

Prophylactic regimens to prevent mother-to-child transmission of HIV and their effect on future therapy

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The use of combination antiretroviral treatment for the prevention of mother-to-child transmission (PMTCT) of HIV has been extremely successful in reducing pediatric HIV infection and is the standard of care in well-resourced settings. In most high-prevalence, less-resourced settings, short-course, single or combination antiretroviral regimens have been the only available PMTCT interventions. Concerns have emerged around the potential impact of viral resistance selected following the use of nevirapine as single-dose or in short-course combination regimens, and the use of lamivudine in short-course dual therapy regimens. Early data have suggested a reduced response to non-nucleoside reverse transcriptase inhibitor-containing treatment regimens where these are started less than 6 months after pregnancy exposure to nevirapine, but no difference in clinical or virologic outcome if initiated more than 6 months after this PMTCT exposure. Treatment response to lamivudine-containing regimens may be diminished following nonsuppressive zidovudine and lamivudine combination PMTCT regimens.

As with all interventions in pregnant women, the marked immediate benefits of antiretroviral prophylaxis for the prevention of mother-to-child transmission (PMTCT) of HIV need to be balanced against potential harm to either the mother or infant. While antiretroviral use, either as single drug or in combination therapy, has been shown to be safe for mother and baby in the short term, there are fewer data on the potential longer-term impact of the use of antiretroviral for PMTCT. In well-resourced settings, women in need of antiretroviral therapy (ART) will generally be able to access it during pregnancy and continue therapy postpartum, while those who do not yet need ongoing treatment will be given a fully suppressive three-drug regimen for PMTCT, stopping shortly after delivery. In Africa and Asia, where most HIV-infected women live, this level of treatment is not yet available to most women; PMTCT interventions reach less than 10% of HIV-infected women in these settings [1] and are generally based on single-dose nevirapine (sdNVP), or single or dual short-course ART. These simpler regimens are less effective in reducing MTCT than three-drug regimens, but have facilitated the expansion of PMTCT programs in poor settings [2]. When they were originally introduced, there was very little access to ART in these regions, but this has changed dramatically over the past 5 years, with the WHO estimating that there were more than 2 million people receiving ART in low- and middle-income countries by December 2006, and

that women were in the majority in treatment programs in many African settings [1]. As treatment access has increased, the potential impact of short-course PMTCT regimens on future treatment options has become more of a concern, given the very large number of HIV-infected women exposed to prophylactic regimens. Single-dose nevirapine, the most common of these, has been used in well over a million women since its introduction in 1999, and should there be a serious adverse impact on future treatment options for women or their HIV-infected children, this could pose a major public-health problem.

Possible impact of mother-to-child transmission prophylaxis on future treatment options

Prophylactic triple-combination therapy is used for most HIV-infected pregnant women in well-resourced settings. Experience from the USA and Europe suggests that this approach is extremely effective, reducing MTCT to less than 2%, and that it is safe in the short term [3–5]. The use of this approach does not appear to adversely affect future maternal prognosis. An observational cohort study in the USA has shown that pregnancy was associated with a lower risk of disease progression in women followed from 1997 to 2004, and one possible explanation for this may be a beneficial interaction between pregnancy and short-term ART [6].

Keywords: antiretroviral therapy, HIV, lamivudine, mother-to-child transmission, nevirapine, PMTCT, pregnancy, resistance, women

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The major impact that PMTCT prophylactic regimens may have on future treatment is through the selection of viral resistance during the use of an incompletely suppressive regimen. HIV replicates inaccurately but extremely rapidly, resulting in a high risk for mutant viruses, some of which may be drug resistant. In the presence of a selection pressure (antiretrovirals), these resistant mutants predominate. This is less likely to happen with zidovudine (ZDV) regimens, where the selection of resistance requires 3–6 months of therapy and multiple mutations. Protease inhibitor resistance is also unlikely to arise following short-course three-drug therapy for PMTCT, and protease inhibitors have not been used alone for this indication. By contrast, both nevirapine and lamivudine (3TC) are of more concern, as they require only a single-point mutation in the viral genome to confer resistance, and this is much more likely to arise from PMTCT use when viral loads are incompletely suppressed and the duration of therapeutic effect is short. Experience with emtricitabine in pregnancy is limited to date. Several studies have shown that the success of subsequent non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART is diminished where there is emergence of demonstrable nevirapine-resistance mutations after a ‘failing’ chronic nonsuppressive antiretroviral regimen, and that this can also happen when only minority populations of NNRTI-resistant virus are detectable [7–9]. It has been argued that the length of nevirapine treatment may affect the later level of phenotypic resistance to efavirenz (a drug in the same class of NNRTI as nevirapine). The use of nevirapine for less than 28 days as part of ART was not associated with an increased risk of treatment failure on a subsequent efavirenz-containing regimen in the HIV Outpatient Study [10]. One interpretation of this may be that the use of single-dose nevirapine may be less likely to affect future treatment [11].

Nevirapine-based PMTCT regimens

The ease of administration, low cost and absence of serious adverse effects of nevirapine as a single dose at the onset of labor for mothers and one dose to newborn infants has enabled massive expansion of PMTCT services in low-resourced settings. Since the initial description in 1999 [12], the regimen has become the mainstay of PMTCT programs, especially in Africa. The manufacturer’s donation program has supplied over a million maternal and infant doses

up to 2006, in addition to the many hundreds of thousands of women and their children who have received it through other programs [101]. More recently, the results of the Perinatal HIV Prevention Trials (PHPT-2) study in Thailand have demonstrated transmission rates of 2% in a nonbreastfeeding population with the addition of the single-dose nevirapine regimen to a base regimen of zidovudine given from 28 weeks gestation [13]. This combined use of ZDV and peripartum NVP has become the first-line recommendation in the 2006 WHO guidelines for PMTCT, ensuring the continued use of nevirapine for this indication [14].

Nevirapine, an NNRTI, has several properties that make it well suited for the prevention of MTCT. It is a potent antiretroviral agent, rapidly absorbed after oral administration and widely distributed in the body, with fast and efficient placental crossing and distribution into breast milk [15,16]. It also has a long half-life, making it suitable for single-dose administration in the pregnancy setting, with a median half-life of 61.3 h [17], although significant levels of nevirapine persist for up to 20 days following the single dose given in labor [18,19]. The use of single-dose NVP has been shown to have minimal side effects [12,20]. By contrast, symptomatic hepatotoxicity and fatal hepatic events have been described more commonly when NVP is used as part of combination ART in women with CD4⁺ cell counts above 250/mm³ [21], leading to recommendations that NVP-containing combination therapy should be used with caution in this group [102].

A longer-term concern is the selection of NNRTI-resistant viral variants following the use of NVP for PMTCT. The long half-life of the drug, which essentially results in prolonged NVP monotherapy, and the low genetic barrier for viral resistance, requiring only one point mutation in the viral codon to confer resistance to NVP and other NNRTI drugs, contribute to the high rates of selection of resistant viral variants. This emergence of resistance has now been well described in a number of settings following single-dose NVP alone, with rates in mothers ranging from 15–75% using standard population sequencing techniques (Table 1) [22–27]. The selection of resistant virus has also been described when NVP is used in conjunction with other antiretrovirals for PMTCT. Firstly, with the addition of intrapartum NVP to ZDV started earlier in pregnancy, 28.4% (95% confidence interval [CI]: 18.4–40.1%) of mothers in the DITRAME-plus

Table 1. Reported rates of NNRTI resistance, detected by standard genotyping, following nevirapine PMTCT regimens.

Regimen	Maternal administration	Reported NNRTI resistance rates with standard genotyping (%)
Single-dose nevirapine (NVP)	Intrapartum NVP	15–75
Single-dose NVP with 4 or 7 days zidovudine (ZDV) + lamivudine (3TC)	Intrapartum NVP + ZDV/3TC Postpartum ZDV/3TC	10–13
Single-dose NVP with antepartum zidovudine	Antepartum ZDV Intrapartum NVP	28–32
Single dose NVP with antepartum zidovudine and lamivudine, and three days postpartum zidovudine + lamivudine	Antepartum ZDV/3TC Intrapartum NVP 3 days postpartum ZDV/3TC	1
NVP containing triple antiretroviral regimen stopped postpartum	Antepartum HAART Intrapartum HAART	13

study [28], and 32% (95% CI: 25–38%) of mothers in the PHPT-2 study [29] had detectable resistant virus. Secondly, the use of short-course NVP-containing ART for MTCT prophylaxis may also carry a resistance risk, with detectable resistance seen after pregnancy in 5/39 (13%) women in a Dublin (Ireland) study [30]. In the ACTG 316 study, where single-dose NVP was added to standard antiretroviral regimens in pregnant women, 15% (95% CI: 8–23%) of women developed an NNRTI-resistance mutation by 6-weeks postpartum [31], but it should be noted that 23% of pregnant women included in this study received ZDV monotherapy during pregnancy, and that only 52.3% of them had suppressed viremia (HIV viral load below 400 copies/ml) at delivery. The risk of selection of resistant mutations following NVP use is influenced by maternal CD4⁺ cell count, viral load and viral subtype [32]. Differences between subtypes have been shown with detectable resistance rates at 6–8-weeks postpartum of 69% in subtype C, 36% in subtype D and 19% in subtype A virus, and with multiple mutations more likely to be present in subtype C [33]. As most infections in the highest prevalence countries in southern Africa are subtype C, this increased susceptibility is alarming. The proportion of women and infants with detectable resistance declines over time after the dose in labor [34], and the rate of decline may differ between viral mutants, with maternal K103N mutations persisting longer than other mutations [35].

Standard population genotyping techniques require at least 10–20% of the viral population to have the mutation for detection, and may thus underestimate the true selection of resistant variants [36]. More sensitive allele-specific techniques, such as real-time PCR and LigAmp, have

shown that the resistant virus is present in up to 80% of women, and that it may persist at a low level for a year or longer [37–39]. The addition of 4–7 days of ZDV and 3TC following intrapartum NVP, to cover the ‘tail’ of the long NVP half-life, has been shown to reduce the prevalence of NNRTI-resistant virus from 60 to approximately 10% [40]. Similarly, a low rate of NNRTI resistance of 1.14% (95% CI: 0.03–6.17%) was also seen in the DIT-RAME-plus study, where women received ZDV and 3TC from 32-weeks gestation and for 3 days postpartum, with intrapartum NVP, although 3TC-resistant mutations were found in 8.33% (95% CI: 3.66–15.7) [28]. A similar 7–10-day course has been shown to be effective in reducing the development of resistance when an NVP-containing chronic-treatment regimen is interrupted [41]. A number of trials are in progress to investigate alternative PMTCT ‘tail’ regimens, with either longer treatment or other antiretrovirals to determine the optimal approach to reduce the risk of selection of NNRTI resistance.

HIV-infected infants exposed to peripartum single-dose NVP also have a high rate of selection of resistant variants, ranging from 20 to 87% [26,34,42,43]. The patterns of mutation seen in infants differs from those in mothers, with predominantly Y181C mutations and less K103N detected [44]. In a South African study of 53 HIV-infected infants exposed to the HIV-NET 012 regimen, 24 (45.3%) had detectable resistance at their first visit, with the most frequent mutations being Y181C (75%), K103N (25%) and Y188C (12%) [34]. Only two of 42 infants with resistance identified before 12 weeks of age shared identical resistance mutations with their mothers, suggesting infant-resistant mutations arise largely *de novo* in the infant,

with a smaller proportion transmitted from their mothers. Of concern was the finding that, by 18 months, 11 of 24 infants with resistance in this study had died and one still had detectable Y181C mutations. While resistant variants also appear to decrease with time in infants when measured by population sequencing, there is little information regarding the persistence of low levels of resistant virus in infants, although NNRTI-resistant virus was found archived in the resting CD4⁺ T cell latent reservoir in NVP-exposed infants [45].

Despite the accumulating knowledge on the selection and persistence of NNRTI-resistant virus following NVP exposure, the long-term relevance of this for future treatment is not completely clear. There are three likely scenarios where resistance may be of harm to mothers and their infants. Firstly, when they require ART themselves, secondly, if NNRTI resistance is transmitted to their sexual partners, and thirdly, if it impacts on the effectiveness of NVP used for a second pregnancy. The first indication that this may affect subsequent use of NNRTI-regimens came from a follow-up study to the PHPT-2 trial in Thailand. This reported similar clinical and immunological outcomes in 48 women previously exposed to NVP for PMTCT compared with 221 unexposed women, but fewer exposed women were able to achieve viral suppression to below 50 copies/ml after 6 months of NVP-containing ART [29]. In this study, 76% of NVP-exposed women and 85% of nonexposed women had a viral load below 400 copies/ml after 6 months on NVP-containing ART. When a more sensitive measure of below 50 copies/ml was used, 49% of NVP-exposed and 68% of unexposed had undetectable viral loads ($p = 0.03$). The virologic response to treatment was worse in these women who had detectable NNRTI-resistance mutations at 3–6-months postpartum. However, longer-term follow-up to 18 months of these women suggested that the rate of treatment failure did not diverge further with time [46], suggesting that a delayed effect of resistance may not be of concern.

Two other observational studies have suggested that outcomes are similar in previously NVP-exposed and unexposed women [47,48]. In a large, programmatic review of 6740 women initiating NNRTI-based ART in Zambia, 11% (751) had been previously exposed to single-dose NVP for PMTCT [49]. Although viral-load data were not available in this group, there was no significant difference in clinical outcome or rise in

CD4⁺ cell counts on ART between the exposed and unexposed women. However, a history of NVP exposure within 6 months of starting treatment was associated with a trend towards an elevated risk for clinical treatment failure (adjusted HR: 1.6; 95% CI: 0.9–2.7).

In Botswana, the response to NVP-based ART was studied in women and infants who had previously participated in the MASHI study, and had been previously randomized to receive either a single dose of NVP or placebo, added to abase ZDV regimen for PMTCT [50]. Women were subsequently started on a NVP-based ART when they became eligible. Of 218 women initiating treatment, 112 had previously received NVP. Virological failure, defined as below 400 copies/ml by 6 months of ART, occurred in 5% of the women who had received placebo, compared with 18.4% of those who had received a single dose of NVP during labour ($p = 0.002$). However, stratified by timing of initiation of ART, in 60 women starting ART within 6 months of the pregnancy, no women in the placebo group and 41.7% in the NVP group had virological failure ($p < 0.001$). Where treatment was started more than 6 months after the PMTCT dosing, virological failure rates were not significantly different (7.8 and 12.0%). The failure rates did not change to a great extent at 12 and 24 months of treatment. In preliminary results of the NEVEREST study in South Africa, women previously exposed to single-dose NVP at least 18 months before starting an NNRTI-based treatment regimen showed no significant differences in virologic response compared with unexposed women [51]. A scenario-modeling exercise, based on African data, has suggested that in the worst case, the increased mortality in women receiving antiretrovirals after exposure to single-dose NVP would be 10.4% (interquartile range (IQR), 10.0–10.8%) at 10 years after the PMTCT intervention [52].

A far stronger effect of exposure to single-dose NVP was seen in infants in the Botswana study [50]. A total of 30 infants initiated ART (15 in the placebo group and 15 in the NVP group). Virological failure within 6 months was found in 9.1% of unexposed infants and 76.9% of NVP-exposed infants.

These data suggest that the effect of NVP PMTCT regimen on the outcome of future treatment in mothers may be most marked where ART is started within 6 months of the pregnancy intervention. Several additional trials are underway to further investigate this. Among

these are two important randomized trials. The AIDS Clinical Trials Group Study A5208 (NCT00089505) [103] is a randomized trial comparing the treatment responses to NNRTI-based regimens in women who have or have not received previous single-dose NVP with treatment responses to protease inhibitor-based regimens. A similar design is in place in the IMPAACT 1060 study in infants (NCT00307151) [104].

From available data, there appears to be relatively little impact of the selection of NNRTI-resistant virus following NVP use for PMTCT if treatment is started more than 6 months after pregnancy [53]. The long-term durability of these treatment regimens in these women is, as yet, unknown, but initial results are encouraging. This further reinforces the need for the diagnosis of HIV infection and early access to antiretroviral care in pregnancy for those women who require treatment [14].

Two recently published reports show that women who have been exposed to NVP in a previous pregnancy do not transmit HIV to their subsequent infants at a markedly higher rate than those attending the program for the first time. The first report compared women's transmission rates after their first and second exposures to NVP [54]; the second compared multiparous women who had never been exposed to NVP with those who had been exposed [55], and both found MTCT rates to be almost the same. However, in the first study transmission rates in women whose interdelivery duration was less than 12 months were almost four-times higher than those whose interdelivery duration was more than 12 months – reinforcing the experience of ART from Botswana and Zambia.

Lamivudine in PMTCT regimens

The use of ZDV and 3TC combination short-course regimens has been studied in several trials [56–58]. The combination provides one of the most effective reductions in transmission at 6 weeks, although in the PETRA study, this relative reduction compared with placebo was not sustained to 18 months after additional transmission from breastfeeding. On the basis of the reduction in transmission, ZDV/3TC regimens have been recommended for PMTCT [59].

3TC resistance requires only one point mutation to M184V, and this is known to occur rapidly with nonsuppressive 3TC-containing regimens. In two studies using ZDV/3TC in France and the USA, ANRS 075 and ACTG

316, genotypic resistance to 3TC was seen in 39 and 60%, respectively [31,58]. Resistance was seen at 1 week postpartum in 12% of women who had received ZDV/3TC from 36 weeks gestation, but was undetectable by population sequencing at 3 months [60]. In the DITRAME-plus study in Abidjan, where women received ZDV/3TC from 32 weeks and for 3 days after delivery, with NVP in labor, 3TC resistance was seen in 8.33% (95% CI: 3.66–15.76%) [61].

Further data from Abidjan have been presented that demonstrated that 14.6% of women exposed to ZDV/3TC developed resistant mutations, and that these women were more likely to fail subsequent 3TC-containing ART (AOR: 6.9; 95% CI: 1.1–42.9) [27]. This high risk of selection of resistance and of impact on future treatment suggests that ZDV/3TC may not be an appropriate short-course PMTCT regimen, despite its efficacy in reducing transmission.

Future perspective

The ideal PMTCT regimen would be one with minimal side effects, which is easily administered and prevents intra-, peri- and post partum transmission. The current concerns regarding the impact of PMTCT prophylaxis on future treatment options are a direct result of the need to use less-than-optimally viral suppressive antiretroviral regimens for HIV-infected pregnant women in low-resourced settings. When these were introduced, the prospect of universal access to combination ART seemed remote, if not impossible. That situation has changed significantly and is likely to improve more in the years to come. As it does, it is likely that more PMTCT programs will be able to move to fully suppressive triple-antiretroviral regimens, as recommended in better-resourced settings [62], first for those women who need ongoing treatment, and then for the others who require only PMTCT prophylaxis. Such improvements in the course of therapy will remove most of the potential impacts of the current regimens. In the shorter term, while single or dual NVP-based regimens have to be used, it is crucially important to identify and treat women who need ongoing ART, which will alleviate the threat for those most at risk (those with low CD4 counts and high viral loads). The development of low-cost, robust point-of-contact CD4 measurement technologies will be a key part of such a strategy, as the lack of availability of CD4 counts remains a barrier to implementation in many settings.

Executive summary

Possible impact of mother-to-child transmission prophylaxis on future treatment options

- Simple prevention of mother-to-child transmission (PMTCT) of HIV regimens have facilitated the expansion of PMTCT services to millions of women in low-resource countries, although many more do not yet have access to these services.
- These short-course nevirapine (NVP) monotherapy or dual therapy regimens carry a higher risk of the selection of resistant virus.
- The full impact of the selection of resistant virus following PMTCT interventions is not yet fully understood.

Nevirapine-based PMTCT regimens

- Non-nucleoside reverse transcriptase inhibitor-resistant virus is detectable in 15–75% of mothers by standard genotyping techniques, following a single dose of NVP, either on its own or in combination with a zidovudine regimen.
- The use of more sensitive allele-specific techniques shows that minority populations of resistant virus are present in an even higher proportion of women.
- The amount of resistant virus decreases with time after the PMTCT dose.
- Available data suggest that this selection of resistance is most likely to adversely affect subsequent response to non-nucleoside reverse transcriptase inhibitor-based treatment when the antiretroviral treatment is started less than 6 months after delivery, and that treatment response in the first year to 18 months is less likely to be compromised where antiretrovirals are started more than 6 months after nevirapine for PMTCT.
- A 7-day course of zidovudine and lamivudine can significantly reduce, but not completely eliminate, the risk of selection of resistance.
- More work is needed to better understand the impact on future treatment and the optimal treatment approach for these women.
- NNRTI resistance is detectable in 20–87% of HIV-infected infants who have been exposed to nevirapine for PMTCT.
- There is some evidence to suggest that a high proportion of nevirapine-exposed infants will fail a nevirapine containing treatment regimen.
- More work is needed to identify appropriate treatment strategies for NVP-exposed infants.

Lamivudine in PMTCT regimens

- Resistance to lamivudine has also been shown in approximately 15–22% of women using zidovudine/lamivudine in short-course PMTCT regimens
- Some data suggest that subsequent treatment response is impaired in these women.

Future perspective

- A move to wider implementation of more effective PMTCT regimens, including access to ongoing treatment for women in need of triple therapy prophylaxis where available or zidovudine with single dose nevirapine and 7-day tail cover will reduce both the emergence of resistance and the potential impact of this on treatment options.

The addition of a dual-therapy ‘tail’ to cover the extended half-life of NVP will further reduce the development of resistance in the others, and at the current state of knowledge, initiating ART more than 6 months after pregnancy appears to improve the prospects of treatment success. The introduction of these elements to PMTCT programs is likely to provide a solution for this problem in the years to come. However, the unwillingness or inability of health services to date to implement even a simple regimen – such as the HIVNET 012 – may mean that sub-optimal methods of PMTCT are in place for years to come. Although the impact on subsequent ART for mothers appears to be small, there does appear to be cause for concern for

HIV-infected infants exposed to this regimen. Efforts should be made to provide the most cost-effective and safe PMTCT regimen, with the fewest concerns regarding resistance, available as widely as possible.

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