only}***

* Shetty AK, Coovadia HM, Mirochnick MM, Maldonado Y, Mofenson LM, Eshleman SH, Fleming T, Emel L, George K, Katzenstein DA, Wells J, Maponga CC, Mwatha A, Jones SA, Abdool Karim SS, Bassett MT, HIVNET 023 Study Team. Safety and trough concentrations of nevirapine prophylaxis given daily, twice weekly, or weekly in breast-feeding infants from birth to 6 months. *J Acquir Immune Defic Syndr.* 2003;**34**:482–90.

SIMBA ***{published data only (unpublished sought but not used)}***

Vyankandondera J, Luchters S, Hassink E, et al.Reducing risk of HIV-1 transmission from mother to infant through breastfeeding using antiretroviral prophylaxis in infants (SIMBA study) [abstract # LB7]. *Paper presented at: the 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment, 2003* Available from: http://www.iasociety.org/Default.aspx?pageId=11&abstractId=11061.

Yoshimoto 2005 ***{published data only}***

Yoshimoto CE, Diniz EM, Vaz FA. Clinical and laboratory evolution of children born to HIV positive mothers [Evolução clínica e laboratorial de recém–nascidos de mães HIV positivas]. *Revista da Associação Médica Brasileira* 2005;**51**:100–5.

References to ongoing studies

BAN 2005 ***{published data only}***

Bentley ME, Corneli AL, Piwoz E, Moses A, Nkhoma J, Tohill BC, et al.Perceptions of the role of maternal nutrition in HIV-positive breast-feeding women in Malawi. *The Journal of Nutrition* 2005;**135**:945–9.

Additional references

Alioum 2003

Alioum A, Cortina-Borja M, Dabis F, Dequa-Merchadou L, Haverkamp G, Highes J, et al.Estimating the efficacy of interventions to prevent mother-to-child transmission of human immunodeficiency virus in breast-feeding populations: comparing statistical methods. *American Journal of Epidemiology* 2003;**158**:596–605.

Altman 2005

RG Newcombe, DG Altman. Proportions and their differences. In: DG Altman, D Machin, TN Bryant, MJ Gardner editor(s). *Statistics with confidence*. 2nd Edition. Bristol: MBJ Books, 2005.

Bartlett 2009

Bartlett JA, Shao JF. Successes, challenges, and limitations of current antiretroviral therapy in low-income and middle-income countries.. *The Lancet infectious diseases* 2009;**9**(10): 637–49.

Birkhead 2000

Birkhead G, Wade N, Storfer-Isser A, Gallagher B, Singh T, Bornschlegel K. Review of deaths among a cohort of New York State (NYS) infants exposed in the perinatal period to HIV and antiretroviral drugs [Abstract 692]. 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA. 2000.

Blanche 1999a

Blanche S, Rouzioux C, Mandelbrot L, Delfraissy J, Mayaux M. Zidovudine-lamivudine for prevention of mother to child HIV-1 transmission. Sixth Conference on Retroviruses and Opportunistic Infections [Abstract 267]. Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, USA. 1999.

Blanche 1999b

Blanche S, Tardieu M, Rustin P, Slama A, Barret B, Firtion G, Ciraru-Vigneron N, Lacroix C, Rouzioux C, Mandelbrot L, Desguerre I, Rotig A, Mayaux M-J, Delfraissy. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* 1999;**354**: 1084–89.

Bulterys 2000

Bulterys M, Nesheim S, Abrams EJ, Palumbo P, Farley J, Lampe M, et al.Lack of evidence of mitochondrial dysfunction in the offspring of HIV-infected women. Retrospective review of perinatal exposure to antiretroviral drugs in the Perinatal AIDS Collaborative Transmission Study. *Annals of the New York Academy of Sciences* 2000; **918**:212–21.

Chaix 2005
Chaix M, Dabis F, Ekouevi D, Rouet F, Tonwe-Gold B, Viho I, et al.Addition of 3 days of ZDV+3TC postpartum to a short course of ZDV+3TC and single-dose NVP provides low rate of NVP resistance mutations and high efficacy in preventing peri-partum HIV-1 transmission: ANRS DITRAME Plus, Abidijan, Cote d'Ivoire [oral LB72]. The 12th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA. 2005.

Chinnock 2005
Chinnock P, Siegfried N, Clarke M. Is evidence-based medicine relevant to the developing world. *PLoS Med* 2005; **Aug 2**(8):e277.

Connor 1994
Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al.Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New England Journal of Medicine* 1994;**331**:1173–80.

Culnane 1999
Culnane M, Fowler M, Lee SS, McSherry G, Brady M, O'Donnell K, et al.Lack of long-term effects of in utero exposure to zidovudine among uninfected childen born to HIV-infected women. *JAMA* 1991;**281**:151–7.

Dabis 1995
Dabis F, Msellati P, Newell ML, Halsey N, Van de Perre P, Peckham C, et al.Methodology of intervention trials to reduce mother-to-child transmission of HIV with special reference to developing countries. *AIDS* 1995;**9 Suppl A**: S67–S74.

Division of AIDS, NIAID 1992
Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Table for Grading Severity of Adult Adverse Experiences. Bethesda, Maryland: National Institutes of Health, August 1992.

Division of AIDS, NIAID 1994a
Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Table for Grading Severity of Pediatric (≤3 Months of Age) Adverse Experiences. Bethesda, Maryland: National Institutes of Health, April 1994.

Division of AIDS, NIAID 1994b
Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Table for Grading Severity of Pediatric (>3 Months of Age) Adverse Experiences. *Bethesda, Maryland: National Institutes of Health, April 1994*.

Dunn 1992
Dunn D, Newell M-L, Ades A, Peckham C. Risk of human immunodeficiency virus type 1 transmission through breast-feeding. *Lancet* 1992;**240**:585–8.

Dunn 1994
Dunn DT, Newell ML, Mayaux MJ, Kind C, Hutto C, Goedert JJ, et al.Mode of delivery and vertical transmission of HIV-1: a review of prospective studies. *Journal of Acquired Immune Deficiency Syndromes* 1994;**7**:1064–6.

Eshleman 2001
Eshleman SH, Mracna M, Guay LA, Deseyve M, Cunningham S, Mirochnick M, Musoke P, Fleming T, Glenn Fowler M, Mofenson LM, Mmiro F, Jackson JB. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET012). *AIDS* 2001;**15**(15):1951–7.

Eshleman 2005a
Eshleman S, Nissley D, Claasen C, Jones D, Shi C, Guay L, et al.Sensitive drug resistance assays reveal long-term persistence of HIV-1 variants with the K103N nNevirapine-resistance mutation in some women and infants after single-dose NVP: HIV-NET 012 [poster 800]. The 12th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA. 2005.

Eshleman 2005b
Eshleman SH, Hoover DR, Chen S, Hudelson SE, Guay LA, Mwatha A, et al.Nevirapine (NVP) resistance in women with HIV-1 subtype C, compared with subtypes A and D, after the administration of single-dose NVP. *Journal of Infectious Diseases* 2005;**192**:30–6.

Eshleman 2005c
Eshleman SH, Guay LA, Mwatha A, Brown E, Musoke P, Mmiro F, et al.Comparison of mother-to-child transmission rates in Ugandan women with subtype A versus D HIV-1 who received single-dose nevirapine prophylaxis: HIV Network For Prevention Trials 012. *Journal of Acquired Immune Deficiency Syndromes* 2005;**39**:593–7.

European Collab 1992
European Collaborative Study. Risk factors for mother-to-child transmission of HIV-1. European Collaborative Study. *Lancet* 1992;**339**:1007–12.

Ghent 2001
The Ghent Group: Alioum A, Dabis F, Dequae-Merchadou L, Haverkamp G, Hudgens M, Hughes J, Karon J, Leroy V, Newell ML, Richardson B, Weverling GJ. Estimating the efficacy of interventions to prevent mother-to-child transmission of HIV in breast-feeding populations: development of consensus methodology. *Statistics in Medicine* 2001;**20**:3539–56.

Giuliano 2005
Giuliano M, Galluzzo C, Germinario E, Amici R, Pirillo M, Bassani L, et al.Selection of resistance mutations in children receiving prophylaxis with lamivudine or nevirapine for the prevention of postnatal transmission of HIV [oral 99]. The 12th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA. 2005.

Giusti 1995
Giusti RM, Iwamoto K, Hatch EE. Diethylstilbestrol revisited: a review of the long-term health effects. *Ann Intern Med* 1995;**15**(122):778–88.

Halliday 2010
Halliday HL, Ehrenkranz RA, Doyle LW. Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [<html><body id=

"body">Issue 1. Art. No.: CD001146. DOI: 10.1002/14651858.CD001146.pub3.%3C/body%3E%3C/html%3E]

Hammer 1997

Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, et al.A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *New England Journal of Medicine* 1997;**337**:725–33.

Hammer 2005

Hammer SM. Single-dose nevirapine and drug resistance: the more you look, the more you find. *Journal of Infectious Diseases* 2005;**192**:1–3.

Hanson 2000

Hanson C, Frederick M, McIntosh K. Evaluation of living uninfected children for mitochondrial defects: Women and Infants Transmission Study. 7th Conference on Retroviruses and Opportunistic Infections, San Francisco. 2000; Vol. Abstract 665.

Hill 1999

AM Hill. A meta-analysis of the effects of HIV-1 RNA methodology on estimates of HIV-1 RNA undetectability in trials of HAART. Conf Retrovirus Opportunistic Infect. 1999; Vol. 6.

HIV Group 1999

The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1. *New England Journal of Medicine* 1999;**340**:977–87.

Horvath 2009

Horvath T, Madi B, Iuppa IM, Kennedy GE, Rutherford GW, Read JS. Interventions for preventing late postnatal mother-to-child transmission of HIV. *Cochrane Database of Systematic Reviews* 2009;**Issue 1**:Art No.: CD006734. DOI: 10.1002/14651858.CD006734.pub2.

Jamieson 2003

Jamieson DJ, Sibailly TS, Sadek R, Roels TH, Ekpini ER, Boni-Ouattara E, et al.HIV-1 viral load and other risk factors for mother-to-child transmission of HIV-1 in a breast-feeding population in Cote d'Ivoire. *Journal of Acquired Immune Deficiency Syndromes* 2003;**34**:430–6.

John 1996

John GC, Kreiss J. Mother-to-child transmission of human immunodeficiency virus type 1. *Epidemiologic Reviews* 1996;**18**:149–57.

Johnson 2005

Johnson JA, Li JF, Morris L, Martinson N, Gray G, McIntyre J, et al.Emergence of drug-resistant HIV-1 after intrapartum administration of single-dose nevirapine is substantially underestimated. *Journal of Infectious Diseases* 2005;**192**:16–23.

Jourdain 2004

Jourdain G, Ngo-Giang-Huong N, Le Coeur S, Bowonwatanuwong C, Kantipong P, Leechanachai P. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *New England Journal of Medicine* 2004;**351**:229–40.

Kenyon 2008

Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A, Taylor DJ. Childhood outcomes following the prescription of antibiotics to pregnant women with spontaneous preterm labour: 7 years follow-up of the ORACLE II trial. *Lancet* 2008;**372**:1319–27.

Khouri 1995

Khouri YF, McIntosh K, Cavacini L, Posner M, Pagano M, Tuomala R, et al.Vertical Transmission of HIV-1. Correlation with maternal viral load and plasma levels of CD4 binding site anti-gp120 antibodies. *Journal of Clinical Investigation* 1995;**95**:732–7.

Lallemant 2010

Lallemant M, Jourdain G. Preventing mother-to-child transmission of HIV-protecting this generation and the next. The New England journal of medicine 2010; Vol. 363, issue 16:1570–2. [PUBMED: 20942674]

Landesman 1996

Landesman SH, Kalish LA, Burns DN, Minkoff H, Fox HE, Zorilla C, et al.Obstetrical factors and the transmission of human immunodeficiency virus type 1 from mother to child. *New England Journal of Medicine* 1996;**334**:1617–23.

Lockman 2010

Lockman S, Hughes MD, McIntyre J, Zheng Y, Chipato T, Conradie F, et al.Antiretroviral therapies in women after single-dose nevirapine exposure. *The New England journal of medicine* 2010;**363**(16):1499–509. [PUBMED: 20942666]

Mandelbrot, 2001

Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, Berrebi A, Benifla JL, Burgard M, Lachassine E, Barret B, Chaix ML, Bongain A, Ciraru-Vigneron N, Crenn-Hebert C, Delfraissy JF, Rouzioux C, Mayaux MJ, Blanche S, Agence Nationale de Recherches sur le SIDA (ANRS) 075 Study Group. Lamivudine-zidovudine combination for prevention of maternal infant transmission of HIV-1. *JAMA* 2001;**285**(16):2083–93.

Marseille 1999

Marseille E, Kahn J, Mmiro F, Guay L, Musoke P, Fowler M-G, et al.Cost effectiveness of single-dose nevirapine regimen for mothers and babies to decrease vertical HIV-1 transmission in sub-Saharan Africa. *Lancet* 1999;**354**:803–809.

McIntyre 2005

McIntyre J. Controversies in the use of nevirapine for the prevention of mother-to-child transmission [Plenary 7]. The 12th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA. 2005.

Minkoff 1995

Minkoff H, Burns DN, Landesman S, Youchah J, Goedert JJ, Nugent RP, et al.The relationship of the duration of ruptured membranes to vertical transmission of human

immunodeficiency virus. *American Journal of Obstetrics and Gynecology* 1995;**173**:585–9.

Miotti 1999
Miotti PG, Taha TE, Kumwenda NI, Broadhead R, Mtimavalye LA, Van der Hoeven L, et al.HIV transmission through breastfeeding: a study in Malawi. *JAMA* 1999; **282**:744–9.

Mirochnick 1998
Mirochnick M, Fenton T, Gagnier P, Pav J, Gwynne M, Siminski S, et al.Pharmacokinetics of nevirapine in human immunodeficiency virus type-1 infected pregnant women and their neonates. *Journal of Infectious Diseases* 1998;**178**: 368–74.

Mofenson 1994
Mofenson LM. Epidemiology and determinants of vertical HIV transmission. *Seminars in Pediatric Infectious Diseases* 1994;**5**:252–6.

Mofenson 1995
Mofenson LM. A critical review of studies evaluating the relationship of mode of delivery to perinatal transmission of human immunodeficiency virus. *Pediatric Infectious Disease Journal* 1995;**14**:169–76.

Mofenson 2010
Mofenson LM. Protecting the next generation--eliminating perinatal HIV-1 infection. The New England journal of medicine 2010; Vol. 362, issue 24:2316–8. [PUBMED: 20554987]

Morcroft 2000
Morcroft A, Katlama C, Johnson A, Pradier C, Antunes F, Mulcahy F, et al.AIDS across Europe, 1994-98: the EUROSIDA study. *Lancet* 2000;**356**:291–96.

Morris 2000
Morris A, Cu-Uvin S, Harwell J, Garb J, Zorrilla C, Vajaranant M, et al.Multicentre review of protease inhibitors in 89 pregnancies. *Journal of Acquired Immune Deficiency Syndromes* 2000;**25**:306–11.

Musoke 1999
Musoke P, Guay L, Bagenda D, Mirochnick M, Nakabiito C, Fleming T, et al.A phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1 infected pregnant Ugandan woman and their neonates (HIVNET 006). *AIDS* 1999;**13**:479–86.

Nair 1993
Nair P, Alger L, Hines S, Seiden S, Hebel R, Johnson JP. Maternal and neonatal characteristics associated with HIV infection in infants of seropositive women. *Journal of Acquired Immune Deficiency Syndromes* 1993;**6**:298–302.

Palmer 2005
Palmer S, Boltz V, Maldarelli F, Martinson N, Gray G, McIntyre J, et al.Persistence of NNRTI-r resistant variants after single-dose nevirapine in HIV-1 subtype-C-infected women [poster 101]. The 12th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA. 2005.

Palumbo 2010
Palumbo P, Lindsey JC, Hughes MD, Cotton MF, Bobat R, Meyers T, et al.Antiretroviral treatment for children with peripartum nevirapine exposure. *The New England journal of medicine* 2010;**363**(16):1510–20. [PUBMED: 20942667]

Semba 1994
Semba RD, Miotti PG, Chiphangwi JD, Saah AJ, Canner JK, Dallabetta GA, et al.Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. *Lancet* 1994;**343**: 1593–7.

Siegfried 2005
Siegfried N, Clarke M, Volmink J. Randomised controlled trials in Africa of HIV and AIDS: descriptive study and spatial distribution. *BMJ* 2005;**331**:742–7.

Sturt 2010
Sturt A, Dokubo EK, Sint TT. Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women. *Cochrane Database of Systematic Reviews* 2010;**Issue 3**:Art. No.: CD008440.

UNICEF 2010
UNICEF, WHO, World Bank, UN Population Division. Levels and trends in child mortality-report 2010. *http://www.childinfo.org/files/Child˙Mortality˙Report˙2010.pdf* (Accessed 11 November 2010).

Volberding 2010
Volberding PA, Deeks SG. Antiretroviral therapy and management of HIV infection. *Lancet* 2010;**376**(9734): 49–62. [PUBMED: 20609987]

Wade 1998
Wade N, Birkhead G, Warren B, Charbonneau T, French P, Wang L, et al.Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *New England Journal of Medicine* 1998;**339**:1409–14.

Walker 2002
Walker N, Schwartlander B, Bryce J. Meeting international goals in child survival and HIV/AIDS. *Lancet* 2002;**360**: 284–9.

WHO 2009
World Health Organization. Rapid Advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. November 2009. Available from: http://www.who.int/hiv/pub/mtct/advice/en.

WHO 2010a
World Health Organization. World Health Statistics 2010. Available from: http://www.who.int/whosis/whostat/2010/en/.

WHO 2010b
World Health Organization. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Recommendations for a public health approach. July 2010. Available from: http://www.who.int/hiv/pub/mtct/antiretroviral2010/en/.

WHO 2011

World Health Organization. Paediatric HIV and treatment of children living with HIV. Available from: http://www.who.int/hiv/topics/paediatric/en/index.html.

Working Group 1995

The Working Group on MTCT of HIV. Rates of mother-to-child transmission of HIV-1 in Africa, America and Europe: results of 13 perinatal studies. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 1995;**8**:506–10.

You 2010

You D, Jones G, Hill K, Wardlaw T, Chopra M. Levels and trends in child mortality, 1990-2009. *Lancet* 2010;**376** (9745):931–3. [PUBMED: 20851244]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bhoopat 2005

Methods	Generation of allocation sequence: Unclear - Participants 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 breast-feed, and had laboratory values within acceptable limits: Hb>8g/dL, absolute neutrophil count >750 cell/cubic mm, SGPT <5x ULN, creatinine <1.5mg/dL Exclusion criteria: Did not fulfil the above criteria, maternal or fetal condition or treatment contraindicating ZDV use, oligohydramnios, unexplained polyhydramnios or in utero anaemia or medical need for TRIPLE
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.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants are reported as 'randomised'
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported.

Bhoopat 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported as 0% as all 50 infants were available for bloods tests at 6 months

Chi 2007

Methods	This trial was conducted in two public sector primary healthcare facilities in an urban environment in Lusaka, Zambia. Enrollment commenced on 16 March 2005 and continued until 13 February 2007 Mothers and their babies were followed-up at 2 weeks and 8 weeks post-partum. Newborn and infant dried blood spots were collected at birth and at 6 weeks. These were tested with Amplicor HIV-1 DNA 1.5 Roche. HIV diagnosis made if two consecutive DNA PCR were positive. Intra-uterine transmission diagnosed if positive at birth and at 6 weeks; intrapartum and early post-partum if test negative at birth but positive at 6 weeks (with another confirmatory test 4 weeks later)
Participants	627 pregnant women were enrolled but only 400 were randomised when they presented in labour. Of these one was excluded because the allocation envelope was incorrectly opened and not replaced Inclusion criteria: 1. HIV-infected pregnant women (HIV determined by dual rapid-test algorithm using COBAS Ampliprep and COBAS Amlpicor HIV-1 monitor, Roche Molecular System) 2. 28 to 38 weeks gestation 3. Need to have self-administered NVP 200mg orally at onset of labour 4. Active labour Exclusion criteria: 1. Requiring antiretrovirals for their health 2. Previous antiretroviral use 3. Clinical indications for referral to tertiary hospital
Interventions	1. Tnf/EM: i) MOTHER: Standard of Care PLUS Tenofovir 300mg and Emtricitabine 200mg (co-formulated as Truvada) orally in labour ii) INFANT: Standard of Care: NVP 2mg/kg once within 72 hours of delivery; ZDV 4mg/kg orally twice daily for 7 days post delivery 2. Standard of Care: i) MOTHER: ZDV 300mg twice daily from 32 weeks until labour, sdNVP 200mg at onset of labour ii) INFANT: NVP 2mg/kg once within 72 hours of delivery; ZDV 4mg/kg orally twice daily for 7 days post delivery
Outcomes	PRIMARY OUTCOME: 1. Maternal resistance to non-nucleoside reverse transcriptase inhibitor drugs at 6 weeks post-partum SECONDARY OUTCOMES: 1. Maternal resistance to non-nucleoside reverse transcriptase inhibitor drugs at 2 weeks post-partum 2. Other maternal drug resistance at 2 and 6 weeks post-partum

Chi 2007 (*Continued*)

	3. Perinatal HIV transmission rates at 2 and 6 weeks post-partum ADVERSE EVENTS: An adverse event was regarded as serious if it was fatal, life-threatening, requires admission to hospital, or resulted in persistent or substantial disability. Events classified as Grade 3 or above according to the tables of the US National Institute of Health Division of AIDS (Division of AIDS, NIAID 1992; Division of AIDS, NIAID 1994a; Division of AIDS, NIAID 1994b) were regarded as serious.
Notes	92% of infants in both arms were breastfeeding at 6 weeks post-partum The study received ethics approval from the Research Ethics Committee at the University of Zambia and from the Instititional Review Board at the University of Alabama at Birmingham and at the Childrens Hospital Los Angeles. Signed informed consent was obtained from all participants prior to enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation with variable block sizes
Allocation concealment (selection bias)	Low risk	An independent research pharmacist prepared a set of sequentially numbered, opaque envelopes and a consecutive envelope was opened for each participant
Blinding (performance bias and detection bias) All outcomes	Low risk	The participants and providers were not blinded but the laboratory personnel were (information confirmed directly with author)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low overall at 10.1% with 8.5% in the Tf/Em arm and 13.1% in the standard of care arm

Chung 2005

Methods	This single-centre trial commenced enrolment on 5 March 2003 and enrolment ended on 31 October 2003. The trial had a 6 week follow-up so assume trial ended in mid November 2003. The trial took place at the Mathare North City Council Clinic in Nairobi in Kenya, an urban setting Post-partum follow-up was for 6 weeks and women were visited at home by peer counsellors at 14 time-points for breast milk collection. At 6 weeks post-partum participants returned to the clinic when maternal blood was drawn for CD4 and HIV-1 RNA virus and infant blood was drawn for HIV-1 DNA
Participants	2,732 pregnant women were offered counselling and testing of whom 1865 agreed to testing. Of these, 319 (17%) were HIV-positive and 76 pregnant women were enrolled.

	Of these, 10 were lost to follow-up before randomisation at 34 weeks gestation with 66 women being randomised Inclusion criteria: 1. At or below 32 weeks gestation 2. Opting to breastfeed 3. Older than 18 years 4. No previous antiretroviral therapy 5. Hb $\geq$ 8g/dL 6. Agreed to home visits 7. Resided in the clinic catchment area Exclusion criteria: Not given but women were reported as being excluded for illness, details of which are not provided
Interventions	1. Thai-CDC i) MOTHER: ZDV 300mg twice daily from 34 weeks until onset of labour; then ZDV 300mg every 3 hours until delivery ii) INFANT: Nil 2. HIVNET012 i) MOTHER: NVP 200mg at onset of labour ii) INFANT: NVP 2mg/kg orally (or 6mg if Birthweight > 2.5kg) within 72 hours of delivery
Outcomes	PRIMARY OUTCOME: 1. HIV-1 RNA viral load in breast milk at 6 weeks post-partum SECONDARY OUTCOMES: 1. HIV infection status at 6 weeks by PCR for HIV-1 DNA ADVERSE EVENTS: Not reported how these were collected or graded.
Notes	At 6 weeks all 56 infants available for follow-up were reported as having been exclusively breastfed Ethics approval received from the institutional review boards at the University of Washington, USA, and the Kenyatta National Hospital in Kenya Written informed consent was obtained from participants. No report of multiple births.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation
Allocation concealment (selection bias)	Unclear risk	Reported as 'randomisation was revealed through numbered envelopes by the study physician who assigned the treatment regimens'

Chung 2005 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and providers were not blinded and it is unclear whether laboratory personnel were
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 27% (56/76) at 6 weeks post-partum but Kaplan Meier estimation was used to calculate rates so censoring would reduce the impact of potential bias from high attrition

Chung 2008

Methods	This single centre trial at the Mathare North City Council Clinic in Nairobi, Kenya commenced enrolment on 3 November 2003 and continued to 11 March 2005. Final follow-up was on 20 April 2006 The trial had a primary aim of assessing the effect of TRIPLE on breastmilk HIV-1 RNA levels in the first month post-partum. In January 2005, the US Food and Drug Administration recommended against prolonged NVP use by women with CD4 cell counts > 250 because of evidence of increased hepatotoxicity. Enrollment of mother-infant pairs was stopped thereafter Mothers and infants were followed-up at the clinic every 2 weeks prior to delivery and at 1 month post-partum and there every three months until 12 months post-partum
Participants	4,429 pregnant women were offered HIV-1 testing and 3,643 (82%) accepted. Of these 533 (15%) were HIV-1 infected and 162 consented to participate. Of these, 58 were eligible to be randomised at 34 weeks gestation Inclusion criteria: 1. HIV-infected 2. Elected to breastfeed 3. Less or equal to 32 weeks gestation 4. Hb $\geqq$ 8g/dL 5. No previous antiretrovirals 6. Agreed to home visits 7. Older than or equal to 18 years 8. Resided in catchment area Exclusion criteria: 1. CD4 < 200 cells/μL 2. CD4 > 500 cells/μL
Interventions	1. TRIPLE i) MOTHER: ZDV 300mg twice daily, Lamivudine 150mg twice daily, NVP 200mg twice daily from 34 weeks until 6 months post delivery ii) INFANT: Nil 2. ZDV/sdNVP i) MOTHER: ZDV 300mg twice daily from 34 weeks until labour, sdNVP 200mg at onset of labour ii) INFANT: sdNVP 2mg/kg within 72 hours of delivery

Outcomes	PRIMARY OUTCOME: 1. Breast milk HIV-RNA levels 2. HIV-1 specific immune responses in breast milk and in infants SECONDARY OUTCOMES: 1. Infant HIV-1 determined by HIV-1 filter paper PCR for HIV-1 DNA at time-points: birth, one month post-partum and then 12 months 2. Infant death 3. Maternal death ADVERSE EVENTS: Adverse events reported and described but not classified according to Grade
Notes	Breastfeeding was an inclusion criteria and collected from mothers so assume over 90% breastfed Ethics approval received from the Instititional Review Board at the University of Washington, USA, and Kenyatta National Hospital in Nairobi, Kenya

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Investigators and participants not blinded. No description of blinding of laboratory personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition at birth was low at 6.8% (4/58) but no details given for at 1 month. At 12 months attrition remained low at 2/26 from the TRIPLE arm and 4/25 from the ZDV/sdNVP arm

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

DITRAME (*Continued*)

	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 of 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central, computerised randomisation in blocks of 10 and stratified by centre
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed packs prepared by an independent, central pharmacy
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and providers were blinded; unclear regarding assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition < 10% at 7.4% overall (32/431) ; 6.5% (14/214) in the ZDV group and 8. 3% (18/217) in the placebo group. Used survival analysis to reduce bias introduced by attrition

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised randomisation
Allocation concealment (selection bias)	Low risk	Allocation provided to study nurses in sequentially numbered, non-transparent envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and providers were not blinded and no details given about blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Large attrition at 31.7% overall (333/1051) with 31.1% (166/533) in the ZDV group and 32.2% (167/518) in the NVP group. Used survival analysis to reduce ef-

		fects of attrition

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 antiretroviral-naive 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 $\leq$1.5x ULN, total serum lipase $\leq$1.4x ULN, aspartate aminotransferase and alanine aminotransferase $\leq$5x ULN Exclusion criteria: severe fetal abnormality; $\geq$ 3 fetuses; newly diagnosed HIV opportunistic infections, malignancy, or other condition requiring acute therapy at time of enrolment; 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported as 'randomised' but no further details given

Gray 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and providers were not blinded and no details given about blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was < 10% at 2.9% (11/373) overall. In the d4T group attrition was 2.2% (2/93); in the ddI group attrition was 1.1% (2/95); in the d4T plus ddI group it was 5.4% (5/95) and in the ZDV group it was 3.4% (3/89)

Gray 2006 a

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Gray 2006 b

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Gray 2006 c

Methods	
Participants	
Interventions	
Outcomes	

Notes	

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 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised randomisation in permuted blocks of 12

HIVNET 012 (*Continued*)

Allocation concealment (selection bias)	Low risk	Sequentially numbered treatment packs prepared by a study pharmacist, according to allocation schedule
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and providers were not blinded but the assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was < 10% with overall attrition = 2.6% (17/645) and 3.5% (11/313) in the ZDV group and 1.6% (5/313) in the NVP group and 5.2% (1/19) in the placebo group

Kesho Bora

Methods	This trial was conducted in five sites in three countries: Bobo Dioulosso, Burkina Faso; Mombasa, Kenya; Nairobi, Kenya; Durban, South Africa; Somkhele, South Africa. Enrollment began in June 2005 and continued to August 2008 Follow-up continued and infant blood samples were taken at birth, then periodically until they were 12 months old for HIV testing
Participants	882 pregnant women were screened and 855 randomised. Inclusion criteria: 1. 28 to 36 weeks gestation 2. HIV-1 infected with WHO clinical stage 1,2, or 3 3. CD4 count between 200 and 500 cells/μL Exclusion criteria: 1. Contraindication to rapid initiation of antiretrovirals: known allergies; treatment with drugs that interact with antiretrovirals; severe anaemia; neutropaenia; liver or renal failure 2. Women with CD4 < 200 or > 500 cells/μL were offered enrolment into parallel cohort study
Interventions	1. TRIPLE: i) MOTHER: Lopinivar 200mg /ritonavir 50mg and ZDV 300mg and Lamivudine 150mg from 26 to 34 weeks gestation through 6 months post-partum ii) INFANT: sdNVP within 72 hours of delivery and ZDV for one week 2. SHORT: i) MOTHER: ZDV from 28 to 36 weeks; ZDV and 3TC and sdNVP at onset of labour; ZDV and 3TC for one week after delivery (amendment introduced from December 2007) ii) INFANT: sdNVP within 72 hours and ZDV for one week
Outcomes	PRIMARY OUTCOMES: 1. HIV-free infant survival at 6 weeks and 12 months 2. HIV-free survival in infants who were breastfed 3. AIDS-free survival in mothers at 18 months

	SECONDARY OUTCOMES: 1. Nil reported ADVERSE EVENTS: Reported according to Grade 3 or 4 events classification for mothers and infants
Notes	Mothers elected to breastfeed or formula feed. At birth 74% (297/402) on TRIPLE and 74% (300/403) on SHORT chose to breastfeed. At 6 weeks this was 71% (285/402) and 70% (278/403) Ethics approval obtained from the WHO Reproductive Health Scientific and Ethical Review Group and WHO Ethical Review Group, the CDC Ethical Review Group and local institutional review boards in the three countries as well as the national drug regulatory authorities where required

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequence using the Statistical Analysis System (SAS) software prepared by the study data coordinating centre. Randomization to intervention or control (allocation ratio one-to-one) was stratified on centre and declared breastfeeding intention and balanced in blocks of six or eight according to centre.
Allocation concealment (selection bias)	Low risk	The assigned treatment group was placed inside sequentially numbered, opaque, sealed envelopes. The investigator allocated the next consecutive randomisation number from the centre-specific lists-one list for women planning to breastfeed their child and a second list for women planning to avoid all breastfeeding as determined from their stated intention at the time of enrolment.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding was used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used survival analysis to address attrition. 27/401 (6%) infants were lost to follow-up at 12 months in the TRIPLE arm and 36/404 (9%) infants were lost follow-up at 12 months in the SHORT arm

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 enrolment 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 antiretrovirals
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.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported only as block randomisation
Allocation concealment (selection bias)	Unclear risk	Reported as "sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and providers were not blinded and blinding of the assessors was unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was > 10% with overall attrition = 20.9% (29/139); and attrition in the 'Thai CDC' group was 21.4% (15/70) and in the HIVNET 012 group attrition was 20.3% (14/69).

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)

Limpongsanurak 2001 (*Continued*)

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 antiretroviral 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported as randomised in permuted blocks of 4.
Allocation concealment (selection bias)	Unclear risk	No method reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, providers and assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was < 10%. Overall attrition was 4.4% (8/182) with (3.3%) 3/90 in the ZDV group and 5.4% (5/92) in the placebo group

Mashi

Methods	This 2x2 factorial compared both peripartum and postpartum strategies for preventing MTCT. For the peripartum intervention, pregnant women from one city, one town and two villages in Botswana were enrolled between 20 June 2002 and 29 October 2003. We report the results of the peripartum antiretroviral intervention in the review Prior to the commencement of the above trial, the trial had aimed to assess the superiority of single-dose NVP given to both mothers and infants over placebo when added to the maternal and infant ZDV prophylaxis regimen. However, after 12 August 2002, the results of the PHPT-2 trial showing the efficacy of NVP for infants, resulted in the trial of NVP versus placebo being terminated after 17 months of enrolment. The comparison was changed to compare only maternal NVP with placebo with all infants receiving sdNVP. Women enrolled between 20 June 2002 and 12 August 2002 were re-consented to the new design
Participants	9031 pregnant women were screened and 3030 (33.6%) were HIV-infected and of these 709 were enrolled Inclusion criteria: 1. HIV-positive (HIV-1 ELISA on two separate samples) 2. 33 - 35 weeks gestation 3. Older than 18 years of age 4. HB $\geq$ 8g/dL 5. Absolute neutrophil count $\geq$ 1000 cells/μL 6. Liver AST/ALT not greater than ten times upper limit of normal 7. Creatinine $\leq$ 1.5mg/dL 8. No known intolerance to NVP or ZDV
Interventions	1. sdNVP: i) MOTHER: sdNVP 200mg at onset of labour; ZDV 300mg twice daily from 34 weeks until onset of labour; then ZDV 300mg orally every 3 hours until delivery ii) INFANT: sdNVP 6mg within 72 hours of delivery (premature < 35 weeks and birthweight < 2kg received sdNVP 3mg); ZDV 4mg/kg orally twice daily for one month 2. Placebo/ZDV: i) MOTHER: PLACEBO for NVP; ZDV 300mg twice daily from 34 weeks until onset of labour; then ZDV 300mg orally every 3 hours until delivery ii) INFANT: PLACEBO for sdNVP until August 2002 and then all infants received sdNVP 6mg within 72 hours after birth (premature < 35 weeks and birthweight < 2kg received sdNVP 3mg); ZDV 4mg/kg orally twice daily for one month In October 2002, TRIPLE became available in Botswana and so all participating women with CD4 < 200 cells/μL or with an AIDS-defining illness were offered HAART and did not receive sdNVP or placebo at onset of labour
Outcomes	PRIMARY OUTCOME: 1. HIV infection in the infant at 1 month post-partum SECONDARY OUTCOMES: 1. Death of infant ADVERSE EVENTS: Grade 3 or greater adverse events reported.

Mashi (*Continued*)

Notes	Mixed feeding as part of the 2x2 factorial design randomised women to breast-feed for 6 months with ZDV prophylaxis for infants for one month or formula-feed with one month of ZDV for infants All live first-born infants of multiple births analysed. Infants were analysed by assigned treatment regardless of drugs received by mother or infant or by feeding practices Ethics approval was received from Health Research Development Committee of Botswana and Harvard School of Public Health Human Subjects Committee All women provided written informed consent.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Described as 2x2 factorial design randomised in permuted blocks of eight and stratified by site. Assume therefore computer-generated
Allocation concealment (selection bias)	Low risk	Centralised randomisation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Placebo-controlled trial and both participants and healthcare providers were blinded. The outcome assessment is not clearly reported as blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition at the primary outcome point of 1 month was low overall at 7.5% overall and equally distributed across arms

Mma Bana

Methods	This multi-centre trial was conducted in the same four sites as the Mashi trial (clinics in one city, one town and two villages) in Botswana with enrolment commencing on 5 July 2006 and final enrolment on 12 May 2008. Women and infants are to be followed-up for 24 months post-partum, but the current available analysis is for the first 6 months post-partum only
Participants	730 pregnant women were enrolled on the study with 285 randomised to TZV and 275 to CBV inclusion criteria: 1. HIV-1 infected 2. 26 to 34 weeks gestation 3. Aged 18 years or older 4. Intention to breast-feed infants 5. CD4 count $\geq$ 200 cells/μL 6. No previous antiretrovirals Exclusion criteria:

	1. AIDS-defining illness or CD4 < 200 cells/μL
Interventions	1. TZV: i) MOTHER: Abacavir 300mg, lamivudine 150mg, ZDV 300mg (co-formulated as Trizivir) one tablet taken twice daily ii) INFANT: sdNVP within 72 hours of delivery and one month of ZDV 2. CBV: i) MOTHER: Lopinivar 400mg /ritonavir 100mg tablet and Combivir (ZDV 300mg and Lamivudine 150mg) taken orally twice daily from 26 to 34 weeks gestation through 6 months post-partum ii) INFANT: sdNVP and one month of ZDV
Outcomes	PRIMARY OUTCOME: 1. Absolute rate of virologic suppression to < 400 copies/ml at delivery 2. Absolute rate of virologic suppression to < 400 copies/ml during the breast-feeding period to 6 months 3. HIV-1 infection in the infant at birth, and at time-points to 6 months (breast-feeding period). The trial was not powered to compare HIV transmission rates. SECONDARY OUTCOMES: 1. Change in maternal CD4 count from baseline to birth 2. Change in maternal CD4 count from baseline to 6 months post-partum 3. Stillbirth 4. Infant death ADVERSE EVENTS: This were reported and classified according to the Level of Expedited Adverse Event (AEA) reporting as defined by the National Institute of Allergy and Infectious Diseases, for adverse events occurring in mothers on TRIPLE and to infants of mothers on TRIPLE through 3 months of age. After that standard levels of adverse events were reported according to US Food and Drug Administration Investigational New Drug application guidelines
Notes	Over 90% of mothers exclusively breast-fed their infants to 6 months: 91% (250/274) in the TZV arm and 91% (245/269) in the CBV arm There were 10 multiple births (twins). As neither of any of the twin sets were infected the analysis choices to a) only analyse first-borns or b) to consider mothers as the unit of analysis and count the numbers of mothers for whom a transmission occurred, would result in identical results The Health Research Development Committee of Botswana and the Human Subjects Committee of the Harvard School of Public Health approved the study protocol and amendments All women provided written consent.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported as in "permuted blocks stratified according to clinical site"

Allocation concealment (selection bias)	Unclear risk	Unclear and will need to confirm with authors
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described in protocol as double-blind to patient and caregiver but received different numbers of daily tablets
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up clearly reported. For infants breastfed up to 6 months, attrition was 88/274 (32.1%) for the TZV group and 84/269 (31.2%) for the CBV group

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 antiretrovirals and laboratory criteria meeting the following criteria: Haemoglobin $\geq$8 g/dL, absolute neutrophils $\leq$1000 cells per cubic mm, platelets >100 000 per cubic mm, serum alanine aminotransferase $\leq$ 2.5X ULN, serum creatinine $\leq$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 antiretroviral 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 followed 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Generation of allocation sequence: Unclear. Randomisation stratified by gestational age (14-26 weeks vs >26 weeks) Allocation concealment: Unclear. Blinding: Exclusions: Overall - 23.9% (114 /477); ZDV - 24.6% (59/239); Placebo - 23.1% (55/238
Allocation concealment (selection bias)	Unclear risk	No method reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants were blinded and the trial is described as "double-blind" - it is not clear if the participants or assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition was > 10% with 23.9% (114/477) overall and 24.6% (59/239) in the ZDV group and 23.1% (55/238) in the placebo group. Survival analysis used to reduce potential bias from high attrition

PACTG 316

Methods	Generation of allocation sequence: unclear. Randomisation stratified by type of standard antiretroviral treatment and baseline CD4 count Allocation concealment: Not stated 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 antiretroviral 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 benzodiazepines, ALT >10 ULN, mother intended to breastfeed, fetus with life threatening abnormality

PACTG 316 (*Continued*)

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' antiretroviral therapy as determined by the clinicians which could include any licensed antiretroviral 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation reported as stratified by type of standard antiretroviral treatment and baseline CD4 count but no specific method described
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and providers were blinded but no details given about blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was > 10%. Overall attrition was 17.1% (258/1506) with attrition in the NVP group 16.3% (123/754) and in the placebo group 18.0% (135/752)

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 discontinued 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 daily 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

PETRA (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Reported as block randomised by site
Allocation concealment (selection bias)	Low risk	Pre-randomised packs labelled by patients' numbers. All the steps following the preparation of the study medication batches were masked
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and providers were blinded but no details given about blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was > 10%. Overall attrition was 29.5% (430/1457) with attrition in Arm A 26.7% (98/366); in Arm B attrition was 32.3% (120/371); in Arm C attrition was 30.7% (113/368); and in the placebo arm attrition was 28.1% (99/352)

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

PETRA b

Methods	
Participants	
Interventions	
Outcomes	
Notes	

PETRA c

Methods	
Participants	
Interventions	
Outcomes	
Notes	

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, haemoglobin < 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.

PHPT-1 (*Continued*)

	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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised in blocks of 6 and changed to 5 after interim analysis
Allocation concealment (selection bias)	Low risk	Treatment packs were centrally prepared and identified by random numbers
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants ad providers were blinded but blinding of assessors was unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was < 10%. First interim analysis (4 December 1998): Overall attrition was 3.6%(17/466); with attrition in the Long-Long group 4.3% (10/230) and in the Short-short group 3. 0% (7/236). Final analysis: Overall attrition was 3.1% (35/1114) with attrition in the Long-long 4. 3% (18/419); in the Long-short 2.9% (10/ 350); and in the Short-long 2.0% (7/345)

PHPT-1 a

Methods	
Participants	
Interventions	
Outcomes	
Notes	

PHPT-1 b

Methods	
Participants	
Interventions	

PHPT-1 b (*Continued*)

Outcomes	
Notes	

PHPT-2

Methods	This placebo-controlled trial in 37 Voluntary and Counseling and Testing (VCT) programme sites in Thailand commenced enrolment on 15 January 2001 and continued with enrolment until 28 February 2003 Follow-up was every two weeks for the women until delivery and after delivery at 10 days, six weeks and four months. Infants were seen and examined at birth, at 10 days post birth and at six weeks and then four, six, nine and twelve months. HIV infection was determined in the infant by PCR DNA assay for HIV (Amplicor HIV-1 DNA, ROche version 1.5) At the first interim analysis on 2 May 2002 the Data and Safety Monitoring Board stopped enrolment in the PLAC-PLAC arm as there was a statistically significant benefit of the Nevirapine group over this PLAC-PLAC group
Participants	1,844 pregnant women participating in a national programme of VCT who all received ZDV prophylaxis from 28 weeks gestation Inclusion criteria: 1. HIV-infected - plasma HIV RNA but method not stipulated 2. 28 weeks 3. Agreed not to breastfeed 4. Had already received 2 weeks of ZDV prophylaxis 5. Written informed consent 6. Laboratory values within prior 21 days: i) Hb > 8.0g/dL ii) ALT < 5 times the ULN iii) Creatinine < 1.5mg/dL iv) Absolute neutrophil count > 750 cells/mm^3 Exclusion criteria: 1. Contraindications to ZDV or NVP (maternal or fetal condition or concomitant treatment) 2. Oligohydramnios 3. Unexplained polyhydramnios 4. In utero anaemia 5. Medical condition that required TRIPLE
Interventions	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 1. NVP-NVP arm: i) MOTHERS: NVP as a single 200mg dose orally at onset of labour. ii) INFANTS - NVP oral suspension as a single fixed dose (6mg in 0.6 ml) 48 to 72 hours after birth. 2. NVP-PLAC arm: i) MOTHERS - NVP as a single 200mg dose orally at onset of labour

PHPT-2 (*Continued*)

	ii) INFANTS - Placebo 48 to 72 hours after birth 3. PLAC-PLAC arm: i) MOTHERS: Placebo given at onset of labour ii) INFANTS: Placebo given 48 to 72 hours after birth
Outcomes	PRIMARY OUTCOME: 1. Infant HIV+ by PCR on two separate occasions - done at birth, six weeks, and four and six months. SECONDARY OUCTOMES: ADVERSE EVENTS: Type of adverse event is reported but not graded.
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 Infection in one or both of twin births was counted as one transmission

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised in permuted blocks of 6 in the ratio 1:1:1 but method of generation not clear
Allocation concealment (selection bias)	Low risk	Centrally prepared treatment packs identified by random numbers
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, providers and assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition rate is unclear. The total number randomised as reported in the text (N = 1844) conflicts with those reported in Figure 1 (N = 1445 for final analysis). This second number likely reflects the total number excluding the PLAC-PLAC group but we have contacted the authors and await their response. Using the numbers reported in the flow diagram: At first interim analysis (2 May 2002) including the PLAC-PLAC group: overall attrition was 4.9%. At final analysis the attrition (excluding those in the PLAC-PLAC group) was 5.5%

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Block randomisation list generated centrally.
Allocation concealment (selection bias)	Low risk	List generated centrally and blister packs prepared at study pharmacy and delivered to site
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and providers were blinded but blinding of assessors was unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition < 10%. Overall attrition was 7.5%(21/280) with attrition in the ZDV group 7.1% (10/140)

		and 7.9% (11/140) in the placebo group

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, antiretroviral-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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer randomised scratch card sheets in permuted blocks of 4 in 2:2 ratio
Allocation concealment (selection bias)	Unclear risk	Reported only as "unknown to investigator until mother prepared to begin treatment" but actual method not described

SAINT (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants or providers but assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition > 10%. Overall attrition was 28.4.0% (375/1319) with attrition in the NVP group 28.9% (190/657) and 27.9% (185/662) in the ZDV-3TC group

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)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated blocks of 10 in a 1:1 ratio, stratified by clinic
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque, sealed envelopes opened after consent given
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants or providers but assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition > 10%. Overall attrition was 22.7% (254/1119) with attrition in the NVP/ZDV group 20.9% (118/562) and 24.4% (136/557) in the NVP group

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 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated blocks of 10 in a 1:1 ratio, stratified by clinic
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque, sealed envelopes opened after consent given
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants or providers but assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition was > 10% but marginal so assessed as unlikely to introduce bias Overall attrition was 10.9% (97/894) with 8.5% (38/446) in the NVP/AZT group and 13.2% (59/448) in the NVP group

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 antiretrovirals 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated blocks randomly varying in size between 4 and 6 Allocation concealment: Adequate - Blinding: Participant - Yes; Provider - Yes; Assessor - Yes Exclusions: Overall -
Allocation concealment (selection bias)	Low risk	Investigators not involved in sequence generation. Treatment allocation concealed from investigators by sequentially numbered drug packs

Thai-CDC (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, providers and assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition < 10%. Overall attrition was 1.2% (5/397); with attrition in the ZDV group 2.0% (4/198) and 0.5% (1/199) in the placebo group

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 after birth
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.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated block randomisation.

Thistle 2004 (*Continued*)

Allocation concealment (selection bias)	Low risk	Allocation schedule prepared by off-site statistician and provided in "ordered opaque envelopes"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participant and provider blinded but blinding of assessor was unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition was > 10%. Overall attrition was 19.4% (43/222) but distribution between groups not provided

Thistle 2007

Methods	The trial commenced enrolment in December 2002 and was terminated early in August 2004 after results from Taha 2004 demonstrated that there was no benefit in ZDV therapy for the neonate alone and an interim analysis of the study in July 2004 showed that the likelihood of detecting a significant difference between arms was extremely low given the present enrolment rates
Participants	7,467 pregnant women presenting to the Salvation Army Howard Hospital in Chiweshe communal land, a rural area 80km north of Harare, Zimbabwe, were screened. 1,610 (21.6%) HIV-positive women were enrolled Inclusion criteria: 1. Pregnant women 2. HIV-positive (determined by HIV serological test using the Dipstick HIV 1 and 2 (Immuno Chemical Lab. All positive results were retested using the Recombigen test kit. Only mothers positive on both tests were enrolled) 3. Ability to give consent 4. antiretroviral-naive Exclusion criteria: 1. Inability of refusal to consent 2. Clinical evidence of significant hepatic disease 3. Receipt of previous antiretroviral therapy
Interventions	1. usZDV/sdNVP i) MOTHER: ZDV: loading dose of 600mg orally at onset of labour and then ZDV 300mg 3 hourly during labour; NVP 200mg orally in labour. ii) INFANT: ZDV 2mg/kg orally four times daily for 72 hours post delivery; NVP 2mg/kg once within 72 hours of delivery 2. Placebo/sdNVP i) MOTHER: PLACEBO: same dose and timing as for ZDV arm; NVP 200mg orally in labour ii) INFANT: PLACEBO: as for ZDV; NVP 2mg/kg orally once within 72 hours of delivery CO-INTERVENTIONS: All mothers offered free cotrimoxazole prophylaxis of opportunistic infections at 3 months after delivery and all infants with unknown or HIV-positive status were also

Thistle 2007 (*Continued*)

	provided with cotrimoxazole prophylaxis
Outcomes	PRIMARY OUTCOME: 1. Infant HIV infection determined by Nuclisens HIV-1 RNA or infant death at 6 weeks of age SECONDARY OUTCOMES: 1. HIV infection status at birth and 2 weeks 2. Maternal death 3. Birth outcomes: Stillbirth; prematurity 4. Admission to nursery ADVERSE EVENTS: Not reported how these were collected or graded.
Notes	At 6 weeks 89.4% of babies in usZDV/sdNVP arm and 91.1% of babies in sdNVP arm were breast-feeding Ethics approval received from Medical Research Council of Zimbabwe and from the Research Ethics Board of Lakeridge Health Center in Canada For twin (18 sets) and multiple births (1 triplet sets) only data for the first-born was included in the analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants and providers were assumed to be blinded as reported as "double-blind, placebo-controlled". Unclear whether assessors in the laboratory were blinded but this is likely
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was > 10%. Very high attrition of 53.4% overall with attrition in the usZDV/sdNVP arm 54.8% and in the sdNVP arm 52% at 6 weeks post-partum

ULN = upper limit normal
IRBs = institutional review board

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
El Beitune 2005	This is a prospective cohort study and is not randomised
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
SIMBA	Abstract only - manuscript was never published. Authors of the study were contacted, but no further information was obtained
Yoshimoto 2005	This is a prospective cohort study and is not randomised (translated from the Portuguese)

Characteristics of ongoing studies *[ordered by study ID]*

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
Methods	
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/μL 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

BAN 2005 (*Continued*)

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 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	

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

DATA AND ANALYSES

Comparison 1. Antiretrovirals versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HIV infection at birth	2		efficacy (%) (Random, 95% CI)	Totals not selected
2 HIV infection at 4 to 8 weeks.	6		efficacy (%) (Random, 95% CI)	Totals not selected
2.1 Breastfeeding	5		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Not breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
3 HIV infection at 3 to 4 months.	2		efficacy (%) (Random, 95% CI)	Totals not selected
3.1 Breastfeeding	2		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
4 HIV infection at 6 months	2		efficacy (%) (Random, 95% CI)	Totals not selected
4.1 Breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Not breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
5 HIV infection at 12 months	1		efficacy (%) (Random, 95% CI)	Totals not selected
5.1 Breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
6 HIV infection at 18 months	5		efficacy (%) (Random, 95% CI)	Totals not selected
6.1 Breastfeeding	4		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Not breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
7 HIV infection or death at 4 to 8 weeks.	3		efficacy (%) (Random, 95% CI)	Totals not selected
7.1 Breastfeeding	3		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
8 HIV infection or death at 18 months.	3		efficacy (%) (Random, 95% CI)	Totals not selected
8.1 Breastfeeding	3		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
9 Number of infants dying during first 8 days after birth	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Number of infants dying during first 4 to 8 weeks after birth	5		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Number of infants dying during first 3 to 4 months after birth	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12 Number of infants dying during first 6 months after birth	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Number of infants dying during first 12 months after birth	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14 Number of infants dying during first 18 months after birth	5		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15 Number of premature babies based on author's definition	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16 Number of babies weighing less than 2.5kg.	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
17 Stillbirth rates	8		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 2. Longer vs shorter regimens of the same antiretrovirals

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HIV infection at birth	3		efficacy (%) (Random, 95% CI)	Totals not selected
2 HIV infection at 4 to 8 weeks.	1		efficacy (%) (Random, 95% CI)	Totals not selected
2.1 Breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
3 HIV infection at 3 to 4 months.	2		efficacy (%) (Random, 95% CI)	Totals not selected
3.1 Breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Not breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
4 HIV infection at 6 months	4		efficacy (%) (Random, 95% CI)	Totals not selected
4.1 Breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Not breastfeeding	3		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
5 HIV infection at 12 months	1		efficacy (%) (Random, 95% CI)	Totals not selected
5.1 Breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
6 HIV infection or death at 6 months.	3		efficacy (%) (Random, 95% CI)	Totals not selected
6.2 Not breastfeeding	3		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
7 Number of infants dying during first 4 to 8 weeks after birth	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Number of infants dying during first 3 to 4 months after birth	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Number of infants dying during first 6 months after birth	4		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Number of infants dying during first 12 months after birth	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Number of premature babies based on author's definition	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12 Number of babies weighing less than 2.5kg.	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Stillbirth rates	5		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 3. Regimens of different antiretrovirals and durations of treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HIV infection at birth	7		efficacy (%) (Random, 95% CI)	Totals not selected
2 HIV infection at 2 weeks.	1		efficacy (%) (Random, 95% CI)	Totals not selected
2.1 Breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
3 HIV infection at 4 to 8 weeks.	14		efficacy (%) (Random, 95% CI)	Totals not selected
3.1 Breastfeeding	6		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Not breastfeeding	8		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
4 HIV infection at 3 to 4 months.	5		efficacy (%) (Random, 95% CI)	Totals not selected
4.1 Breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Not breastfeeding	4		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]

5 HIV infection at 6 months	3	efficacy (%) (Random, 95% CI)	Totals not selected
5.2 Not breastfeeding	3	efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
6 HIV infection at 12 months	1	efficacy (%) (Random, 95% CI)	Totals not selected
6.1 Breastfeeding	1	efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
7 HIV infection at 18 months	1	efficacy (%) (Random, 95% CI)	Totals not selected
7.1 Breastfeeding	1	efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
8 HIV infection or death at 4 to 8 weeks.	2	efficacy (%) (Random, 95% CI)	Totals not selected
8.1 Breastfeeding	2	efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
9 HIV infection or death at 3 to 4 months.	1	efficacy (%) (Random, 95% CI)	Totals not selected
9.1 Breastfeeding	1	efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
10 HIV infection or death at 12 months.	1	efficacy (%) (Random, 95% CI)	Totals not selected
10.1 Breastfeeding	1	efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
11 HIV infection or death at 18 months.	1	efficacy (%) (Random, 95% CI)	Totals not selected
11.1 Breastfeeding	1	efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
12 Number of infants dying during first 8 days after birth	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Number of infants dying during first 4 to 8 weeks after birth	11	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14 Number of infants dying during first 6 months after birth	3	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15 Number of infants dying during first 18 months after birth	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16 Number of premature babies based on author's definition	3	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
17 Number of babies weighing less than 2.5kg, except SAINT: <2 kg.	5	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18 Stillbirth rates	6	Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 4. TRIPLE regimens versus other

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HIV infection at birth	2		efficacy (%) (Random, 95% CI)	Totals not selected
2 HIV infection at 4 to 8 weeks.	1		efficacy (%) (Random, 95% CI)	Totals not selected
2.2 Not breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
3 HIV infection at 6 months	2		efficacy (%) (Random, 95% CI)	Totals not selected
3.1 Breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Not breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
4 HIV infection at 12 months	1		efficacy (%) (Random, 95% CI)	Totals not selected
4.2 Not breastfeeding	1		efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]

5 HIV infection or death at 2 weeks	1	efficacy (%) (Random, 95% CI)	Totals not selected
5.1 Breastfeeding	1	efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
6 HIV infection or death at 4 to 8 weeks.	1	efficacy (%) (Random, 95% CI)	Totals not selected
6.2 Not breastfeeding	1	efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
7 HIV infection or death at 6 months	1	efficacy (%) (Random, 95% CI)	Totals not selected
7.2 Not breastfeeding	1	efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
8 HIV infection or death at 12 months	2	efficacy (%) (Random, 95% CI)	Totals not selected
8.1 Breastfeeding	1	efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Not breastfeeding	1	efficacy (%) (Random, 95% CI)	0.0 [0.0, 0.0]
9 Number of infants dying during first 8 days after birth	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Number of infants dying during first 4 to 8 weeks after birth	2	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Number of infants dying during first 6 months after birth	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12 Number of infants dying during first 12 months after birth	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Number of premature babies based on author's definition	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14 Number of babies weighing less than 2.5kg.	2	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15 Stillbirth rates	2	Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 5. TRIPLE regimen vs TRIPLE regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HIV infection at birth	1		Efficacy (Random, 95% CI)	Totals not selected
2 HIV infection at 6 months	1		Efficacy (Random, 95% CI)	Totals not selected
2.1 Breastfeeding	1		Efficacy (Random, 95% CI)	0.0 [0.0, 0.0]
3 Number of infants dying during first 8 days after birth	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Number of infants dying during first 6 months after birth	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Number of premature babies based on author's definition	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Number of babies weighing less than 2.5kg	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Stillbirth rates	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Antiretrovirals versus Placebo, Outcome 1 HIV infection at birth.

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 1 HIV infection at birth

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
RETRO-CI	129	135	-13.95 (76.43)		-13.95 [-163.75, 135.85]
Thai-CDC	196	199	29.71 (37.34)		29.71 [-43.48, 102.90]

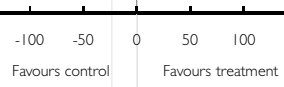
Analysis 1.2. Comparison 1 Antiretrovirals versus Placebo, Outcome 2 HIV infection at 4 to 8 weeks..

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 2 HIV infection at 4 to 8 weeks.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
DITRAME	193	198	32 (15.56)		32.00 [1.50, 62.50]
RETRO-CI	129	135	43.78 (17.86)		43.78 [8.78, 78.78]
PETRA a	467	352	62.75 (11.22)		62.75 [40.76, 84.74]
PETRA b	467	352	41.83 (14.8)		41.83 [12.82, 70.84]
PETRA c	467	352	7.19 (19.9)		7.19 [-31.81, 46.19]
2 Not breastfeeding					
Thai-CDC	196	199	50.26 (18.6)		50.26 [13.80, 86.72]



Analysis 1.3. Comparison 1 Antiretrovirals versus Placebo, Outcome 3 HIV infection at 3 to 4 months..

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 3 HIV infection at 3 to 4 months.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
DITRAME	193	198	33.07 (14.03)		33.07 [5.57, 60.57]
RETRO-CI	129	135	36.95 (17.35)		36.95 [2.94, 70.96]

Analysis 1.4. Comparison 1 Antiretrovirals versus Placebo, Outcome 4 HIV infection at 6 months.

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 4 HIV infection at 6 months

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
DITRAME	193	198	34.55 (13.01)		34.55 [9.05, 60.05]
2 Not breastfeeding					
Limpongsanurak 2001	90	92	8.59 (17.97)		8.59 [-26.63, 43.81]

Analysis 1.5. Comparison 1 Antiretrovirals versus Placebo, Outcome 5 HIV infection at 12 months.

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 5 HIV infection at 12 months

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
DITRAME	193	198	34.31 (12.76)		34.31 [9.30, 59.32]

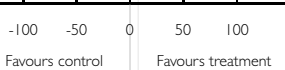
Analysis 1.6. Comparison 1 Antiretrovirals versus Placebo, Outcome 6 HIV infection at 18 months.

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 6 HIV infection at 18 months

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
DITRAME	193	198	29.74 (13.78)		29.74 [2.73, 56.75]
PETRA a	467	352	32.88 (22.77)		32.88 [-11.75, 77.51]
PETRA b	467	352	18.47 (23.28)		18.47 [-27.16, 64.10]
PETRA c	468	352	9.91 (25.97)		9.91 [-40.99, 60.81]
2 Not breastfeeding					
PACTG 076	198	204	66.22 (16.47)		66.22 [33.94, 98.50]



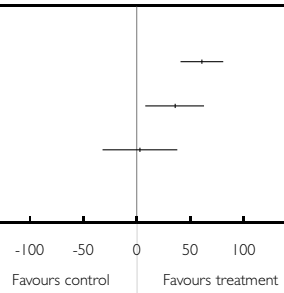
Analysis 1.7. Comparison 1 Antiretrovirals versus Placebo, Outcome 7 HIV infection or death at 4 to 8 weeks..

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 7 HIV infection or death at 4 to 8 weeks.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
PETRA a	467	352	61.33 (10.2)		61.33 [41.34, 81.32]
PETRA b	467	352	35.91 (14.03)		35.91 [8.41, 63.41]
PETRA c	468	352	3.31 (17.86)		3.31 [-31.69, 38.31]



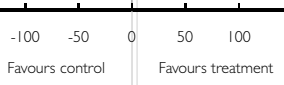
Analysis 1.8. Comparison 1 Antiretrovirals versus Placebo, Outcome 8 HIV infection or death at 18 months..

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 8 HIV infection or death at 18 months.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
PETRA a	467	352	26.17 (20.3)		26.17 [-13.62, 65.96]
PETRA b	467	352	7.03 (23.57)		7.03 [-39.17, 53.23]
PETRA c	468	352	1.56 (23.55)		1.56 [-44.60, 47.72]



Analysis 1.9. Comparison 1 Antiretrovirals versus Placebo, Outcome 9 Number of infants dying during first 8 days after birth.

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 9 Number of infants dying during first 8 days after birth

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,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]

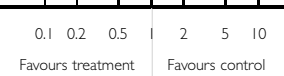
Analysis 1.10. Comparison 1 Antiretrovirals versus Placebo, Outcome 10 Number of infants dying during first 4 to 8 weeks after birth.

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 10 Number of infants dying during first 4 to 8 weeks after birth

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
DITRAME	7/214	4/217		1.77 [0.53, 5.97]
Thai-CDC	1/198	2/199		0.50 [0.05, 5.50]
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]



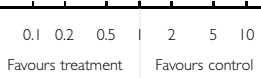
Analysis 1.11. Comparison 1 Antiretrovirals versus Placebo, Outcome 11 Number of infants dying during first 3 to 4 months after birth.

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 11 Number of infants dying during first 3 to 4 months after birth

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,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 1.12. Comparison 1 Antiretrovirals versus Placebo, Outcome 12 Number of infants dying during first 6 months after birth.

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 12 Number of infants dying during first 6 months after birth

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
DITRAME	17/214	28/217		0.62 [0.35, 1.09]

Analysis 1.13. Comparison 1 Antiretrovirals versus Placebo, Outcome 13 Number of infants dying during first 12 months after birth.

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 13 Number of infants dying during first 12 months after birth

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
DITRAME	28/214	38/217		0.75 [0.48, 1.17]

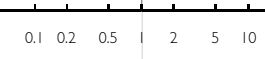
Analysis 1.14. Comparison 1 Antiretrovirals versus Placebo, Outcome 14 Number of infants dying during first 18 months after birth.

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 14 Number of infants dying during first 18 months after birth

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
PACTG 076	4/239	3/238		1.33 [0.30, 5.87]
DITRAME	33/214	42/217		0.80 [0.53, 1.21]
PETRA a	37/366	47/352		0.76 [0.50, 1.14]
PETRA b	52/371	47/352		1.05 [0.73, 1.51]
PETRA c	47/368	47/352		0.96 [0.66, 1.39]



Analysis 1.15. Comparison 1 Antiretrovirals versus Placebo, Outcome 15 Number of premature babies based on author's definition.

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 15 Number of premature babies based on author's definition

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
PACTG 076	16/239	13/238		1.23 [0.60, 2.49]
DITRAME	2/214	15/217		0.14 [0.03, 0.58]

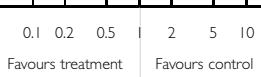
Analysis 1.16. Comparison 1 Antiretrovirals versus Placebo, Outcome 16 Number of babies weighing less than 2.5kg..

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 16 Number of babies weighing less than 2.5kg.

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



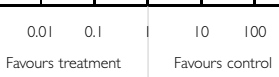
Analysis 1.17. Comparison 1 Antiretrovirals versus Placebo, Outcome 17 Stillbirth rates.

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

Comparison: 1 Antiretrovirals versus Placebo

Outcome: 17 Stillbirth rates

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
PACTG 076	0/239	1/238		0.33 [0.01, 8.11]
DITRAME	1/214	7/217		0.14 [0.02, 1.17]
Limpongsanurak 2001	1/90	0/92		3.07 [0.13, 74.28]
RETRO-CI	7/140	2/140		3.50 [0.74, 16.55]
Thai-CDC	1/198	0/199		3.02 [0.12, 73.57]
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]



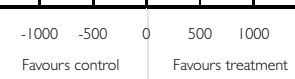
Analysis 2.1. Comparison 2 Longer vs shorter regimens of the same antiretrovirals, Outcome 1 HIV infection at birth.

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

Comparison: 2 Longer vs shorter regimens of the same antiretrovirals

Outcome: 1 HIV infection at birth

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
Thistle 2004	111	111	-15.1 (69.89)		-15.10 [-152.08, 121.88]
PHPT-2	693	672	37.5 (40.02)		37.50 [-40.94, 115.94]
Bhoopat 2005	23	27	100 (201.21)		100.00 [-294.36, 494.36]



Analysis 2.2. Comparison 2 Longer vs shorter regimens of the same antiretrovirals, Outcome 2 HIV infection at 4 to 8 weeks..

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

Comparison: 2 Longer vs shorter regimens of the same antiretrovirals

Outcome: 2 HIV infection at 4 to 8 weeks.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
Thistle 2004	111	111	16.72 (30.18)		16.72 [-42.43, 75.87]

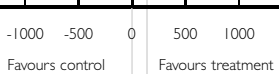
Analysis 2.3. Comparison 2 Longer vs shorter regimens of the same antiretrovirals, Outcome 3 HIV infection at 3 to 4 months..

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

Comparison: 2 Longer vs shorter regimens of the same antiretrovirals

Outcome: 3 HIV infection at 3 to 4 months.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
Thistle 2004	111	111	13.95 (26.76)		13.95 [-38.50, 66.40]
2 Not breastfeeding					
Bhoopat 2005	23	27	100 (59.44)		100.00 [-16.50, 216.50]



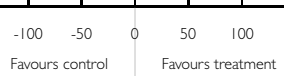
Analysis 2.4. Comparison 2 Longer vs shorter regimens of the same antiretrovirals, Outcome 4 HIV infection at 6 months.

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

Comparison: 2 Longer vs shorter regimens of the same antiretrovirals

Outcome: 4 HIV infection at 6 months

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
Thistle 2004	111	111	8.28 (25.53)		8.28 [-41.76, 58.32]
2 Not breastfeeding					
PHPT-1 a	401	338	24.42 (22.79)		24.42 [-20.25, 69.09]
PHPT-1 b	340	338	45.35 (22.43)		45.35 [1.39, 89.31]
PHPT-2	693	672	28.57 (27.89)		28.57 [-26.09, 83.23]



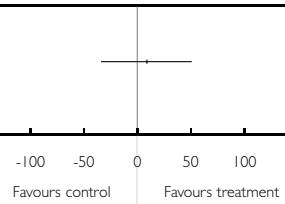
Analysis 2.5. Comparison 2 Longer vs shorter regimens of the same antiretrovirals, Outcome 5 HIV infection at 12 months.

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

Comparison: 2 Longer vs shorter regimens of the same antiretrovirals

Outcome: 5 HIV infection at 12 months

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
Thistle 2004	111	111	8.62 (21.71)		8.62 [-33.93, 51.17]



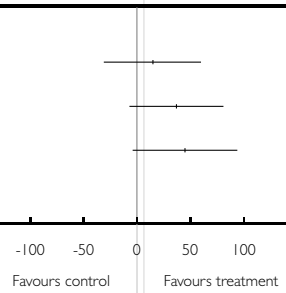
Analysis 2.6. Comparison 2 Longer vs shorter regimens of the same antiretrovirals, Outcome 6 HIV infection or death at 6 months..

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

Comparison: 2 Longer vs shorter regimens of the same antiretrovirals

Outcome: 6 HIV infection or death at 6 months.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
2 Not breastfeeding					
PHPT-1 a	401	338	14.61 (23.17)		14.61 [-30.80, 60.02]
PHPT-1 b	340	338	37.08 (22.43)		37.08 [-6.88, 81.04]
PHPT-2	693	672	45 (25)		45.00 [-4.00, 94.00]

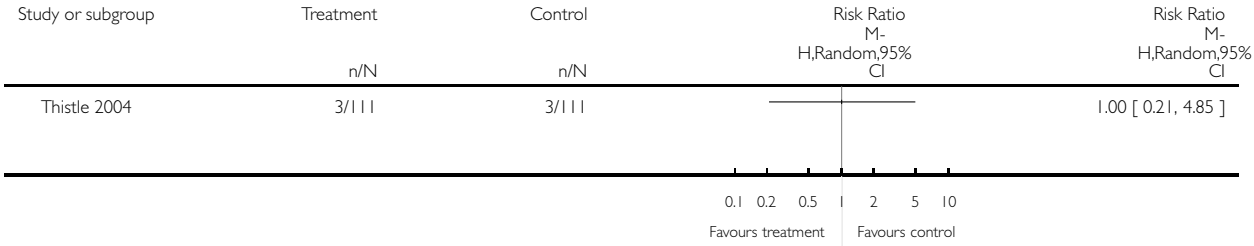


Analysis 2.7. Comparison 2 Longer vs shorter regimens of the same antiretrovirals, Outcome 7 Number of infants dying during first 4 to 8 weeks after birth.

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

Comparison: 2 Longer vs shorter regimens of the same antiretrovirals

Outcome: 7 Number of infants dying during first 4 to 8 weeks after birth

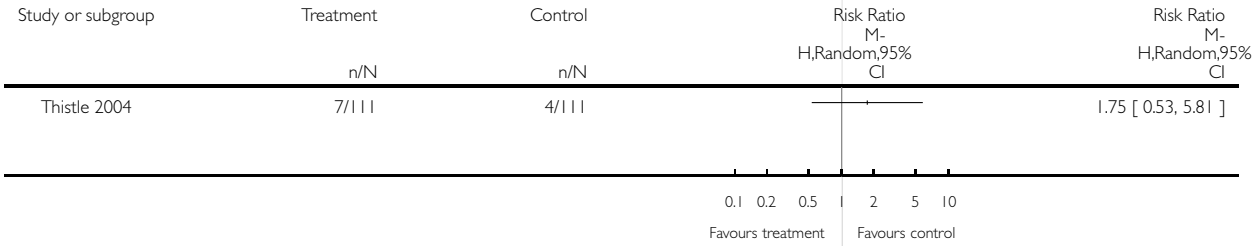


Analysis 2.8. Comparison 2 Longer vs shorter regimens of the same antiretrovirals, Outcome 8 Number of infants dying during first 3 to 4 months after birth.

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

Comparison: 2 Longer vs shorter regimens of the same antiretrovirals

Outcome: 8 Number of infants dying during first 3 to 4 months after birth

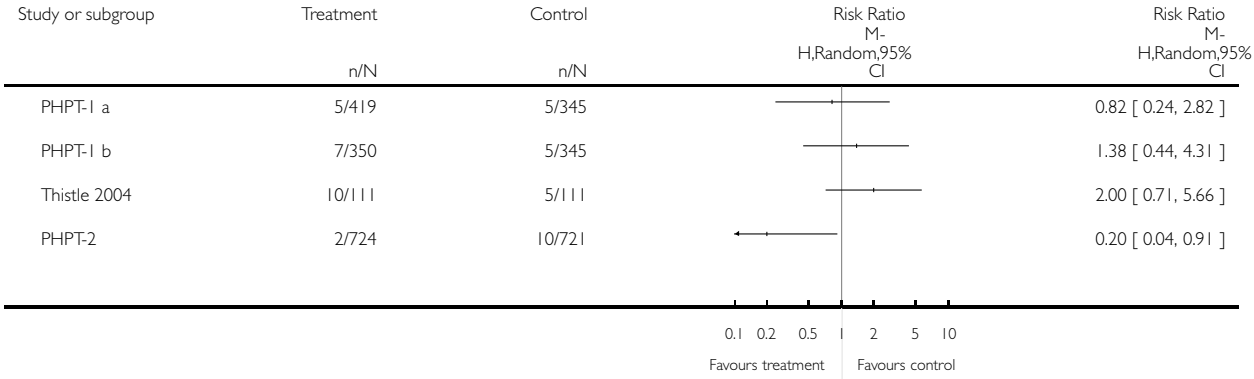


Analysis 2.9. Comparison 2 Longer vs shorter regimens of the same antiretrovirals, Outcome 9 Number of infants dying during first 6 months after birth.

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

Comparison: 2 Longer vs shorter regimens of the same antiretrovirals

Outcome: 9 Number of infants dying during first 6 months after birth

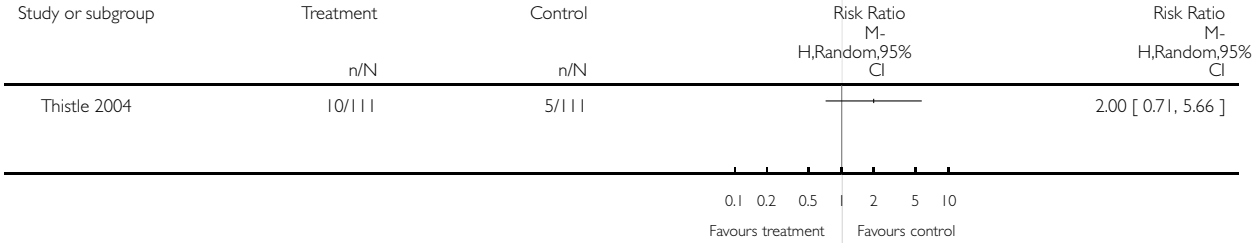


Analysis 2.10. Comparison 2 Longer vs shorter regimens of the same antiretrovirals, Outcome 10 Number of infants dying during first 12 months after birth.

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

Comparison: 2 Longer vs shorter regimens of the same antiretrovirals

Outcome: 10 Number of infants dying during first 12 months after birth

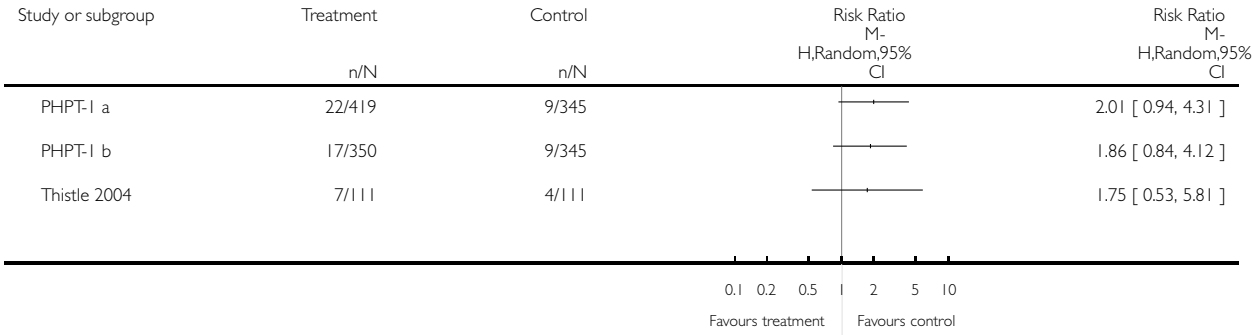


Analysis 2.11. Comparison 2 Longer vs shorter regimens of the same antiretrovirals, Outcome 11 Number of premature babies based on author's definition.

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

Comparison: 2 Longer vs shorter regimens of the same antiretrovirals

Outcome: 11 Number of premature babies based on author's definition

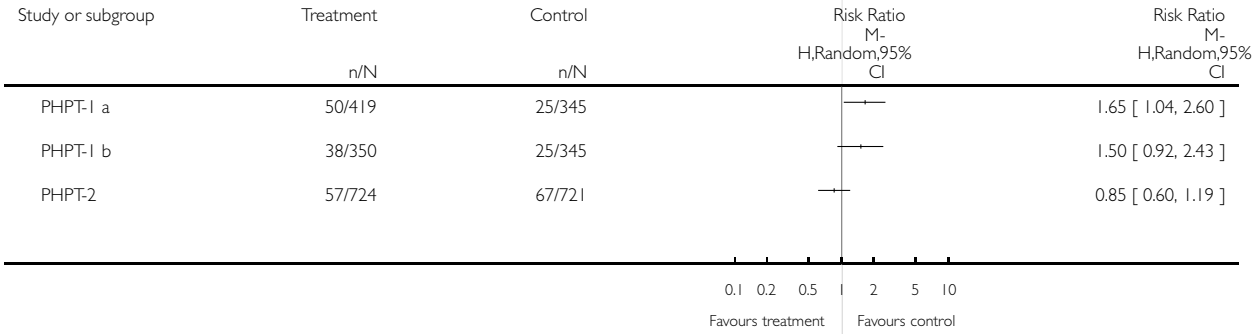


Analysis 2.12. Comparison 2 Longer vs shorter regimens of the same antiretrovirals, Outcome 12 Number of babies weighing less than 2.5kg..

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

Comparison: 2 Longer vs shorter regimens of the same antiretrovirals

Outcome: 12 Number of babies weighing less than 2.5kg.



Analysis 2.13. Comparison 2 Longer vs shorter regimens of the same antiretrovirals, Outcome 13 Stillbirth rates.

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

Comparison: 2 Longer vs shorter regimens of the same antiretrovirals

Outcome: 13 Stillbirth rates

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
PHPT-1 a	8/419	12/345		0.55 [0.23, 1.33]
PHPT-1 b	4/350	12/345		0.33 [0.11, 1.01]
Thistle 2004	0/111	0/111		Not estimable
PHPT-2	2/724	8/721		0.25 [0.05, 1.17]
Bhoopat 2005	0/23	0/27		Not estimable

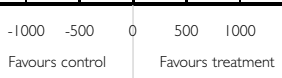
Analysis 3.1. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 1 HIV infection at birth.

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 1 HIV infection at birth

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
Gray 2006 a	91	92	26.65 (76.07)		26.65 [-122.44, 175.74]
PACTG 316	631	637	2.22 (72.76)		2.22 [-140.39, 144.83]
Gray 2006 b	94	92	52.66 (71.77)		52.66 [-88.01, 193.33]
Gray 2006 c	88	92	49.43 (73.63)		49.43 [-94.88, 193.74]
Thistle 2007	438	433	-5.45 (38.01)		-5.45 [-79.95, 69.05]
Chi 2007	198	199	20.4 (44.52)		20.40 [-66.86, 107.66]
Mashi	345	349	-64.38 (60.89)		-64.38 [-183.72, 54.96]



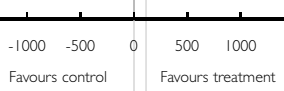
Analysis 3.2. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 2 HIV infection at 2 weeks..

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 2 HIV infection at 2 weeks.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
Chung 2005	30	30	-100 (222.65)		-100.00 [-536.39, 336.39]



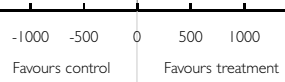
Analysis 3.3. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 3 HIV infection at 4 to 8 weeks..

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 3 HIV infection at 4 to 8 weeks.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
HIVNET 012	310	370	41 (14.88)		41.00 [11.84, 70.16]
Taha 2003	444	421	36.79 (16.95)		36.79 [3.57, 70.01]
Taha 2004	444	445	-15.6 (17.66)		-15.60 [-50.21, 19.01]
Thistle 2007	438	433	9.21 (18.76)		9.21 [-27.56, 45.98]
Chung 2005	30	30	-345.59 (145.11)		-345.59 [-630.00, -61.18]
Chi 2007	198	199	28.93 (35.6)		28.93 [-40.84, 98.70]
2 Not breastfeeding					
PACTG 316	631	637	12.5 (48.67)		12.50 [-82.89, 107.89]
SAINT	477	467	24.39 (14.56)		24.39 [-4.15, 52.93]
Gray 2006 a	91	92	-120.05 (92.36)		-120.05 [-301.07, 60.97]
Gray 2006 b	94	92	-42.02 (83.56)		-42.02 [-205.79, 121.75]
Gray 2006 c	88	92	24.15 (77.17)		24.15 [-127.10, 175.40]
Kiarie 2003	55	55	59.09 (32.14)		59.09 [-3.90, 122.08]
Gray 2005	473	491	35.37 (23.15)		35.37 [-10.00, 80.74]
Mashi	345	349	-16.22 (43.89)		-16.22 [-102.24, 69.80]



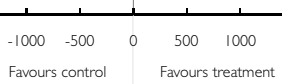
Analysis 3.4. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 4 HIV infection at 3 to 4 months..

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 4 HIV infection at 3 to 4 months.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
HIVNET 012	310	370	38.91 (14.12)		38.91 [11.24, 66.58]
2 Not breastfeeding					
Gray 2006 a	91	92	-144.51 (94.59)		-144.51 [-329.90, 40.88]
Gray 2006 b	94	92	-113.03 (90.72)		-113.03 [-290.84, 64.78]
Gray 2006 c	88	92	-1.14 (80.46)		-1.14 [-158.84, 156.56]
Gray 2005	473	491	39.69 (20.8)		39.69 [-1.08, 80.46]



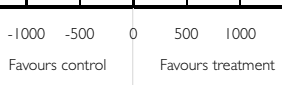
Analysis 3.5. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 5 HIV infection at 6 months.

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 5 HIV infection at 6 months

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
2 Not breastfeeding					
Gray 2006 a	91	92	-116.07 (83.93)		-116.07 [-280.57, 48.43]
Gray 2006 b	94	92	-89.29 (80.84)		-89.29 [-247.73, 69.15]
Gray 2006 c	88	92	17.86 (69.72)		17.86 [-118.79, 154.51]



Analysis 3.6. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 6 HIV infection at 12 months.

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 6 HIV infection at 12 months

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
HIVNET 012	310	370	35.98 (13.64)		35.98 [9.25, 62.71]

Analysis 3.7. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 7 HIV infection at 18 months.

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 7 HIV infection at 18 months

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
HIVNET 012	310	370	39.15 (12.93)		39.15 [13.81, 64.49]

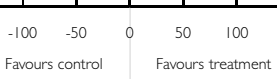
Analysis 3.8. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 8 HIV infection or death at 4 to 8 weeks..

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

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

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
HIVNET 012	310	370	41.74 (14)		41.74 [14.30, 69.18]
Thistle 2007	438	433	3.97 (15.36)		3.97 [-26.14, 34.08]



Analysis 3.9. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 9 HIV infection or death at 3 to 4 months..

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 9 HIV infection or death at 3 to 4 months.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
HIVNET 012	310	370	40 (13.09)		40.00 [14.34, 65.66]

Analysis 3.10. Comparison 3 Regimens of different antiretrovirals 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: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 10 HIV infection or death at 12 months.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
HIVNET 012	310	370	32.17 (12.07)		32.17 [8.51, 55.83]

Analysis 3.11. Comparison 3 Regimens of different antiretrovirals 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: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 11 HIV infection or death at 18 months.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
HIVNET 012	310	370	32.57 (11.55)		32.57 [9.93, 55.21]

Analysis 3.12. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 12 Number of infants dying during first 8 days after birth.

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 12 Number of infants dying during first 8 days after birth

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
HIVNET 012	5/313	2/313		2.50 [0.49, 12.79]

Analysis 3.13. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 13 Number of infants dying during first 4 to 8 weeks after birth.

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

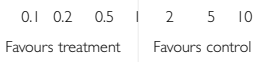
Outcome: 13 Number of infants dying during first 4 to 8 weeks after birth

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
PACTG 316	3/754	5/752		0.60 [0.14, 2.50]
HIVNET 012	10/313	4/313		2.50 [0.79, 7.89]
SAINT	19/657	19/662		1.01 [0.54, 1.89]
Kiarie 2003	3/70	3/69		0.99 [0.21, 4.72]
Taha 2003	15/557	12/562		1.26 [0.60, 2.67]
Taha 2004	7/448	4/446		1.74 [0.51, 5.91]
Gray 2005	13/533	11/518		1.15 [0.52, 2.54]
Mashi	7/345	13/349		0.54 [0.22, 1.35]
Thistle 2007	23/440	21/434		1.08 [0.61, 1.92]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Chung 2005	2/30	0/30		5.00 [0.25, 99.95]
Chi 2007	5/198	4/199		1.26 [0.34, 4.61]



Analysis 3.14. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 14 Number of infants dying during first 6 months after birth.

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 14 Number of infants dying during first 6 months after birth

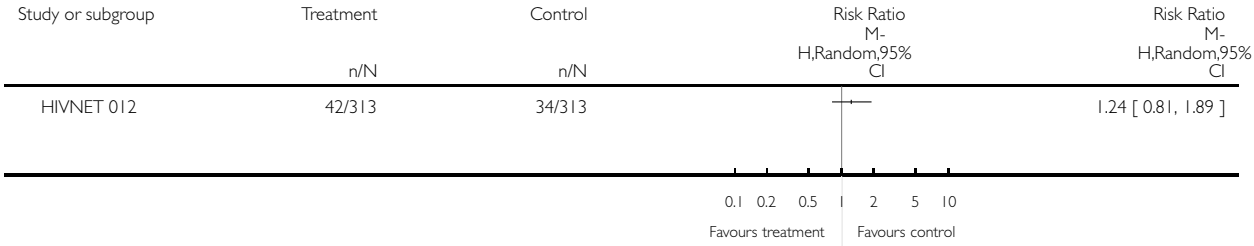
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Gray 2006 a	9/93	3/92		2.97 [0.83, 10.61]
Gray 2006 b	6/95	3/92		1.94 [0.50, 7.52]
Gray 2006 c	2/93	3/92		0.66 [0.11, 3.86]

Analysis 3.15. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 15 Number of infants dying during first 18 months after birth.

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 15 Number of infants dying during first 18 months after birth

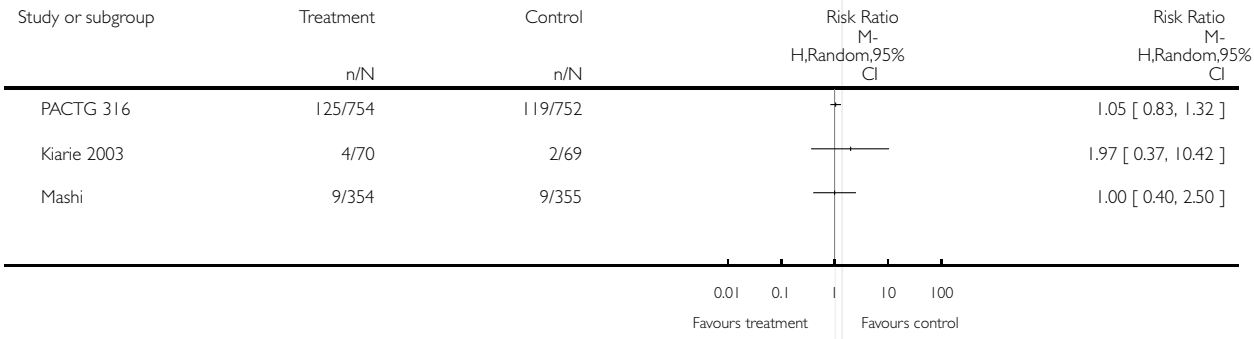


Analysis 3.16. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 16 Number of premature babies based on author's definition.

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 16 Number of premature babies based on author's definition



Analysis 3.17. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 17 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: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 17 Number of babies weighing less than 2.5kg, except SAINT: <2 kg.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
PACTG 316	86/754	75/752		1.14 [0.85, 1.53]
HIVNET 012	14/313	21/313		0.67 [0.35, 1.29]
SAINT	7/657	5/662		1.41 [0.45, 4.42]
Kiarie 2003	2/70	1/69		1.97 [0.18, 21.24]
Chung 2005	2/30	4/30		0.50 [0.10, 2.53]

Analysis 3.18. Comparison 3 Regimens of different antiretrovirals and durations of treatment, Outcome 18 Stillbirth rates.

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

Comparison: 3 Regimens of different antiretrovirals and durations of treatment

Outcome: 18 Stillbirth rates

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
PACTG 316	1/754	0/752		2.99 [0.12, 73.33]
HIVNET 012	2/313	1/313		2.00 [0.18, 21.94]
Kiarie 2003	3/70	2/69		1.48 [0.25, 8.58]
Mashi	6/354	4/355		1.50 [0.43, 5.28]
Thistle 2007	2/440	1/434		1.97 [0.18, 21.68]
Chi 2007	2/200	1/199		1.99 [0.18, 21.77]

Analysis 4.1. Comparison 4 TRIPLE regimens versus other, Outcome 1 HIV infection at birth.

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 1 HIV infection at birth

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
Chung 2008	26	25	0 (0)		Not estimable
Kesho Bora	402	403	18.18 (51.87)		18.18 [-83.48, 119.84]

Analysis 4.2. Comparison 4 TRIPLE regimens versus other, Outcome 2 HIV infection at 4 to 8 weeks..

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 2 HIV infection at 4 to 8 weeks.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
2 Not breastfeeding					
Kesho Bora	402	403	31.25 (30.89)		31.25 [-29.29, 91.79]

Analysis 4.3. Comparison 4 TRIPLE regimens versus other, Outcome 3 HIV infection at 6 months.

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 3 HIV infection at 6 months

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
Chung 2008	26	25	-84.62 (207.01)		-84.62 [-490.35, 321.11]
2 Not breastfeeding					
Kesho Bora	402	403	42.35 (21.9)		42.35 [-0.57, 85.27]

Analysis 4.4. Comparison 4 TRIPLE regimens versus other, Outcome 4 HIV infection at 12 months.

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 4 HIV infection at 12 months

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
2 Not breastfeeding					
Kesho Bora	402	403	42.11 (21.15)		42.11 [0.66, 83.56]

Analysis 4.5. Comparison 4 TRIPLE regimens versus other, Outcome 5 HIV infection or death at 2 weeks.

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 5 HIV infection or death at 2 weeks

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
Chung 2008	26	25	-84.62 (207.01)		-84.62 [-490.35, 321.11]

Analysis 4.6. Comparison 4 TRIPLE regimens versus other, Outcome 6 HIV infection or death at 4 to 8 weeks..

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 6 HIV infection or death at 4 to 8 weeks.

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
2 Not breastfeeding					
Kesho Bora	402	403	20 (27.62)		20.00 [-34.13, 74.13]

Analysis 4.7. Comparison 4 TRIPLE regimens versus other, Outcome 7 HIV infection or death at 6 months.

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 7 HIV infection or death at 6 months

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
2 Not breastfeeding					
Kesho Bora	402	403	34.13 (17.56)		34.13 [-0.29, 68.55]

Analysis 4.8. Comparison 4 TRIPLE regimens versus other, Outcome 8 HIV infection or death at 12 months.

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 8 HIV infection or death at 12 months

Study or subgroup	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) IV,Random,95% CI	efficacy (%) IV,Random,95% CI
1 Breastfeeding					
Chung 2008	26	25	35.9 (78.69)		35.90 [-118.33, 190.13]
2 Not breastfeeding					
Kesho Bora	402	403	36.2 (15.45)		36.20 [5.92, 66.48]

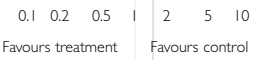
Analysis 4.9. Comparison 4 TRIPLE regimens versus other, Outcome 9 Number of infants dying during first 8 days after birth.

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 9 Number of infants dying during first 8 days after birth

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Kesho Bora	4/402	2/403		2.00 [0.37, 10.88]



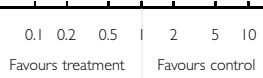
Analysis 4.10. Comparison 4 TRIPLE regimens versus other, Outcome 10 Number of infants dying during first 4 to 8 weeks after birth.

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 10 Number of infants dying during first 4 to 8 weeks after birth

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Chung 2008	0/28	1/26		0.31 [0.01, 7.30]
Kesho Bora	6/402	7/403		0.86 [0.29, 2.53]



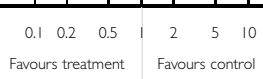
Analysis 4.11. Comparison 4 TRIPLE regimens versus other, Outcome 11 Number of infants dying during first 6 months after birth.

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 11 Number of infants dying during first 6 months after birth

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Kesho Bora	18/402	23/403		0.78 [0.43, 1.43]

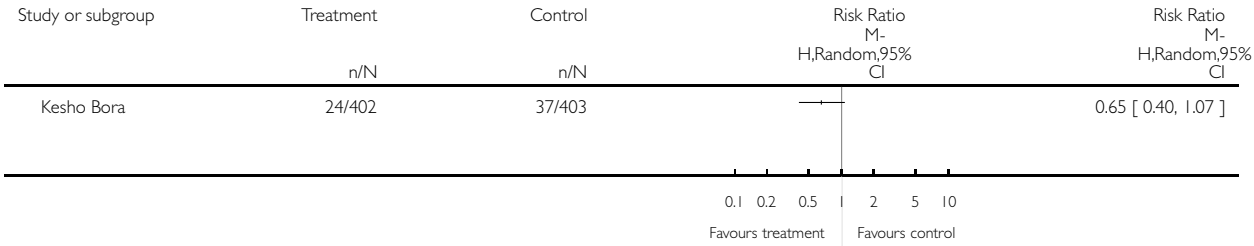


Analysis 4.12. Comparison 4 TRIPLE regimens versus other, Outcome 12 Number of infants dying during first 12 months after birth.

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 12 Number of infants dying during first 12 months after birth

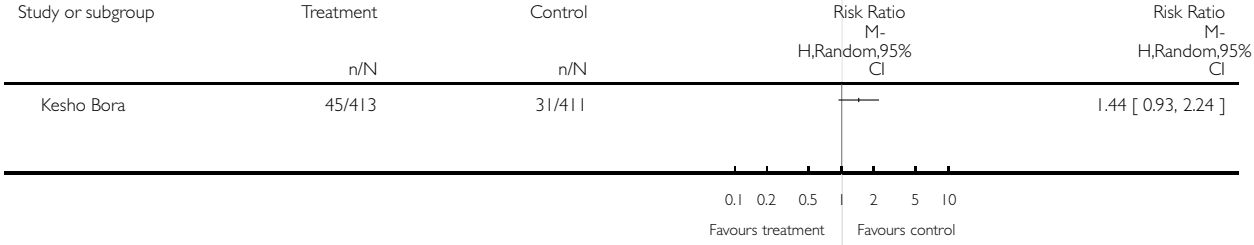


Analysis 4.13. Comparison 4 TRIPLE regimens versus other, Outcome 13 Number of premature babies based on author's definition.

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 13 Number of premature babies based on author's definition



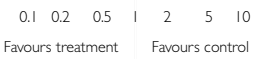
Analysis 4.14. Comparison 4 TRIPLE regimens versus other, Outcome 14 Number of babies weighing less than 2.5kg..

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 14 Number of babies weighing less than 2.5kg.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Chung 2008	5/30	0/28		10.29 [0.59, 177.97]
Kesho Bora	54/413	43/411		1.25 [0.86, 1.82]



Analysis 4.15. Comparison 4 TRIPLE regimens versus other, Outcome 15 Stillbirth rates.

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

Comparison: 4 TRIPLE regimens versus other

Outcome: 15 Stillbirth rates

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Chung 2008	2/30	1/28		1.87 [0.18, 19.47]
Kesho Bora	4/413	4/411		1.00 [0.25, 3.95]

Analysis 5.1. Comparison 5 TRIPLE regimen vs TRIPLE regimen, Outcome 1 HIV infection at birth.

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

Comparison: 5 TRIPLE regimen vs TRIPLE regimen

Outcome: 1 HIV infection at birth

Study or subgroup	TZV N	CBV N	Efficacy (SE)	Efficacy IV,Random,95% CI	Efficacy IV,Random,95% CI
Mma Bana	274	269	-189.47 (268.28)		-189.47 [-715.29, 336.35]

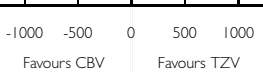
Analysis 5.2. Comparison 5 TRIPLE regimen vs TRIPLE regimen, Outcome 2 HIV infection at 6 months.

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

Comparison: 5 TRIPLE regimen vs TRIPLE regimen

Outcome: 2 HIV infection at 6 months

Study or subgroup	TZV N	CBV N	Efficacy (SE)	Efficacy IV,Random,95% CI	Efficacy IV,Random,95% CI
1 Breastfeeding					
Mma Bana	274	269	-390.88 (301.41)		-390.88 [-981.63, 199.87]

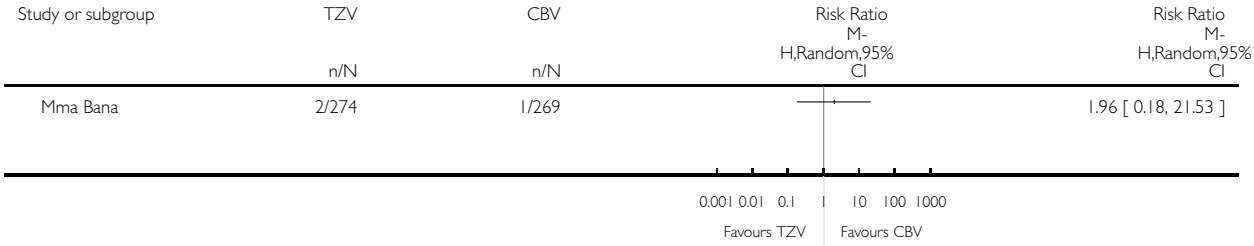


Analysis 5.3. Comparison 5 TRIPLE regimen vs TRIPLE regimen, Outcome 3 Number of infants dying during first 8 days after birth.

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

Comparison: 5 TRIPLE regimen vs TRIPLE regimen

Outcome: 3 Number of infants dying during first 8 days after birth

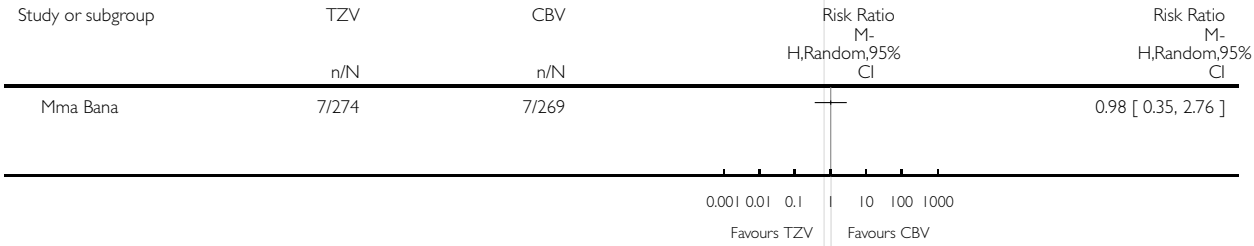


Analysis 5.4. Comparison 5 TRIPLE regimen vs TRIPLE regimen, Outcome 4 Number of infants dying during first 6 months after birth.

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

Comparison: 5 TRIPLE regimen vs TRIPLE regimen

Outcome: 4 Number of infants dying during first 6 months after birth

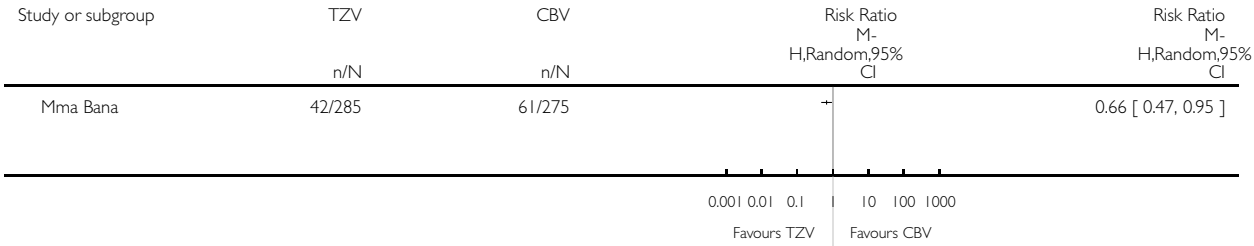


Analysis 5.5. Comparison 5 TRIPLE regimen vs TRIPLE regimen, Outcome 5 Number of premature babies based on author's definition.

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

Comparison: 5 TRIPLE regimen vs TRIPLE regimen

Outcome: 5 Number of premature babies based on author's definition

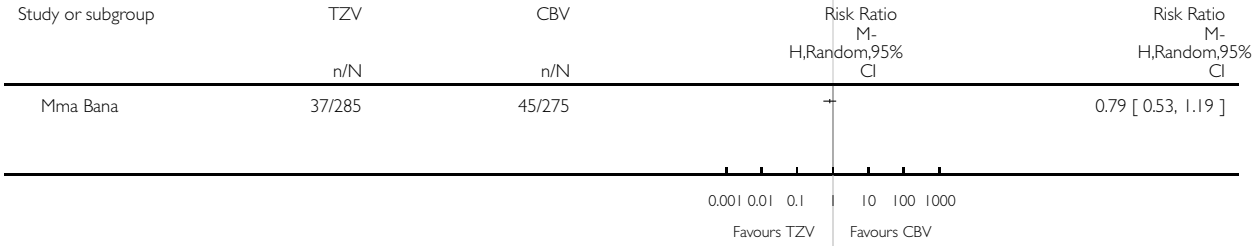


Analysis 5.6. Comparison 5 TRIPLE regimen vs TRIPLE regimen, Outcome 6 Number of babies weighing less than 2.5kg.

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

Comparison: 5 TRIPLE regimen vs TRIPLE regimen

Outcome: 6 Number of babies weighing less than 2.5kg

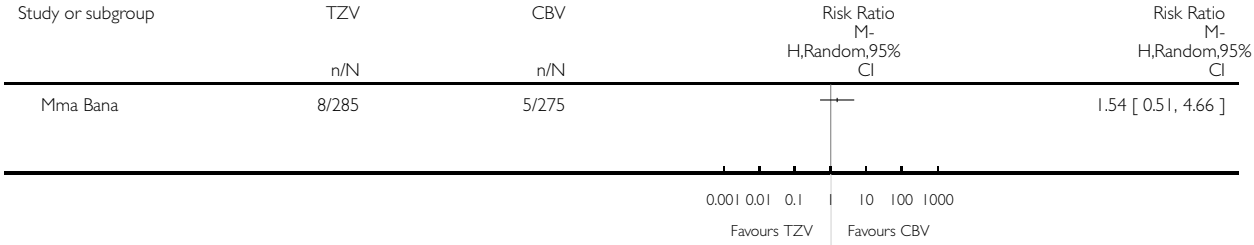


Analysis 5.7. Comparison 5 TRIPLE regimen vs TRIPLE regimen, Outcome 7 Stillbirth rates.

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

Comparison: 5 TRIPLE regimen vs TRIPLE regimen

Outcome: 7 Stillbirth rates



ADDITIONAL TABLES

Table 1. Search methods 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
#6	(DISEASE TRANSMISSION, VERTICAL)

Table 1. Search methods for MEDLINE (*Continued*)

#7	#4 OR #5 OR #6
#8	#1 AND #2 AND #3 AND #7

Table 2. Search methods 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

Table 2. Search methods for EMBASE (*Continued*)

#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 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))

Table 2. Search methods for EMBASE (*Continued*)

#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 3. Search methods 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*

Table 3. Search methods for AIDSearch (*Continued*)

#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 4. Search methods for NLM Gateway

Search Number	Strategy	Items found
#5	Search: ((((HIV INFECTIONS) OR HIV OR HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR (HIV INFECT*) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR ((HUMAN IMMUN*) AND (DEFICIENCY VIRUS)) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME))) OR (((ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR ((ACQUIRED IMMUN*) AND (DEFICIENCY SYNDROME)) OR (SEXUALLY TRANSMITTED DISEASES, VIRAL)))) AND ((((RANDOMIZED CONTROLLED TRIAL) OR (CONTROLLED CLINICAL TRIAL) OR (RANDOMIZED CONTROLLED TRIALS) OR	105

Table 4. Search methods for NLM Gateway (*Continued*)

	(RANDOM ALLOCATION) OR (DOUBLE-BLIND METHOD) OR (SINGLE-BLIND METHOD) OR (CLINICAL TRIAL) OR (CLINICAL TRIALS) OR (CLINICAL TRIAL) OR ((SINGL* OR DOUBL* OR TREBL* OR TRIPL*) AND (MASK* OR BLIND*)))) OR ((PLACEBOS OR PLACEBO* OR RANDOM* OR (COMPARATIVE STUDY) OR (EVALUATION STUDIES) OR (FOLLOW-UP STUDIES) OR (PROSPECTIVE STUDIES) OR CONTROL* OR PROSPECTIV* OR VOLUNTEER*))) AND ((MOTHER-TO-CHILD TRANSMISSION) OR (MOTHER TO CHILD TRANSMISSION) OR (ADULT TO CHILD TRANSMISSION) OR (ADULT-TO-CHILD TRANSMISSION) OR (MATERNAL TO CHILD TRANSMISSION) OR (MATERNAL-TO-CHILD TRANSMISSION) OR (VERTICAL TRANSMISSION) OR (DISEASE TRANSMISSION, VERTICAL) OR MTCT) Limit: 2007/01/01:2009/04/17	
#4	Search: ((((HIV INFECTIONS) OR HIV OR HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR (HIV INFECT*) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNO-DEFICIENCY VIRUS) OR (HUMAN IMMUNE-DEFICIENCY VIRUS) OR ((HUMAN IMMUN*) AND (DEFICIENCY VIRUS)) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME))) OR (((ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR ((ACQUIRED IMMUN*) AND (DEFICIENCY SYNDROME)) OR (SEXUALLY TRANSMITTED DISEASES, VIRAL)))) AND ((((RANDOMIZED CONTROLLED TRIAL) OR (CONTROLLED CLINICAL TRIAL) OR (RANDOMIZED CONTROLLED TRIALS) OR (RANDOM ALLOCATION) OR (DOUBLE-BLIND METHOD) OR (SINGLE-BLIND METHOD) OR (CLINICAL TRIAL) OR (CLINICAL TRIALS) OR (CLINICAL TRIAL) OR ((SINGL* OR DOUBL* OR TREBL* OR TRIPL*) AND (MASK* OR BLIND*)))) OR ((PLACEBOS OR PLACEBO* OR RANDOM* OR (COMPARATIVE STUDY) OR (EVALUATION STUDIES) OR (FOLLOW-UP STUDIES) OR (PROSPECTIVE STUDIES) OR CONTROL* OR PROSPECTIV* OR VOLUNTEER*))) AND ((MOTHER-TO-CHILD TRANS-	1197

Table 4. Search methods for NLM Gateway (*Continued*)

	MISSION) OR (MOTHER TO CHILD TRANSMISSION) OR (ADULT TO CHILD TRANSMISSION) OR (ADULT-TO-CHILD TRANSMISSION) OR (MATERNAL TO CHILD TRANSMISSION) OR (MATERNAL-TO-CHILD TRANSMISSION) OR (VERTICAL TRANSMISSION) OR (DISEASE TRANSMISSION, VERTICAL) OR MTCT)	
#3	Search: (MOTHER-TO-CHILD TRANSMISSION) OR (MOTHER TO CHILD TRANSMISSION) OR (ADULT TO CHILD TRANSMISSION) OR (ADULT-TO-CHILD TRANSMISSION) OR (MATERNAL TO CHILD TRANSMISSION) OR (MATERNAL-TO-CHILD TRANSMISSION) OR (VERTICAL TRANSMISSION) OR (DISEASE TRANSMISSION, VERTICAL) OR MTCT	30804
#2	Search: (((RANDOMIZED CONTROLLED TRIAL) OR (CONTROLLED CLINICAL TRIAL) OR (RANDOMIZED CONTROLLED TRIALS) OR (RANDOM ALLOCATION) OR (DOUBLE-BLIND METHOD) OR (SINGLE-BLIND METHOD) OR (CLINICAL TRIAL) OR (CLINICAL TRIALS) OR (CLINICAL TRIAL) OR ((SINGL* OR DOUBL* OR TREBL* OR TRIPL*) AND (MASK* OR BLIND*)))) OR ((PLACEBOS OR PLACEBO* OR RANDOM* OR (COMPARATIVE STUDY) OR (EVALUATION STUDIES) OR (FOLLOW-UP STUDIES) OR (PROSPECTIVE STUDIES) OR CONTROL* OR PROSPECTIV* OR VOLUNTEER*))	5051201
#1	Search: (((HIV INFECTIONS) OR HIV OR HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR (HIV INFECT*) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNO-DEFICIENCY VIRUS) OR (HUMAN IMMUNE-DEFICIENCY VIRUS) OR ((HUMAN IMMUN*) AND (DEFICIENCY VIRUS)) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME))) OR (((ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR ((ACQUIRED IMMUN*) AND (DEFICIENCY SYNDROME)) OR (SEXUALLY TRANSMITTED DISEASES, VIRAL)))	365531

Table 5. Search methods 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)

WHAT'S NEW

Last assessed as up-to-date: 17 January 2011.

Date	Event	Description
11 May 2011	New search has been performed	New searches done in 2009; comprehensive update.
11 May 2011	New citation required and conclusions have changed	Updated, conclusions changed.

HISTORY

Review first published: Issue 2, 1995

Date	Event	Description
29 October 2008	Amended	Converted to new review format.
8 November 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

For the 2009 update Nandi Siegfried and Liesl Grobler conducted the eligibility process. Nandi Siegfried and Lize van der Merwe extracted numerical data and checked these together. Nandi Siegfried extracted qualitative data and the risk of bias data about each new trial and this was checked by Peter Brocklehurst. Lize van der Merwe conducted the analysis for the new trial data and updated the analyses of the data from trials included previously. Nandi Siegfried revised the risk of bias data on all the trials included previously. All authors contributed to the interpretation and conclusions of the review and the writing of the final manuscript.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Biostatistics Unit, Medical Research Council, South Africa.
- South African Cochrane Centre, South Africa.

External sources

- World Health Organization, Switzerland.

#200123310. Systematic reviews and development of GRADE profiles, based on the 2008 WHO GRC guidelines, for the "WHO Guidelines on Antiretroviral Drugs for Treating Pregnant Women Living with HIV and Preventing HIV Infection in Infants - 2009 revision"

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans; Pregnancy