Use of single-dose nevirapine for the prevention of mother-to-child transmission of HIV-1: does development of resistance matter?

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The World Health Organization (WHO) estimated that, in 2005, 40.3 million people were living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) worldwide, with most of these people in sub-Saharan Africa. With current standards for HIV treatment in the United States, Canada, and Western Europe, approximately 9 million of those individuals meet the criteria for antiretroviral treatment. With increasing availability of antiretroviral drugs in resource-poor settings, an increasing number of HIV-infected people are now being placed on treatment.

Despite increased attention to the global AIDS epidemic, HIV-1 mother-to-child transmission (MTCT) continues to be a problem, with >600,000 children infected every year. In resource-rich countries, potent antiretroviral drug regimens are available for the prevention of MTCT (PMTCT); guidelines for pregnant HIV-infected women include zidovudine (ZDV) from 28 weeks of gestation, through delivery, and after delivery to the infant. Combination treatment is provided to women with viral loads of >1000 copies/mL and may also be considered for women with viral loads of <1000 copies/mL. Nonpregnant HIV-infected patients in developed countries qualify for antiretroviral treatment if they are symptomatic or have a CD4 count of <200 cells/mm³, and consideration is given to the initiation of treatment in patients with CD4 counts of 201-350 cells/mm³. However, in resource-limited settings, many women are unaware of their HIV status, and access to antiretrovirals is often limited. Even if antiretrovirals are available for HIV treatment, only 10%-20% of pregnant HIV-positive women in Africa are expected to be eligible for highly active antiretroviral therapy (HAART) for their own health. Therefore, 80%-90% of women will continue to rely on simpler regimens for PMTCT, which include single-dose nevirapine (SD-NVP) or combination regimens that include SD-NVP.

In 1999, the HIV Network for Prevention Trials (HIVNET) 012 trial in Uganda demonstrated that the provision of a single 200 mg dose of NVP to women in labor and a single 2 mg/kg dose of NVP to their infants within 72 hours of birth could reduce the risk of MTCT by nearly one-half. This is the simplest PMTCT regimen to implement; at least 7 clinical trials that included >4000 mother-infant pairs have documented its safety and efficacy. SD-NVP is also the least expensive regimen available for PMTCT. Although greater efficacy has been demonstrated using more complex antiretroviral regimens, SD-NVP is often the most deliverable and sustainable option for PMTCT in settings with limited resources. Currently, the WHO recommends that women...
are not eligible for HAART for their own health receive ZDV, starting at 28 weeks of gestation or as soon as possible thereafter, with SD-NVP and lamivudine (3TC) at the onset of labor and ZDV/3TC for 7 days after delivery. The administration of ZDV/3TC after delivery is recommended to reduce the development of NVP resistance. Infants should receive SD-NVP after birth plus ZDV for 7 days. In areas that do not have the capacity to deliver this regimen, SD-NVP alone is recommended.\(^\text{15,16}\)

Despite the programmatic advantages and efficacy of SD-NVP, several studies have demonstrated the selection of NVP-resistant HIV-1 variants after SD-NVP exposure.\(^\text{17,18}\) Other studies have demonstrated the emergence of NVP resistance after SD-NVP in combination with other antiretrovirals.\(^\text{19-21}\) This is in contrast to ZDV, which is also given for PMTCT prophylaxis, in which resistance requires multiple mutations and generally develops after months of drug exposure.\(^\text{22}\)

The high prevalence of NVP resistance after SD-NVP prophylaxis raises 2 concerns: (1) that SD-NVP may not be as effective for PMTCT in repeat pregnancies and (2) that persistence of NVP-resistant strains may compromise the future treatment of women with nonnucleoside reverse transcriptase inhibitor (NNRTI)-containing regimens. This is a major concern, because the first-line treatment regimen for women who require HAART for their own health in most resource-limited settings is an NNRTI-based regimen.\(^\text{23}\) With the growing availability of antiretrovirals in resource-limited countries, an increasing number of SD-NVP−exposed women are expected to initiate treatment with an NNRTI-based HAART regimen in the years to come.

This article reviews data on NVP resistance after SD-NVP prophylaxis, on what is known currently about the effectiveness of NNRTI-based HAART after SD-NVP, and on the effectiveness of SD-NVP in repeat pregnancies. It also highlights areas for additional research.

### NVP Resistance in Women After SD-NVP

Antiretroviral resistance is detected most commonly through the use of genotypic assays. Genotyping assays detect viral resistance-associated mutations in the relevant viral genes. Most commonly used genotyping assays can detect drug-resistant viruses that represent at least 10%-20% of the circulating virus population. More sensitive assays can detect specific resistance-associated mutations at lower levels.

NVP resistance frequently emerges after SD-NVP exposure and has been detected in 19%-76% of women 2-8 weeks after the administration of SD-NVP.\(^\text{17,19,24-26}\) HIV-1 variants with NVP resistance mutations also may exist at low levels in some HIV-1-infected individuals even before antiretroviral drug exposure.\(^\text{27,28}\) NVP can often be detected in maternal serum for 2-3 weeks after delivery\(^\text{29-31}\) in women who are exposed to a single 200 mg oral dose at delivery. This provides time for the selection of NVP-resistant strains. Different rates of NVP resistance are seen in women with different HIV-1 subtypes after SD-NVP (eg, 19% in subtype A, 36% in subtype D, and 69% in subtype C).\(^\text{24,32}\) It is particularly concerning that subtype C is associated with high rates of NVP resistance, because most HIV infections in southern Africa are subtype C and because this is precisely where SD-NVP is used most commonly. The emergence of NVP resistance after SD-NVP is also associated with higher viral loads and lower CD4 cell counts at the time of exposure\(^\text{17}\) and with increased pharmacokinetic exposure to NVP after a single dose (longer median NVP elimination half-life and decreased median oral clearance).\(^\text{33,34}\) NVP resistance is detected after SD-NVP in an even greater portion of women with the use of more sensitive resistance assays, such as mutation-specific polymerase chain reaction and LigAmp assay.\(^\text{18,35-37}\)

The most common NVP mutation that is seen in women after SD-NVP exposure is the lysine (K) to asparagine (N) mutation at codon 103 (K103N). In some patients who are infected with K103N-containing strains, these variants may persist for years, even with no further antiretroviral drug exposure.\(^\text{38}\) K103N-containing variants can also persist for extended periods in patients after the discontinuation of NNRTI-containing treatment regimens.\(^\text{39}\) Testing of SD-NVP-exposed women with the use of sensitive resistance assays has shown that NVP-resistant variants fade to undetectable levels in most women within a year of SD-NVP exposure but that these variants can persist at low levels in some women for \(\geq 1\) year after SD-NVP exposure.\(^\text{18,35,40,41}\) Persistence of K103N-containing variants in cellular DNA after SD-NVP exposure appears to be uncommon.\(^\text{40}\) However, further studies are needed both to confirm these findings and to evaluate the persistence of NVP-resistant strains in other cellular compartments after the administration of SD-NVP. Studies are also needed to determine whether repeated use of SD-NVP influences emergence or persistence of NVP-resistant strains.

### NVP Resistance in Infants After SD-NVP

NVP resistance is also seen in infants who become HIV-infected, despite SD-NVP prophylaxis. At 6-8 weeks of age, NVP resistance was detected in 46% of infected Ugandan infants\(^\text{17}\) and 87% of Malawian infants\(^\text{42}\) and at 4-12 weeks in 45% of South African infants.\(^\text{43}\) The most common NVP-resistance mutation that has been detected in infants after SD-NVP exposure is tyrosine to cysteine at HIV reverse transcriptase codon 181.\(^\text{17,25}\) Routine genotyping assays suggest that most NVP-resistant strains fade from detection in infants by 12 months of age.\(^\text{17}\) However, more sensitive assays show that NVP-resistant strains can persist in infants above baseline levels for at least 1 year after SD-NVP.\(^\text{35}\) Further studies are needed to evaluate the impact of previous SD-NVP exposure on future treatment of HIV-infected children with NNRTI-containing regimens.

NVP is also transferred to breast milk after women receive SD-NVP. NVP concentrations in breast milk and the half-life of NVP in breast milk are slightly less than or similar to the levels in maternal serum.\(^\text{44}\) The presence of NVP in breast...
milk may help to reduce the risk of MTCT during breastfeeding by suppressing breast milk viral load,43 but this also allows for the selection of NVP-resistant strains in breast milk,46 which may be transmitted to breastfeeding infants.17 In 1 study, 65% of women had at least 1 NVP resistance mutation detected in breast milk 8 weeks after receiving SD-NVP.46 There are little data available on the long-term persistence of NVP-resistant strains in breast milk, despite the fact that many women breastfeed for ≥1 year in resource-limited settings. Further studies are needed to identify factors that influence the emergence and persistence of NVP resistance in breast milk after SD-NVP and to assess the impact of NVP resistance on MTCT and transmission of NVP-resistant strains to breastfeeding infants.

**Response to Treatment After SD-NVP**

Several studies suggest that NNRTI-containing treatment regimens may still be effective as first-line therapy in women with previous SD-NVP exposure, particularly if, as 1 study suggests, there is sufficient time between SD-NVP dosing and treatment initiation. (Table 1).

The Thai Perinatal HIV Prevention Trials (PHPT)-2 study assessed the efficacy of an NNRTI-based treatment regimen in SD-NVP–exposed vs unexposed women.18 The analysis included 269 women who had previously received short- or long-course ZDV (from 35 or 28 weeks of gestation, respectively), 221 of whom (85%) also received SD-NVP in labor for PMTCT. Baseline characteristics, such as viral load and CD4 cell count, were comparable among NVP-exposed and unexposed women. However, the time between delivery and treatment initiation differed in the 2 groups (median, 6.1 months in the NVP-exposed group and 14.9 months in the unexposed group). A lower rate of virologic response was seen in NVP-exposed women compared with unexposed women; 49% and 68% of women, respectively, had a viral load of <50 copies/mL after 6 months of treatment ($P < .03$). However, this difference was not seen when the analysis was restricted to a subset of unexposed women with a median time between delivery and treatment initiation similar to that of the SD-NVP–exposed group of women. The authors also reported that, among SD-NVP–exposed women, there were no differences in virologic response between those who started HAART within 6 months of exposure to SD-NVP and those who started HAART >6 months after exposure to SD-NVP, although the specific response rates in these 2 groups were not reported.

The Mashi study in Botswana randomly assigned women during pregnancy to receive SD-NVP or placebo at delivery in addition to short-course ZDV from 34 weeks of gestation to prevent MTCT.47 After delivery, women who had either a CD4 cell count of <200 cells/mm$^3$ or an AIDS-defining illness were offered HAART. NVP-based HAART was initiated in 218 women after SD-NVP exposure. More than 90% of women had follow-up virologic measurements available at 6 months, and 87%-89% of NVP-exposed and unexposed women, respectively, had follow-up at 12 months after treatment initiation. In 60 of those women (28%), HAART was initiated within 6 months of

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**Table 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>PMTCT regimen for exposed women</th>
<th>Patients (n)</th>
<th>Viral load threshold for treatment response</th>
<th>Time since nevirapine-based HAART was started until assessment of virologic response</th>
<th>SD-NVP–exposed women who responded to treatment (%)</th>
<th>Un-exposed women who responded to treatment (%)</th>
<th>$P$ value for difference in treatment response</th>
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<tbody>
<tr>
<td>Thailand$^\dagger$</td>
<td>ZDV + SD-NVP</td>
<td>269$^*$</td>
<td>&lt;50</td>
<td>6 mo</td>
<td>49</td>
<td>68</td>
<td>.03</td>
</tr>
<tr>
<td>Botswana$^\dagger$</td>
<td>ZDV + SD-NVP</td>
<td>158$^\dagger$ (&gt;6 mo since exposure)</td>
<td>&lt;400</td>
<td>6 mo</td>
<td>88</td>
<td>92</td>
<td>.39</td>
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<tr>
<td>South Africa$^\dagger$</td>
<td>SD-NVP</td>
<td>90$^\dagger$</td>
<td>&lt;50</td>
<td>6 mo</td>
<td>100</td>
<td>76</td>
<td>Not reported</td>
</tr>
<tr>
<td>Zimbabwe$^\dagger$</td>
<td>ZDV or SD-NVP</td>
<td>41$^\dagger$</td>
<td>&lt;500</td>
<td>12 mo</td>
<td>71</td>
<td>70</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

$^\dagger$ Thailand: 269 women (48 SD-NVP–exposed; 221 unexposed).

$^\dagger$ Botswana: 218 women (112 SD-NVP–exposed; 106 unexposed).

$^\dagger$ South Africa: 90 women (60 SD-NVP–exposed; 30 unexposed); results are an interim analysis of first 55 women (38 SD-NVP–exposed; 17 unexposed) who had viral load data completed at 6 months.

$^\dagger$ Zimbabwe: 41 women (27 SD-NVP–exposed; 14 unexposed).
NVP exposure. When treatment was initiated at least 6 months after SD-NVP exposure, there was no difference in virologic response (viral load <400 copies/mL) between SD-NVP–exposed vs unexposed women. In contrast, when HAART was initiated <6 months after SD-NVP exposure, a poorer virologic response was seen in NVP-exposed women compared with unexposed women, with 42% and 0% of women, respectively, failing to respond after 6 months of treatment (P < .0001). Similar results were obtained at 12 and 24 months after treatment initiation. Among 30 infants who received either SD-NVP or placebo within 72 hours of birth and who had data available after a later start of NVP-based antiretroviral therapy, there was a higher rate of virologic failure among the SD-NVP–exposed infants than the unexposed infants. At 6 months, 77% of SD-NVP–exposed vs 9% of unexposed infants had virologic failure (P < .0001).

Similarly, in a South African study, 90 women with previous deliveries were followed for treatment outcomes after the initiation of an NNRTI-based regimen; 60 of the women (67%) were SD-NVP–exposed. The median time between delivery and treatment initiation was 18 months in NVP-exposed women and 36 months in unexposed women. There were no significant differences in virologic response among the SD-NVP–exposed vs unexposed women. Among 53 SD-NVP–exposed women who had 24-week outcome data, all had viral loads of <50 copies/mL.

A smaller study in Zimbabwe that assessed treatment response at 48 weeks in 41 women and 28 men included 27 women who previously had received ZDV and 14 women who previously had received SD-NVP for PMTCT. There were no significant differences in virologic suppression between SD-NVP–exposed and unexposed women. However, the virologic response was better in men than women overall (viral loads of <500 copies/mL were achieved in 93% of men and 71% of women; viral loads of <50 copies/mL were achieved in 79% of men and 53% of women; P < .025).

A study from Cote d’Ivoire evaluated immunologic response to an NNRTI-containing regimen among 115 SD-NVP–exposed and 94 unexposed women. The median time between delivery and treatment initiation was 19 months. At 6 months after treatment initiation, there were no significant differences in immunologic response, which was measured by a change in CD4 cell count between SD-NVP–exposed and unexposed women (median increase, 189 CD4 cells/mm$^3$ vs 222 CD4 cells/mm$^3$, respectively; P = .53). Previous SD-NVP also did not appear to influence immunologic response to treatment in the other studies that were described earlier. In Zambia, an analysis of maternal immune response and clinical outcomes on NNRTI-based HAART after self-reported exposure to SD-NVP compared NVP-exposed women to unexposed women. Increases in CD4 count from baseline among SD-NVP–exposed vs unexposed women were similar at 6 months (mean increase, 202 vs 182 cells/mm$^3$; P = .20) and 12 months (mean increase, 201 vs 211 cells/mm$^3$; P = .94). However, among women who initiated treatment within 6 months of SD-NVP exposure vs women who initiated treatment >6 months after SD-NVP exposure, there was a trend towards a less favorable CD4+ cell response at 6 months (mean increase, 150 vs 219 cells/mm$^3$; P = .06) and at 12 months (mean increase, 149 vs 215 cells/mm$^3$; P = .39).

Further research is needed to confirm the findings of available studies and to determine the optimal time to initiate treatment for HIV infection in SD-NVP–exposed women with different HIV subtypes and different stages of HIV disease. Additional studies are also needed to examine the risk of the reemergence of NVP resistance in NVP-unexposed vs -exposed women who start treatment with NNRTI-containing regimens.

Similar studies are needed in children who are infected with HIV, despite prophylaxis with SD-NVP or other NVP-containing regimens. HIV-1 disease often progresses quickly in infants, and the mortality rate of HIV-1–infected infants is high in the first 2 years of life. Antiretroviral treatment is often indicated in very young infants, when NVP-resistant virus may still be circulating.

**Effectiveness of SD-NVP in Subsequent Pregnancies**

Two studies have evaluated the effectiveness of SD-NVP prophylaxis in women who received the same regimen in a previous pregnancy. A follow-up study of 207 women from the HIVNET 012 cohort and a PMTCT program in Uganda found no difference in transmission risk among NVP-exposed women compared with unexposed women (20.6% vs 18.7%, respectively; P = .81). In that study, the median time between delivery and previous SD-NVP exposure was 32 months. Similar results were seen in a study that was conducted in South Africa and Cote d’Ivoire. In both first and subsequent pregnancies, women in South Africa received SD-NVP and women in Cote d’Ivoire received SD-NVP plus a short-course of other antiretrovirals for PMTCT. The median time between delivery and previous SD-NVP exposure was 22 months in South Africa and 23 months in Cote d’Ivoire. Among 108 women in both studies, HIV transmission risk was equal in first and second pregnancies (10.5% in both first and second pregnancies in South Africa and 8.6% in both pregnancies in Cote d’Ivoire).

**Addition of Antiretrovirals After Delivery to Reduce the Risk of NVP Resistance After SD-NVP**

Two studies have investigated whether the risk of NVP resistance after SD-NVP can be reduced by the addition of ZDV/3TC for 3-7 days after delivery. This “tail” provides additional antiretroviral coverage while NVP levels in plasma are declining. A study from South Africa compared NVP resistance among 226 women who received a short antenatal course of ZDV plus either SD-NVP alone or SD-NVP plus a 4- or 7-day ZDV/3TC tail. The risk of NVP resistance was 60% lower in women who received the ZDV/3TC tail.
in women and 78% in infants with SD-NVP alone at 6 weeks after exposure. In contrast, when the mother received a 4-day ZDV/3TC tail, the risk of NVP resistance was 13% in both women and infants; when the mother received a 7-day ZDV/3TC tail, the risk was 9% in women and 0% in infants. Similarly, a study in Cote d’Ivoire compared NVP resistance in women who received ZDV from 36 weeks of gestation plus either SD-NVP alone or SD-NVP plus a 3-day postpartum course of ZDV/3TC. NVP resistance was detected at 4 weeks after delivery in 33% of women in the SD-NVP alone arm and in 1% of women who received the 3-day ZDV/3TC tail.

Additional studies are needed to determine whether a postpartum course of 7 days of ZDV/3TC after SD-NVP is optimal for reduction of the risk of NVP resistance. Studies are also needed to determine whether the addition of a ZDV/3TC tail influences the subsequent response of women to an NNRTI-containing treatment regimen. And finally, in resource-limited settings, one must consider whether it is logistically feasible to provide a ZDV/3TC tail after SD-NVP exposure.

ONGOING AND PLANNED STUDIES

At least 4 ongoing studies are evaluating interventions to complement NVP-containing PMTCT regimens and to reduce the development of NNRTI resistance mutations. These include (1) a US Centers for Disease Control and Prevention–sponsored study of 200 mother-infant pairs in Lilongwe, Malawi, where women and newborn infants receive SD-NVP plus a 7-day tail of ZDV/3TC or SD-NVP alone; (2) a study in Lusaka, Zambia, where 400 women who accessed SD-NVP in addition to ZDV in antenatal care are randomly assigned at delivery to receive a single dose of tenofovir/emtricitabine or no additional intervention; (3) a US National Institutes of Health–sponsored study by the AIDS Clinical Trials Group in India, Haiti, and possibly other countries where 420 mother-infant pairs will be provided 1 of 3 antiretroviral regimens (ZDV/3TC, tenofovir/emtricitabine, and ritonavir-boosted lopinavir) for either 7 or 21 days after SD-NVP exposure; and (4) a 3-arm Pediatric AIDS Clinical Trials Group study that compares 7 days of ZDV + didanosine + ritonavir-boosted lopinavir vs 30 days of ZDV + didanosine + ritonavir-boosted lopinavir vs 30 days of ZDV + didanosine.

Three ongoing studies are assessing maternal response to NNRTI-containing HAART after SD-NVP exposure for PMTCT. These include (1) a US Centers for Disease Control and Prevention–sponsored study in Thailand, Kenya, and Zambia that is prospectively enrolling SD-NVP–exposed and unexposed women who are matched for CD4 count and clinical disease stage and commencing NNRTI-containing HAART (women with varying time periods between exposure and treatment initiation are enrolled and rates of viral suppression [defined as <400 copies/mL] are being compared; (2) a US National Institutes of Health–sponsored AIDS Clinical Trials Group study at several sites in Africa that is randomly assigning SD-NVP–exposed and unexposed women to NNRTI vs protease inhibitor–containing HAART in 2 parallel randomized trials; all participants have >6 months since exposure and (3) a study in South Africa that is also assessing the response of SD-NVP–exposed and unexposed women to NNRTI-based treatment; all participants in this study have at least 18 months between SD-NVP exposure and the start of therapy. This is an important entry criterion, because it likely will be the most common scenario in real practice as women who require HAART for their own health increasingly initiate treatment during pregnancy (Table 2).

COMMENT

Although preliminary, currently available data indicate that SD-NVP is effective for PMTCT in repeat pregnancies and that SD-NVP exposure does not compromise future treatment with an NNRTI-regimen, so long as treatment is initiated at least 6 months after SD-NVP exposure. The 1 study that assessed virologic response rates among women who initiated treatment within 6 months of SD-NVP exposure found a suboptimal response rate in these women, compared with women who began treatment >6

### Table 2

**Summary of ongoing evaluations to determine virologic consequences of previous SD-NVP exposure among women who start NNRTI-containing HAART**

<table>
<thead>
<tr>
<th>Name</th>
<th>Sponsor</th>
<th>Countries</th>
<th>Design</th>
<th>N</th>
<th>Exposure Interval</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI Response Study</td>
<td>US Centers for Disease Control and Prevention</td>
<td>Zambia, Thailand, Kenya</td>
<td>Prospective cohort; SD-NVP–exposed and unexposed</td>
<td>900</td>
<td>Any</td>
<td>Percentage with viral load &lt;400 copies/mL at 12 mo</td>
</tr>
<tr>
<td>AIDS Clinical Trial Group 5206 (OCTANE)</td>
<td>US National Institutes of Health</td>
<td>Botswana, South Africa, Malawi, Kenya, Zambia, Zimbabwe</td>
<td>Parallel randomized clinical trials of NNRTI vs protease inhibitor–based antiretroviral therapy in SD-NVP–exposed and unexposed women</td>
<td>640</td>
<td>&gt;6 mo</td>
<td>Percentage with either (1) viral load &lt;400 copies/mL at 6 mo or (2) viral load &lt;1 log10 below baseline at 3 mo</td>
</tr>
<tr>
<td>Nevirapine Resistance Study (NEVEREST)</td>
<td>US National Institutes of Health</td>
<td>South Africa</td>
<td>Prospective cohort; SD-NVP–exposed and unexposed</td>
<td>&gt;18 mo</td>
<td>Percentage with viral load &lt;50 copies/mL at 12 mo</td>
<td></td>
</tr>
</tbody>
</table>
months after exposure to SD-NVP. Currently, only 10%-20% of women being seen for pregnancy care in resource-poor settings are expected to meet criteria for HAART for their own health. Antiretroviral treatment is becoming more widely available in resource-poor settings, and pregnant women who require treatment for their own care increasingly are able to access it. Therefore, in most women, sufficient time should elapse between SD-NVP exposure and treatment initiation to allow for the fading of NVP-resistant strains. However, additional studies are needed to confirm these findings, to evaluate treatment response in women who initiate HAART close to the time of SD-NVP exposure, to evaluate the time to fading of NVP-resistant variants in women with different HIV subtypes and its impact on treatment outcome, and to evaluate the impact of SD-NVP exposure on subsequent treatment response in infants.

Many of the world’s poorest countries with the greatest HIV burden face significant obstacles to the implementation of PMTCT programs. Current estimates indicate that >90% of HIV-infected women in many resource-poor settings still do not have access to any antiretroviral prophylaxis, including SD-NVP. Even when SD-NVP is available, uptake into many PMTCT programs has been limited because of infrequent offering of rapid HIV testing in many antenatal settings that rely on an opt-in strategy, refusal of women to be tested for HIV, inconsistent supply of NVP and HIV test kits, inadequate numbers of counselors, lack of space for counseling, poor delivery of NVP to mothers, evaluation of women at delivery without previous HIV testing, and reluctance of women to disclose their HIV status to caregivers at delivery.

As a result, only approximately one half of eligible women receive even the simplest and most deliverable regimen, SD-NVP, in settings where PMTCT programs are in place. To maximally reduce mother-to-child HIV transmission, additional efforts are needed to scale-up PMTCT programs, but in many settings, SD-NVP will continue as the most feasible option for prophylaxis.

To address growing concerns of NVP resistance, some resource-limited countries have proposed changes to their national guidelines, recommending HAART for all pregnant HIV-infected women, regardless of immunologic criteria. Although HAART should be offered when indicated and feasible, these efforts should not detract from routine PMTCT implementation efforts. The implementation of PMTCT programs has been slow in resource-limited countries, even with a regimen as simple as SD-NVP, and the implementation of HAART for PMTCT is expected to be a far greater challenge. In addition, the provision of NVP-based HAART during pregnancy for PMTCT may add additional risk to pregnant women and their infants. The extended use of NVP in pregnancy is associated with toxicity in some women, especially those women with higher CD4+ lymphocyte counts. Efavirenz should be avoided in pregnancy because of its teratogenic potential. The use of protease inhibitors may be problematic in resource-limited settings because of cost, a requirement for refrigeration for some, and the need for more intensive toxicity monitoring. Importantly, clinical trials have not shown any appreciable increase in the efficacy of HAART for PMTCT over combination prophylaxis regimens such as long-course ZDV plus SD-NVP. Furthermore, even when NVP-based HAART is used for PMTCT, NVP resistance can still be observed. In the Drug Resource and Enhancement Against AIDS and Malnutrition (DREAM) cohort in Mozambique, NVP resistance was seen in 5 of 42 women (12%) who did not require HAART for their own health but who received NVP-based HAART for PMTCT. NVP resistance was also seen in 5 of 29 women (17%) in Ireland who received HAART for PMTCT, even though the dual NNRTI component of the regimen was continued for 3-5 days after NVP was stopped.

In summary, it is likely that NNRTI-based HAART regimens will continue to be offered for some time as first-line treatment for HIV-infected patients in resource-limited settings and that SD-NVP will continue as an option for PMTCT. In these settings, public health decision makers must consider the concerns that are associated with the use of SD-NVP for PMTCT and balance them against the low cost, safety, and simplicity of this regimen. Current studies suggest that the consequences of NVP resistance after SD-NVP may be less than previously feared. On the other hand, given the challenges that are recognized in the implementation of even SD-NVP for PMTCT, the exclusion of SD-NVP as an option for PMTCT would further reduce the effectiveness of the existing PMTCT programs and likely result in an increase in the already staggering number of HIV-infected infants worldwide.

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