Another Milestone in Minimizing Risks to Mothers Exposed to Single-Dose Nevirapine for Prevention of Vertical Transmission of HIV-1 to Infants: What Next?

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(See the article by Lallemant et al, on pages 898–908.)

The PACTG 076 study, conducted between 1991 and 1993, not only established the principle of reducing vertical transmission of human immunodeficiency virus (HIV–1) to infants with an antiretroviral agent, but it was also the first antiretroviral success story [1]. The study used zidovudine monotherapy and predated the enormous benefits of highly active antiretroviral therapy (HAART) for treatment by a few years [2]. The key components of PACTG 076—oral zidovudine beginning during weeks 14–34 of gestation, given intravenously during labor, and given for 6 weeks thereafter to the infant—reduced HIV-1 transmission by 67.5% in infants given replacement feeding. PACTG 076 was rapidly implemented in industrialized countries. Then, starting in 1998, HAART became a key component to prevent vertical transmission, and reduced the perinatal transmission to <2% [3].

These interventions were not implemented in low-resource, high-burden countries, where most vertical transmissions occur, because of cost and the lack of infrastructure. Progress was made towards simplifying the zidovudine component. The frequency of antenatal administration was reduced from 5 times to 2 times daily. Giving zidovudine by mouth at 3-h intervals replaced intravenous administration during labor [4, 5]. The optimal duration of zidovudine administration was defined by Lallemant et al [4, 5] in the Perinatal of HIV Prevention Trial (PHPT-1), which showed that initiating zidovudine from 28 weeks gestation rather than from 36 weeks gestation was the most effective component [6]. The zidovudine regimen was initially considered difficult to implement in resource-constrained settings.

The HIV NET 012 Study had as momentous an impact for resource-constrained settings, as did PACTG 076 in the developed world [7]. Single-dose nevirapine given to the mother in active labor and to the newborn within 72 h after birth reduced the HIV transmission rate to 11.9% by 6–8 weeks of age in breast-fed infants. This simple regimen was sufficient to stimulate the establishment of extensive programs to prevent vertical HIV transmission in low-resource settings worldwide, despite concerns about later transmission through breast-feeding. Other essential components of a vertical transmission reduction program included antenatal identification and counselling of HIV-infected pregnant women, assessing HIV disease progression, and evaluating for HAART. The infant component included advice about infant feeding, trimethoprim-sulfamethoxazole prophylaxis, and diagnosis of HIV status by DNA polymerase chain reaction at 6 weeks of age.

The history of HIV is replete with progress in one area compromising another area of care. Single-dose nevirapine is associated with resistance mutations in mothers and their HIV-infected infants [8]. This translates into diminished efficacy and increased virological failure in women and their infants commencing nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based therapy [9, 10].

Because of the long half-life and low genetic threshold for nevirapine resistance, investigators using the principle that triple combination antiretroviral therapy gives durable viral suppression, soon showed that by giving the mother additional antiretrovirals while nevirapine was eliminated from the body over a 3-week period, reduced nevirapine resistance. Giving the
mother zidovudine and lamivudine for 4–7 days after delivery reduced the rate of NNRTI mutations to 9%–14% [11] In an even simpler approach—giving a single dose of emtricitabine and tenofovir in 1 tablet with single-dose nevirapine during labor—reduced the frequency of mutations from 25% to 12% [12].

In this edition of the journal, Lallemant et al [13], in the PHPT-4 study, provide a robust and simple antiretroviral alternative for reducing nevirapine resistance after maternal single-dose nevirapine. They hypothesized that more durable protection of nevirapine would be obtained if additional antiretrovirals were given for 1 month (the period of nevirapine plasma clearance) with effective combination therapy. They therefore selected 2 nucleoside reverse-transcriptase inhibitors (NRTIs), zidovudine and enteric-coated didanosine, both of which have a high genetic barrier to developing resistance, deliberately avoiding lamivudine with its low genetic barrier. Because the prevalence of hepatitis B is 10% in Thailand, avoiding lamivudine also prevented hepatitis B flare-ups during lamivudine withdrawal or compromising future therapy for hepatitis B. Didanosine was given at the same time as single-dose nevirapine. The enteric-coated formulation was given as a single daily dose, without food restrictions, thus enhancing the simplicity of the regimen.

The control population came from well-characterized stored samples from women who participated in the PHPT-2 study, in which single-dose nevirapine without post-exposure antiretroviral protection was given [14]. The PHPT-4 strategy was successful. Major NNRTI mutations were detected in 18.9% of controls versus only 1.8% of study patients. The medications were well tolerated. A similar strategy that included administration of a protease inhibitor for 7 days had identical efficacy [15].

This strategy needs to be replicated in Africa, where HIV-1 subtype C has a higher propensity to NNRTI resistance and where women may be sicker. In the PPHT-4 study, the women were relatively healthy, with a median CD4 cell counts well above 250 cells/mm³. Also, despite a prevalence of chronic hepatitis B in Africa of >8% [16], routine antenatal screening for hepatitis B does not occur. Therefore, avoidance of lamivudine in this situation is prudent, although screening is preferable [17]. In studies from South Africa and Kenya, the prevalence of HIV and hepatitis B virus surface antigenemia was 4% [18, 19].

With the welcome move to begin HAART at higher CD4 cell counts, there will be less need for single-dose nevirapine. However, many pregnant women present late. PACTG 316 found no benefit from adding single-dose nevirapine to regimens for women in industrialized countries who present for antenatal care at a median of 34 weeks [20]. For optimal efficacy, early initiation of HAART is optimal. In countries such as South Africa, where maternal mortality is high, access to antenatal care can occur late [21]. Therefore, single-dose nevirapine will likely remain an important option for many women. Unbooked mothers, entering obstetric health care services for the first time when in active labor, who are at great risk for HIV infection, can account for up to 20% of deliveries [21, 22]. Therefore, single-dose nevirapine treatment is likely to remain an important component of management strategies.

An important question is whether both the mother and infant need single-dose nevirapine. In the PHPT-2 study, the efficacy of single-dose nevirapine was evaluated for women starting antenatal zidovudine from 28 weeks versus placebo and was not compared for the mother and infant. The study established that single-dose nevirapine was unnecessary for the infant if the mother had received it, but not the converse [14]. PHPT-2, however, did establish the efficacy of adding single-dose nevirapine to antenatal zidovudine. Interestingly, single-dose nevirapine had no benefit when women received antenatal zidovudine for more than 10.5 weeks. An evaluation of neonatal versus maternal single-dose nevirapine was done performed Shapiro et al [23] in the MASHI study, in which 694 pregnancies were evaluated. Women had initiated zidovudine from 34 weeks gestation and infants were given zidovudine for the first 4 weeks of life. Mothers were randomized to receive single-dose nevirapine or placebo, and all infants received open-label, single-dose nevirapine as soon as possible after birth (median, 0.4 h after birth). Transmission was low in both groups. The study took place in the context of a comparison of replacement (ie, formula) feeding versus exclusive breast-feeding, which did not affect outcome in an interaction analysis. By 1 month of age, 4.3% of infants whose mothers received nevirapine and 3.7% of those receiving placebo were HIV infected [23]. Median CD4 counts tended to be lower than in the PHPT-2 study. Giving single-dose nevirapine to the infant only could also eliminates the risk of inadvertent administration of nevirapine in false labor—another risk factor for maternal resistance [24].

As costs increase, programs become more expensive, because of increased uptake and need for medicines. Global economic issues threaten funding for HIV programs. The cost efficacy of giving single-dose nevirapine to mothers rather than infants should be urgently evaluated. Nevirapine is an inexpensive medication for first-line HAART, as opposed to alternatives, such as lopinavir-ritonavir. By 2008, the uptake of pregnant women offered an HIV test in middle- and lower-income countries had risen to 28%, with 45% being offered an antiretroviral agent, indicative both gratifying progress and increased costs [25].

Then what about the nevirapine-exposed, HIV-infected infant? Fortunately, more infants will be HIV uninfected as a result of vertical transmission prophylaxis. The poorer performance in nevirapine-exposed infants receiving nevirapine-based antiretroviral therapy is now well documented [26, 27], although nevirapine can
possibly replace lopinavir-ritonavir once viral suppression has been attained for 6 months [28]. There is an urgent need to develop strategies to protect HIV-infected infants from developing NNRTI resistance, both from single-dose nevirapine and more prolonged exposure to nevirapine during breast-feeding [29], possibly along the lines developed in PHPT-4. Alternative antiretroviral choices, such as the second-generation NNRTI etravirine, are urgently needed at an affordable price to give children better treatment options.

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References


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