Single-Dose Nevirapine to Prevent Mother-to-Child Transmission of HIV Type 1: Balancing the Benefits and Risks

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(See the article by Coovadia et al. on pages 462–72)

Ever since the magnitude of the global AIDS epidemic was recognized, much effort has been directed toward understanding and decreasing mother-to-child transmission (MTCT) of HIV-1. The biologic complexity of the problem is compounded by the intertwined issues of poverty and limited access to care, leading scientists and policy makers to search for solutions that are both effective and practical in resource-constrained settings. These forces were the impetus for tests of short courses of antiretroviral therapy for prevention of MTCT of HIV-1, such as third-trimester and neonatal administration of zidovudine [1] or a single intrapartum dose of nevirapine [2]. HIVNET 012 found that nevirapine (NVP) given as a single dose (sdNVP) decreased the risk of transmission of HIV-1 from mother to infant by 47%, compared with a short intrapartum and neonatal course of zidovudine [2]. This success, coupled with its economic feasibility and simplicity, led to adoption of sdNVP treatment for prevention of MTCT in many developing countries [3].

Potential maternal consequences of this approach became evident, however, with the important observation that NVP-resistant HIV-1 variants were selected in a substantial fraction of women who had received sdNVP [4, 5]. Whether these NVP-resistant variants would affect subsequent virologic response to antiretroviral therapies containing NVP or other nonnucleoside reverse-transcriptase inhibitors (NNRTIs) was not initially known. A subsequent study by Jourdain et al. [6] demonstrated that sdNVP treatment increased the risk of virologic failure in women who commenced NVP-containing antiretroviral therapy a median of 6.1 months after receipt of sdNVP, especially if NVP-resistant mutants were detected by a standard genotype assessment method when antiretroviral therapy was started. A subsequent study by Lockman et al. [7] provided some reassurance that the negative consequences of sdNVP therapy were temporary. Specifically, women who received NVP-containing antiretroviral therapy after sdNVP had no higher risk of virologic failure if NVP-containing antiretroviral therapy was initiated >6 months after delivery, suggesting that NVP-resistant mutants decrease in frequency to less than clinically relevant levels within 6 months. However, a study using more-sensitive assays to quantify low-frequency NVP-resistant mutants showed that such mutants can persist in ~20% of women for at least 1 year after receipt of sdNVP [8].

In this issue of Clinical Infectious Diseases, Coovadia et al. [9] present new data that help elucidate the influence of minor populations of NVP-resistant mutants (i.e., those that are not detected by standard genotype methods) on virologic response to NNRTI-containing antiretroviral therapy that was initiated 18–36 months after receipt of sdNVP. Significantly, their results show that detection of NNRTI-resistant variants encoding the K103N mutation by allele-specific realtime PCR (AS-PCR) is strongly associated with inadequate virologic response to antiretroviral therapy. In fact, 58% of patients for whom the K103N mutation was detected by AS-PCR before initiation of NNRTI-containing antiretroviral therapy had poor virologic responses. There was no difference in virologic response among women who did not have the K103N mutation detected by AS-PCR before initiation of NNRTI-containing antiretroviral therapy had poor virologic responses. There was no difference in virologic response among women who did not have the K103N mutation detected, regardless of whether they had received sdNVP. Thus, this study establishes a strong and important association between low-frequency K103N mutations and poor response to antiretroviral...
therapy that is independent of the time since sdNVP exposure.

However, the larger question of the long-term effects of sdNVP on treatment response was not conclusively answered by this study. Surprisingly, there was little difference in the pretherapy frequency of K103N mutations between the sdNVP-exposed and sdNVP-unexposed groups (10.6% and 15%, respectively, had detectable K103N mutations); thus, the K103N mutations detected could not be linked to sdNVP exposure. Although the authors suggest possible reasons for resistance mutations in the sdNVP-unexposed group, including prior exposure to other NNRTIs and transmitted resistance, the observation is difficult to reconcile. Of note, only 23 of 94 sdNVP-exposed women had confirmed, documented exposure, making improper assignment of sdNVP exposure a possible explanation.

In addition, a limitation of using the AS-PCR approach is that other NNRTI-resistance mutations that may affect response to antiretroviral therapy are not detected. Such mutations may explain the variable response observed to antiretroviral therapy among women for whom the K103N mutation was detected before the commencement of therapy. Furthermore, without more-complete characterization of pretherapy samples, it is not possible to determine whether the mutations detected at the time of virologic failure represent new mutation events or selection of preexisting mutants. Newer sequencing technologies, such as single-genome sequencing [10] or high-throughput pyrosequencing [11], can be used to more fully characterize virus populations and to show linkage among mutations [10], although cost is a significant limitation.

Nevertheless, the article by Coovadia et al. [9] adds to the growing body of evidence that low-frequency drug-resistant variants are important determinants of response to antiretroviral therapy [12]. The question of whether there is a long-term increased risk of virologic failure among women who have received sdNVP treatment still remains to be answered. The subset of women at risk cannot be readily identified without use of new technologies for detection of low-frequency mutants. With accurate characterization of mutant populations by AS-PCR and single-genome sequencing or pyrosequencing, it may be possible to define a threshold of mutation frequency that predicts suboptimal response to NNRTI-containing regimens. Studies are currently underway that apply these technologies to well-controlled, randomized trials that are comparing sdNVP-exposed and sdNVP-unexposed groups and assessing their responses to NVP-containing antiretroviral therapy, as well as to regimens that do not contain NVP. These data will further elucidate the complex interplay between prior drug exposure and subsequent treatment response for sdNVP and other antiretrovirals.

In the meantime, a prudent strategy would be to minimize the selection of drug-resistance mutations in women who receive sdNVP for prevention of MTCT of HIV-1. Several promising strategies have been shown to reduce the selection of NVP-resistant mutations, including single doses or short courses of antiretroviral combinations, such as tenofovir-emtricitabine or zidovudine and lamivudine [13, 14]. Prevention of MTCT of HIV-1 continues to be an area of great challenge and potential public health benefit. As more is learned and as access to antiretrovirals increases, better outcomes for both infants and mothers should be realized.

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