High Genetic Barrier Antiretroviral Drugs in Human Immunodeficiency Virus–Positive Pregnancy

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(See the article by Gingelmaier et al, on pages 890–894.)

Suppression of human immunodeficiency virus (HIV) replication during pregnancy is a key factor to decrease the risk of mother to child transmission (MTCT) [1]. Contrary to the wide experimentation with many different antiretroviral drug combinations performed in the general HIV-positive population over the past years, treatment regimens used in pregnant women to prevent MTCT have been explored to a much lesser extent. Reasons for such limited use of the antiretroviral armamentarium in this context include drug safety concerns and, most importantly, the fact that the vast majority of the HIV-positive pregnancies occur in the developing world, where access to anti-HIV drugs has been and is still limited. Most studies have evaluated strategies combining antepartum, intrapartum, and postpartum zidovudine (a nucleoside reverse-transcriptase inhibitor) and/or nevirapine (a nonnucleoside reverse-transcriptase inhibitor [NNRTI]), both of which are relatively well-tolerated and low-cost drugs [2]. Although treatment with zidovudine for some weeks has been the strategy of choice for years, nevirapine has recently gained popularity because of its convenience and efficacy even when used as a single-dose intrapartum and neonatal administration. A major concern about the use of a single drug, particularly nevirapine, in MTCT prevention is the high propensity to select for drug-resistant HIV in the mother and possibly, in the event of virus transmission, in the infant too [3, 4]. Indeed, a general concept in antiretroviral therapy is that HIV has an extraordinary intrapatient evolution rate that translates into generation of drug-resistant variants under suboptimal drug pressure. Although even a single mutation in the HIV genome can confer complete resistance to nevirapine and other NNRTIs, protease inhibitors (PI) boosted with a pharmacokinetic enhancer have a much higher genetic barrier to resistance. Wide experience in the general HIV population has convincingly demonstrated a greatly reduced probability of drug resistance at treatment failure of a boosted PI-based versus an NNRTI-based therapy, despite comparable overall efficacy and a generally better long-term tolerability of NNRTI drugs [5]. Although the mechanism is not completely understood, failure of a first-line boosted PI-based regimen appears to occur virtually in the absence of drug resistance mutations. By contrast, failure of an NNRTI-based regimen almost invariably occurs with an NNRTI-resistant virus. In addition, boosted PI therapy provides a notable degree of protection against resistance to the nucleoside reverse-transcriptase inhibitor drugs typically combined with 1 PI or 1 NNRTI in clinical practice. Thus, failure of a boosted PI regimen is much more conservative than failure of an NNRTI regimen in terms of preservation of future treatment options.

The paper by Gingelmaier et al [6] published in this issue of Clinical Infectious Diseases is a proof of concept of this knowledge in the context of pregnancy. By treating 40 pregnant women with a PI-based combination therapy for a median of 8 weeks up to delivery, not only did none of the newborns become infected, but also none of the 36 mothers with available follow-up had any new resistance mutation in their own virus population. This result compares favorably with previous attempts to use combination antiretroviral therapy regimens, including nevirapine [3, 7], and supports the use of high genetic barrier treatment regimens in pregnancy. However, it must be noted that the women in the study reported by Gingelmaier et al [6] had good immunological status and were without an indication for antiretroviral therapy according to current guidelines. They received their first antiretroviral treatment during pregnancy, except for a few exceptions who had a previous
experience with MTCT prophylaxis. Thus, although 2 women harbored drug-resistant HIV variants at baseline, likely as a result of transmission from treated individuals, this patient group was expected to attain maximum benefit from first-line combination therapy. The picture could be different for pregnant women with more-advanced stages of disease, particularly when multiple treatment failures may have occurred and resistance mutations have accumulated in the virus genome. In the event of extensive resistance, use of new drug classes could be advisable to suppress HIV replication, but these should be used with caution in the absence of solid evidence of safety and efficacy during pregnancy. Indeed, PI use in MTCT prevention has also been limited, but sufficient evidence supports their efficacy, which is sometimes subject to dosage adjustments, and relative safety [8]. Although a possible association with premature delivery has been anecdotally reported, overall prevention of MTCT far outweighs the potential for adverse effects [9].

Use of high genetic barrier drug regimens for MTCT prophylaxis is not a concern in Western countries where access to drugs and accurate pregnancy monitoring are standard of care. In fact, HIV specialists are using boosted PI therapy in HIV-positive pregnant women. The paper by Gingelmaier et al [6] substantiates this attitude, showing its additional benefit in terms of maintenance of future therapy options for the mother. Clearly, the challenge is to export the approach applied by Gingelmaier et al [6] in Germany to low-income countries, such as sub-Saharan Africa, where >90% of mother-to-child infections occur [10]. Barriers to this strategy can be easily listed, including lack of infrastructure, drug costs, and unawareness of HIV status coupled with late presentation at delivery. However, antiretroviral treatment coverage is increasing at an encouraging pace [11], and multiple governmental and nongovernmental programs have been launched, setting up the basis for moving forward to expanding anti-HIV therapy. Although recently released high-cost drugs are unlikely to be available, many previous-generation antiretrovirals, including boosted PIs, can be obtained at greatly reduced cost yet provide effective MTCT prevention and minimize the risk of development of drug resistance. Educational programs are also a fundamental complement to introduce more-effective MTCT prevention strategies. For example, HIV-infected pregnant women may present late for delivery, making any strategy of antenatal treatment impossible. Although Gingelmaier et al [6] adopted antepartum treatment for several weeks in their work, a short late course of boosted PI therapy could also be evaluated in such cases as a measure to prevent both MTCT and selection of drug resistance in the mother. Following delivery of an uninfected child, a special issue in low-income countries is prevention of MTCT via breast-feeding because of the limited availability of replacement feeding. Should a short course of boosted PI therapy prove effective in halting HIV transmission at delivery, then extending treatment of the mother for at least 6 months postpartum could be a better way to exploit partial access to therapy with respect to prolonged antepartum therapy [12].

As a general consideration, control of HIV disease (but not infection) has dramatically improved in high-income countries. The challenge is to export knowledge, tools, and strategies to low-income countries where most of the HIV-infected population lives. Pregnant women are a special case in which treatment success entails not only prevention of MTCT but also preservation of treatment options for the mother by avoiding drug resistance issues. These issues are still associated with HIV-related death, even in Western countries [13], and would be particularly serious in developing countries where a complete antiretroviral armamentarium will probably not be available for a long time.

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References


