

What antiretroviral agents and regimens are effective in the prevention of mother-to-child transmission of HIV?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: **What antiretroviral agents and regimens are effective in the prevention of mother-to-child transmission of HIV?**

The **WHO Pocketbook of Hospital Care for Children** recommends that if an HIV infected woman becomes pregnant she should be provided with services including prophylactic antiretroviral drugs (and ART where clinically indicated), safer obstetric practices and infant feeding counseling and support.

Introduction:

UNAIDS estimates that around 640,000 children would have become infected with HIV in 2004, with over 90% of these infections being due to mother-to-child transmissionⁱ (MTCT). The WHO estimates a vertical transmission rate of 15-30% during pregnancy and delivery, with an additional 10-20% risk of transmission through breastmilkⁱⁱ. Antiretroviral (ARV) agents have been shown to significantly reduce MTCT of HIV in clinical trials over the past decade. Most regimens are simple and involve a relatively small number of drugs, making them useful in the resource-limited setting. ARV therapy is only part of a broader approach to MTCT, which also includes primary prevention of maternal infection, antenatal care, obstetric care and breastfeeding advice appropriate to local

conditions and resources. This review aims to summarise the evidence available for effective ARV use to prevent MTCT in resource-poor settings.

Methodology

The Cochrane Database of Systematic Reviews was searched and found to have a review examining directly this topicⁱⁱⁱ. The review was last updated in 2002, and so a further search for more recent systematic reviews was made using Clinical Queries in PubMed using combinations of search terms “antiretroviral”, “mother-to-child transmission”, “peripartum” and “HIV” or “human immunodeficiency virus”. This yielded three other reviews published since Cochrane which had relevance to the developing world setting. One was a meta-analysis^{iv}, another a review from the publication Clinical Evidence^v, and finally a recently published review in AIDS Reader^{vi}.

The meta-analysis pooled data from six randomised trials in Africa, and compared directly the efficacy of various antiretroviral regimens, controlling for potential confounders such as advanced maternal disease, low birth weight and breastfeeding.

Recent randomised controlled trials were identified using the *Search by Clinical Study Category* option in Clinical Queries, with the same search terms as above. Individual drug names were also used as search terms. Eight of relevance were found. In addition, references to trials documented as ongoing or incomplete at the time of the Cochrane review were followed.

Abstracts from all searches were read to determine relevance, and in most cases the original article was sourced to provide further information.

Results

Zidovudine (ZDV) monotherapy

The Cochrane review pooled data from four randomised trials of zidovudine (ZDV) versus placebo. One was set in USA/France (PACTG 076/ANRS 024)^{vii}, another in Thailand^{viii}, and two in Africa (CDC Côte d'Ivoire^{ix} and the ANRS 049 DITRAME trial in Côte d'Ivoire/Burkina Faso^x). Only women in the African trials breastfed their infants. The breastfed African infants had higher rates of transmission. The overall odds ratio for MTCT was 0.46 [95%CI: 0.35-0.60] at 6-8wks, when comparing the ZDV arms to the placebo arms.

The CDC Côte d'Ivoire trial tested antenatal (from 36wks gestation) and intrapartum ZDV against placebo in an identical regimen to that used in the non-breastfeeding Thai study. The ZDV group had MTCT rate of 16.5% at 3 months (cf. 26.1% in the placebo group). Efficacy (relative risk reduction) was thus 37%, as compared with 50% in the Thai study.

An additional week of postnatal ZDV treatment was given to mothers in the DITRAME trial to try to reduce early breastmilk transmission. This did not seem to confer any additional benefit.

Subsequent to the Cochrane review, 24 month follow-up data from the two African ZDV trials have been pooled and analysed^{xi}. The cumulative risk of MTCT at 24 months was 0.225 in the ZDV and 0.302 in the placebo group, significantly different, and representing a 26% reduction.

Another trial in a non-breastfeeding Thai population (PHPT-1) examined differing lengths of antenatal and neonatal ZDV^{xii}. The long-long (mother from 28 weeks gestation and infant until 6 weeks), short-long (35 weeks gestation to 6 weeks postnatal) and long-short (28 weeks gestation to 3 days postnatal) arms were found to be equivalent but better than the short-short (35weeks gestation to 3 days postnatal) arm. The odds ratio for MCTC in the short-short group compared to long-long group was 2.33 [95% CI: 1.16-4.68]. The study concluded that longer antenatal therapy with ZDV appears to be more

effective than shorter antenatal therapy, but that longer postnatal therapy does not appear to confer benefit.

Combination therapy

The Cochrane review examined two trials using a combination of ZDV and lamivudine (3TC). One was conducted in France among a non-breastfeeding group of women^{xiii}, and the other took place in South Africa/Tanzania/Uganda where 74% of infants were breastfed (the PETRA trial)^{xiv}.

In the French study (ANRS 075), both drugs were given from 32 weeks gestation, and to the infant until 6 weeks postpartum. These infants were compared to historical controls from the PACTG 076/ANRS 024 trial (and subsequent ZDV-exposed cohort followed in France). Adding 3TC in this way reduced transmission rates (at 18 months) from 6.8% to 1.6%. Almost 40% of women who received the combination longer than four weeks tested positive for resistant virus to 3TC (M184 mutation).

In the PETRA trial three arms of combination ZDV+3TC were compared with placebo: antenatal (from 36 weeks) plus intrapartum plus postnatal mother and baby for 1 week; intrapartum plus postnatal; intrapartum alone. The results of this trial have been published since the last Cochrane review. At six weeks, the efficacy of the first arm compared with placebo was 63%, while that of the second arm as 42%. There was no significant risk reduction in the intrapartum only arm. At 18 months, only the first arm sustained a significant risk reduction, dropping to 33% (MTCT rate 14.1% compared with placebo 22.2%). This study had lower rates of resistant virus isolation than the French study, presumably because of shorter duration of 3TC exposure.

Nevirapine (NVP) vs ZDV or ZDV/3TC

The Cochrane review described one randomised trial in Uganda (HIVNET 012^{xv}) which compared NVP (one dose in labour, and one to the infant within 72 hours of birth), to intrapartum ZDV plus 1 week of ZDV treatment to the infant. NVP was found to be superior than ZDV in these intrapartum-postpartum regimens (OR 0.51 [95%CI 0.33-0.71]. At 14-16 weeks, 13% of the NVP infants were HIV positive, compared with 25% of the ZDV group. At 18 months follow-up,

the rates were 15.7% and 25.5% respectively^{xvi}. This represents a 41% efficacy [95%CI: 16-59] in terms of HIV infection, but there was no difference in overall mortality which may reflect the effect of maternal or other family HIV burden.

In South Africa, the SAINT trial^{xvii} tested NVP (one dose intrapartum, and one postpartum to both mother and infant) against combined ZDV-3TC (intrapartum and 1 week postnatally to mother and infant). There was no significant difference between the two arms (12.3% vs 9.3% at 8 weeks). The extra dose of NVP postnatally to the mother did not appear to reduce transmission when compared with the regimen as used in HIVNET 012.

NVP in addition to ZDV regimens

The PHPT2^{xviii} trial in non-breastfeeding women in Thailand examined the effect of adding NVP (intrapartum, or intrapartum plus single dose neonatal) to a ZDV regimen (from 28 weeks gestation, with 1 week neonatal treatment). The addition of NVP significantly reduced transmission rates (2.8% for single dose intrapartum and 1.9% intrapartum and neonatal dose) compared with ZDV alone (6.3%). The additional benefit of the neonatal dose was not statistically significant, although there may not have been sufficient power to detect a difference.

In Côte d'Ivoire the ANRS1201 DITRAME PLUS^{xix} open-label study compared ZDV+NVP with ZDV+3TC+NVP. During one study period, women were given 4 weeks of antenatal ZDV then intrapartum ZDV+NVP and infants given a single dose of NVP and one week of ZDV. In the second study period, women commenced ZDV+3TC from 32 weeks and also received these drugs with single dose NVP intrapartum. Neonatal therapy was the same. The two groups were compared with each other, and also with the original ANRS049 DITRAME cohort (ZDV alone). The MTCT rate at 6 weeks was 6.5% in the ZDV+NVP group, a significant 72% reduction compared with the ZDV only group [95%CI: 52-88%]. The rate in the ZDV+3TC+NVP group was 4.7% but not significantly different from the ZDV+NVP cohort. Although only 50% of the DITRAME PLUS women breastfed, there were no differences in transmission rates between breastfed and formula-fed infants at six weeks of age.

Adding the HIVNET012 NVP regimen to situations where women are already on standard antiretroviral therapy was of no benefit in a multicentre trial in industrialised countries, where infants were not breastfed and the caesarean section rate was 34%^{xx}.

A randomised open-label trial in Malawi^{xxi} examined the effect of adding a week of neonatal ZDV treatment to HIVNET012 NVP regimen. The additional ZDV did not confer any significant benefit at 6 weeks, with HIV infection rates at 14.1% and 16.3% in the NVP and NVP/ZDV groups respectively.

Neonatal ARV prophylaxis only

In situations where no antenatal care is received, or antepartum or intrapartum treatment is not possible, neonates can be given ART as a form of postexposure prophylaxis.

In Malawi, the NVAZ trial^{xxii} looked at neonatal treatment with single dose NVP, or single dose NVP plus one week of ZDV (ie. no treatment to mother) in a breastfeeding population. Overall MTCT rates at 6-8 weeks were 15.3% with combination therapy, and 20.8% with NVP alone (p=0.03). The difference was not significant in the subgroups where mothers had high viral loads (>100,000 copies/mL).

A South African trial^{xxiii} compared single dose neonatal NVP with six weeks of ZDV in infants whose mothers had received no ART. Overall MTCT was 16.3% at 12 weeks. Infection rates were not significantly different between the two groups, however on multivariate analysis, ZDV was less protective (Odd Ratio: 1.8, [95%CI: 1.1-3.2]). In this trial, less than 20% of infants were breastfed and 20% were lost to follow-up.

In Rwanda and Uganda, the SIMBA trial^{xxiv} is investigating whether ongoing infant prophylaxis during breastfeeding can reduce postnatal transmission. The infants were randomised to receive either NVP or 3TC. Mothers in both groups received ZDV and didanosine from 36 weeks until 1 week post-delivery. Interim results suggest the postnatal transmission rate can be reduced by both regimens.

Discussion

The lowest rates of MTCT were achieved by combining antenatal, intrapartum and postpartum ARV therapy. The PHPT2 trial in a non-breastfeeding Thai population (ZDV from 32 weeks + intrapartum NVP + neonatal NVP and ZDV for 1 week) reduced MTCT to less than 2%. The DITRAME PLUS study (antenatal ZDV with or without 3TC + intrapartum NVP + neonatal NVP dose with 1 week of ZDV) showed MTCT rates in a 50% breastfed population could be brought below 7%.

Most of the randomised trials reviewed above were undertaken in developing countries. There were still variations in confounding factors between the trials, such as breastfeeding rates and maternal disease progression, which make direct comparisons between some of the trials difficult. The meta-analysis of African studies provides adjusted odd ratios adjusting for various confounders. It found that ZDV and 3TC from 36 weeks, intrapartum and postpartum (as with the PETRA long arm) was more effective than the two-dose NVP regimen (adjusted odd ratio 0.39, $p < 0.0005$). Recent trials such as the DITRAME PLUS trial were not included in the meta-analysis.

Resistant virus has been isolated in patients treated with single agent antiretrovirals, particularly with NVP and longer courses of ZDV. The clinical significance of this is still somewhat unclear.

Summary

Antenatal therapy with ZDV or ZDV+3TC, intrapartum NVP, and postnatal NVP or ZDV have all been shown to be effective in reducing MTCT of HIV (Grade A evidence). Combining some of these elements has improved efficacy.

Most benefit is gained by combining:

- antenatal therapy with ZDV (with or without 3TC), preferably before 36 weeks,
- NVP (1 dose intrapartum, 1 dose neonatal within 72 hours) and
- 1 week of neonatal ZDV.

In situations where no antenatal therapy is possible, a single intrapartum NVP dose plus a single neonatal dose administered within 72 hours

should be given. Intrapartum ZDV+3TC plus one week postpartum treatment to mother and baby have similar efficacy.

If no intrapartum NVP was given, then a single neonatal dose is still effective, preferably with one week of ZDV.

If NVP is not available, neonatal therapy with ZDV is effective (6 weeks appears to be better than 1 week) though inferior.

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