The controversies of nevirapine for preventing mother-to-child HIV transmission

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Keywords: drug resistance, mother-to-child HIV transmission, nevirapine

The efficacy of antiretroviral therapy to prevent mother-to-child HIV transmission (MTCT) was first established in 1994. In that study by Connor and colleagues (PACTG 076) both mother and infant were treated with long courses of zidovudine, which reduced HIV transmission from 25 to 8% [1]. Since then, improved interventions in industrialized nations have further reduced MTCT rates to less than 2% through access to HAART, caesarian deliveries when indicated and formula feeding [2–4]. In developing nations, however, full access to HAART is not yet a reality and MTCT rates remain high [5]. An ideal method would be one that is convenient to administer, safe for both mother and infant, inexpensive and offering complete protection from transmission.

Nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor (NNRTI), has become an especially attractive option to decrease MTCT because it is lipophilic and easily absorbed [6]. It achieves high blood concentrations with a single oral 200 mg dose, often reaching plasma concentrations 10 times that needed to inhibit viral replication by 50% (IC_{50}). Nevirapine also penetrates well into breast milk and readily crosses the placenta [6,7]. Taken together, these characteristics of NVP explain the success of the HIVNET 012 study in Uganda, which demonstrated that a single 200 mg dose of NVP taken by an HIV-infected mother at the onset of labor and a 2 mg/kg dose of NVP given to the infant within 72 h of birth could reduce the MTCT rate by 42% at 6 weeks of the infant’s life [8,9].

In this issue of AIDS, Jackson and colleagues report a sub-study of HIVNET 012. They correlated the concentration of NVP in the cord blood of infants, self-reported administration of the maternal NVP dose and HIV transmission to better define the optimal timing of maternal dosing [10]. When and how to administer the maternal NVP dose is important because previous studies have reported higher transmission rates if the maternal dose was taken less than 2 h before delivery [11]. Jackson and colleagues confirmed previous reports [12] that NVP levels in cord blood are high, especially for women who reported taking the dose more than 1 h prior to delivery and that HIV transmission risk is increased if the dosing occurred within 2 h of delivery [10]. Their data further support the feasibility of NVP self-administration by the mother before delivery to increase the duration of NVP protection to the infant.

Despite the demonstrated efficacy of reducing MTCT rates, single-dose NVP regimens are temporizing at best. The half-life of NVP is very long with detectable levels in maternal blood and breast milk for up to 3 weeks after a single 200 mg dose [13]. This may explain why single dose NVP was shown to be more effective than zidovudine in HIVNET 012 [13], since 30–50% of MTCT occurs through breast feeding [14,15]. However, this amounts to protracted monotherapy, which readily selects for NNRTI resistance in 15–40% of post-partum women [16–18] and 23% of the infants where transmission does occur [19]. More sensitive techniques, such as allele-specific polymerase chain reaction, has identified NNRTI drug-resistant rates as high as 75% in mothers receiving a single dose of NVP [20] and 78% of infants in which the NVP regimen failed [4]. Selection for NNRTI resistance in the mother has been shown to decrease the effectiveness of subsequent antiretroviral therapy, especially since NNRTI-based antiretroviral...
regimens are recommended first-line treatments in resource-limited settings [21]. This is especially poignant in Africa where maternal death is associated with an increase in infant death by three to fourfold independent of maternal HIV status, child birth weight, socioeconomic status, and maternal age and parity [22]. Furthermore, the development of NNRTI resistance may lessen the protection of NVP for future pregnancies [2].

Today, one infant will be born infected with HIV in either the United States or Europe, which sharply contrasts with the 1900 infants who will be born infected with HIV in Africa [5]. This study by Jackson and colleagues, in conjunction with HIVNET 012, has shown that NVP can be a convenient and inexpensive method to decrease MTCT in these resource-limited settings [8,10]. However, the single dose NVP is not a permanent solution. Although no significant short-term toxicities have been documented with the single dose regimen [7,13], the real price is paid with the development of NNRTI resistance, which decreases the effectiveness of this class of antiretroviral drugs [23]. The selection for HIV drug resistance may not only have detrimental effects on the mother or infant treated with NVP, but also on the HIV-infected population as a whole, as NNRTI resistance has been shown to be relatively transmissible [24]. This is disappointing since we know that improving access to HAART will further reduce MTCT and increase the life span of the mother through HAART. Although we currently lack the resources, universal access to HAART would probably decrease all transmissions, both horizontal and vertical, while improving the quantity and quality of life all those affected [25]. However, this remains hopelessly optimistic as fewer than 10% of all pregnant women in Africa have access to NVP prophylaxis [26]. More than a decade has passed since zidovudine was found to reduce MTCT rates, and we still grapple with preventing MTCT in resource-limited settings. Although NVP regimens offer considerable benefits, they remain only a temporary and imperfect solution to a long-term crisis.

Acknowledgments

I would like to thank Terry Albritton and Susan Little for their editorial assistance.

References


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