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

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Short-course zidovudine and single-dose nevirapine are effective therapies for reducing mother-to-child transmission of HIV. Implementation of this intervention would require antenatal care services to be available and utilized early enough to identify HIV-positive mothers.

RHL Commentary by McIntyre J

1. EVIDENCE SUMMARY

The use of antiretroviral therapies to reduce mother-to-child transmission of HIV (MTCT) is an important advance in preventing HIV infections in children. In well-resourced settings, treatment has evolved from initial monotherapy with zidovudine (ZDV) to the use of combination antiretroviral therapy in pregnancy. Although this approach has not been subject to a randomized trial of efficacy, the reduction of transmission rates to below 2% has made it the standard of care in these settings. In poorer countries, combination ART is not available for most people and research has focused on investigating shorter, more feasible and less expensive antiretroviral regimens. This review includes randomized controlled trials of any antiretroviral regimen aimed at decreasing the risk of mother-to-child transmission of HIV infection (MTCT) compared with placebo or no treatment, and randomized controlled trials comparing two or more antiretroviral regimens aimed at decreasing the risk of MTCT (1). The review does not include those trials designed to investigate the interruption of postnatal transmission through breast milk. Eighteen trials, including more than 14,000 participants in 16 countries were eligible for inclusion in the review, conducted over the period 1991 to 2006, which met the inclusion criteria. The median trial sample size was 795, ranging from 50 (2) to 1,797 participants (3). As the design and strategies of these trials vary considerably, the reviewers divided the trials into several sections.
The first section considered trials of antiretroviral therapy vs. placebo in breastfeeding populations (three: DITRAME (4), RETRO-CI (5); PETRA (3)) and in non-breastfeeding populations (three: PACTG 076 (6); Limpongsanurak 2001(7); Thai-CDC (8)). These trials showed the efficacy of long course zidovudine (ZDV) in reducing transmission by 66% (6), and varying levels of efficacy with shorter regimens of ZDV alone or ZDV with lamivudine (3TC). Of the early short course regimens studied, the “PETRA A” regimen using ZDV and 3TC had the greatest efficacy at 6 week (63%) but this had diminished by 18 months (33%) (3). Since a significant decrease in the risk of MTCT has been demonstrated in these trials with antiretroviral use, compared to placebo, it is not necessary or ethical to conduct further placebo controlled trials. The other twelve studies therefore examine either different dosing strategies of the same drug, or compare different antiretroviral regimens against each other.

This is a complex task, given the range of comparison regimens which are different in all of the trials. Most of these were investigated at a time when researchers were trying to find effective and feasible alternatives to longer course antiretroviral therapy, and so were not designed to compare a new treatment against a “gold standard” one, but rather to find new and feasible options. Most trials comparing longer courses of zidovudine (ZDV) or ZDV/3TC have shown an advantage to longer treatment compared to shorter, although two smaller studies did not demonstrate this (9, 2).

The trials of short course antiretroviral regimens have shown varying efficacy in preventing transmission. Nevirapine, used as a single dose to mother and a single dose to the child (HIVNET 012), reduced transmission by 40% compared to a very short ZDV regimen, an effect which was maintained out to 18 months (10, 11). The longest arm of ZDV/3TC in the PETRA study (PETRA “A”) had an efficacy of 63% compared to placebo at six weeks, although this relative efficacy was not maintained at 18 months in this study (3). The reviewers note in the review that this is one of the most effective regimens.

None of the trials showed any safety concerns for the use of short course antiretrovirals, but the issue of the selection of resistant virus with the use of nevirapine or lamivudine in non-suppressive regimens is raised by the reviewers and remains a concern. The reviewers point out that in developed countries, treatment of the mother with triple antiretrovirals in pregnancy has become the standard of care and that this has dramatically reduced MTCT rates in these settings.

There are two areas of concern in the review which may mislead the reader. The first is in the review of the PHPT-2 trial (12). This trial investigated the addition of nevirapine, as a single dose to mother, or to mother and baby, to a short course ZDV regimen. The original trial design included a “placebo” arm, in which no additional nevirapine was added to the ZDV regimen for mother and baby. This arm was stopped after a pre-planned interim review by the Data Safety and Monitoring Board, because the as-randomized Kaplan–Meier estimates of transmission rates were 1.1 percent (95 percent CI, 0.3 to 2.2) in the nevirapine–nevirapine group and 6.3 percent (95 percent CI 3.8 to 8.9) in the placebo–placebo group (P<0.001). The very low transmission rates achieved with the addition of maternal (2.8%; 95% C.I. 1.5 to 4.1) or maternal and infant (1.9%; 95% C.I. 0.9 to 3.0) single doses of NVP to the ZDV regimen were confirmed in the final analysis. The reviewers correctly note that, where mothers were routinely receiving ZDV in the last trimester of pregnancy and their babies were receiving ZDV in the first week of life, the addition of a nevirapine dose to mother compared to mother and baby NVP dosing showed similar reductions in transmission, but do not comment on the significant reduction with either of these compared to ZDV alone in the first part of the study. These transmission rates of around 2% in a non-breastfeeding population are similar to those reported with the use of combination therapy, although no head-to-head comparison has been done. On this basis, this regimen is the first line recommendation in the WHO 2006 PMTCT guidelines, and its exclusion from comment in a review which sets out to determine which antiretroviral therapies may “achieve a clinically useful decrease in transmission risk”, may appear to conflict with these recommendations. The reviewers’ recommendation that either a combination of ZDV/3TC or “single dose” nevirapine (HIVNET 012), may be the most effective regimens, should be seen in the light of their exclusion of the full PHPT-2 findings.

The second concern is about the recommendation for mothers who present late for delivery. Two studies of
Post-exposure prophylaxis are reviewed: the first compared a single dose of NVP immediately after birth to a single dose nevirapine immediately after birth and ZDV for one week to the infant (Taha 2003) (13), and showed a significantly reduced rate with the NVP plus one week of ZDV compared to NVP alone. The second study compared single dose nevirapine to six weeks of ZDV to the infant (Gray 2005), and showed similar rates of transmission with both of these interventions (14). The reviewers correctly describe the Taha study in the review, but in the discussion, recommendations and abstract state that “Where HIV infected women present late for delivery post-exposure prophylaxis for the infant with a single dose of NVP immediately after birth plus ZDV for the first 6 weeks of life is beneficial” As neither of the trials investigated such a regimen, the basis for this recommendation is unclear, and policy makers should be aware of this.

The reviewers note that the long term implications of the emergence of resistant mutations following the use of these short course regimens require further study. Emerging data on the potential adverse effect of this resistance on future treatment options for women suggests that this should form part of the considerations for choosing a regimen, particularly the longer ZDV/3TC combination regimen.

2. RELEVANCE TO UNDER-RESOURCED SETTINGS

2.1. Magnitude of the problem

An estimated 530,000 children were infected with HIV in 2006, predominantly through mother-to-child transmission (MTCT) (15). More than 85% of HIV-infected pregnant women are in sub-Saharan Africa (16). There has been significant progress in developing and implementing treatment strategies, but, despite this, UNAIDS estimated that in 2006 less than 8% of all pregnant women globally, and less than 6% in sub-Saharan Africa, were offered access to HIV diagnosis and prevention services, and that only 9% of HIV-infected women received an antiretroviral regimen for PMTCT. In well resourced settings, the dual approach of starting ongoing combination antiretroviral therapy (ART) in pregnancy for those women who qualify for it, and using ART through the pregnancy and stopping post-partum for those with higher CD4 counts, combined with the avoidance of breastfeeding, has become the routine management in pregnancy. This has resulted in a drop in MTCT rates to below 2% (17). In most under-resourced settings, this combination therapy has been unavailable to date, and this lack of access is reflected in the estimates of transmission: a rate of 26% is estimated in the thirty-three most affected countries – a ten fold increase over the rates now seen in better resourced settings.

2.2. Applicability of the results of the Cochrane Review

The prevention of MTCT is a priority for improving child survival in many countries in Africa and Asia. The review examines the complex array of trials which have attempted to find effective and feasible short course antiretroviral regimens. These are important for programme managers and clinicians in under-resourced settings, where the combination antiretroviral therapies used in richer countries may not be available.

Of these, the “single dose” nevirapine regimen, of a dose of NVP to the mother at the onset of labour and one dose of NVP syrup to the infant, has become the most widely implemented strategy, reaching more than a million women and infants since 1999. As the review demonstrates, this is an effective intervention, but there are more efficacious antiretroviral combinations. Few low-resourced country programmes have yet been able to extend beyond single dose NVP, or even to achieve good coverage with this. Estimates of the proportion of HIV-infected pregnant women receiving antiretroviral prophylaxis in 2005 varied from under 1% to 54% in sub-Saharan Africa, with overall regional coverage of 11% (8%-15%). Coverage in Eastern Europe and Central Asia is estimated at 75% (38%-95%) in Eastern Europe and Central Asia, 24% (13%-46%) in Latin America and the Caribbean, 5% (3%-10%) in East, South and South-East Asia, and <1% in
North Africa and the Middle East (16).

The initial focus of PMTCT programmes was solely on the prevention of transmission, where more complex therapy was not an option for most programmes. The availability of antiretroviral therapy has changed dramatically since 2002. WHO now estimates that more than two million people in low and middle income countries were receiving antiretroviral therapy by December 2006 – approximately 28% of the estimated 7 million in need of ART (16). With this increasing access to antiretroviral therapy, the provision of PMTCT services in low-resourced settings needs to be seen more as an integral part of the continuum of care and treatment for HIV infected women. A new paradigm for PMTCT services is required in these settings, with a baseline short course treatment regimen for those who do not yet require ART treatment and access to combination treatment for those who do. This makes it important to identify pregnant women in need of ART and to initiate therapy as soon as possible in pregnancy, as the use of effective ART in these women will both benefit their own health and be the best prophylaxis against MTCT.

The 2006 WHO guidelines recommend that women with CD4 counts less than 200/mm³ or Stage 3 or 4 clinical disease start and continue ART. In addition, the guidelines recommend starting ongoing ART in women with CD4 counts between 200 and 350/mm³ where this is feasible in the services (18).

The research reviewed in the Cochrane review should be able to inform the choice of effective short course regimens, although, as noted above, the current review appears to differ in recommendations from international guidelines. The antenatal zidovudine with intrapartum nevirapine regimen (PHPT-2) has become the first line recommendation in the WHO PMTCT guidelines for low resourced settings (18), on the basis of the reduction in transmission to around 2% in the original study, and on data from the DITRAME 1201/1202 cohort studies in Côte d'Ivoire, which showed a 72% reduction with the joint regimen, compared with ZDV alone (95% CI, 52-88%) [COHORT] (19). Where women present too late in pregnancy for this approach, where no other antiretrovirals are available or in emergency settings, the single dose nevirapine regimen can still provide some protection against MTCT, as can the other short term strategies reviewed in the Cochrane review.

Decisions on the choice of antiretroviral regimen for PMTCT need to take into account efficacy and potential adverse events. The studies reviewed confirm the short term safety of the use of short course antiretroviral regimens, across a range of geographical settings. Concern has also emerged about the potential adverse effect of the selection of viral resistance following use of short course regimens, based in large part on resistance analyses from several of the initial RCT’s including HIVNET 012, NVAZ and PETRA. The two drugs most likely to select for resistance in these regimens are nevirapine and lamivudine (3 TC), both of which require only one point mutation in the viral codon to confer resistance. The use of the drugs in virologically non-suppressive regimens, coupled with the long half life of nevirapine, facilitates the selection of resistance. The selection of non-nucleoside reverse transcriptase inhibitor resistance (NNRTI) following NVP use, either alone or in combination has now been reported from a number of studies, ranging from 20% to over 60% of exposed women, depending on the viral subtype and timing of resistance testing (20, 21). When more sensitive techniques, such as allele specific real time PCR and LigAmp are used, resistant virus can be detected in over 80% of exposed women (22, 23). Although levels of resistant mutations drop with time, persistence can be demonstrated with these techniques for several years in a minority of women (24). One randomized controlled trial has demonstrated a partial protective effect of the addition of four or seven days of ZDV/3TC postpartum to the intrapartum NVP regimens to reduce the selection of resistance (25), and this is now included in the WHO PMTCT guidelines.
Reported data now suggests that there is little impact on the efficacy of nevirapine used in subsequent pregnancies (26) [Cohort]. There has been more concern about the impact on future treatment options for mothers, following initial data from Thailand that suggested a reduced virological response in NVP-exposed women (27). A study from Botswana, following up women initially randomized to a trial in which they received NVP or placebo as part of a PMTCT regimen, showed that those NVP-exposed women who started NVP-containing ART less than six months after exposure to NVP for PMTCT were more likely to fail the ART regimen at six and twelve months than unexposed women.

Addition data has emerged on the effect of 3TC resistance with ZDV/3TC regimens used for more than a week. Data from a sub-study of the PETRA study showed that 12% of women receiving the PETRA “A” regimen had detectable 3TC resistance (29). A higher rate of 14.6% is described in women from a prospective cohort in Abidjan, and subsequent antiretroviral treatment response was compromised in these women [COHORT] (30), leading to recommendations that this dual therapy ZDV/3TC regimens should be used with caution.

### 2.3. Implementation of the Intervention

In order to implement the use of antiretroviral regimens for the prevention of mother-to-child transmission of HIV, antenatal care services must be available and utilized early enough to identify HIV-positive mothers to start treatment. These services must incorporate voluntary counselling and testing services for HIV and there must be acceptance of HIV testing by pregnant women in order to identify those infected. The entry point for access to PMTCT interventions is HIV testing. In some settings, uptake of testing has been dramatically improved by offering “routine” testing to pregnant women – rather than putting the onus on the woman to decide on testing. As an example of this, in Botswana, this approach in one region increased the proportion of HIV-infected women who knew their HIV status from 47% to 78% and the percentage receiving PMTCT interventions increased from 29% to 56% (31). There have been suggestions that nevirapine is an effective and inexpensive intervention that could be given to all women in labour in high prevalence settings. This approach has not been evaluated and many concerns have been raised, including the rights of women to know their HIV status, development of resistance, effect on infant feeding practices and the loss of opportunities for HIV prevention education in the antenatal setting.

In order to fully implement an integrated strategy of providing ART for women with low CD4 counts or clinical symptoms of AIDS and a “dual therapy” regimen for other HIV-positive women, the services need to be able to undertake clinical assessment and do a baseline CD4 count. This is not yet available in antenatal services in less-resourced settings. Drug supply logistics must be in place to provide ART for pregnant women and their children, as does access to diagnostic HIV testing for exposed children.

### 3. Research

Research is in progress, and more is required, on the efficacy of antiretroviral therapy in reducing the risk of transmission of HIV through breastfeeding. While preliminary results appear encouraging, this remains a priority research area for low-resourced settings where replacement feeding may not be feasible or affordable. Additional research is needed on the impact of PMTCT regimens containing NVP or 3TC on future treatment options for mothers and children, and the impact of the selection of drug resistant mutations. There are also some concerns about the use of nevirapine in combination antiretroviral regimens in women with high CD4 counts (although not about the use of “single dose” nevirapine regimens), as this has been associated with an increased rate of hepatotoxicity. This may become more of an issue as antiretrovirals become more available and the use of combination ART only for PMTCT purposes becomes more common in less-resourced settings. There is also a need to investigate alternative regimens, particularly the use of tenofovir alone or in combination as a potential strategy for PMTCT.
References


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