Early Infant Treatment: Still a Long Way to Go to Reach Human Immunodeficiency Virus Remission

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(See the Major Article by Maswabi et al on pages 388–93.)

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Studies among adults identified and treated very soon after primary human immunodeficiency virus (HIV) infection have observed that 10%–15% of patients experience reasonably long periods of viral control if antiretroviral treatment (ART) is interrupted [1, 2]. This phenomenon, usually referred to as posttreatment control or, sometimes, HIV remission, led to the hypothesis that starting ART close in time to acute infection would lead to reduced seeding of the viral reservoir. The smaller viral reservoir would, in turn, make it more likely that viral control achieved with early ART could be sustained if ART was withdrawn [2].

Identifying primary HIV infection in adults is no mean feat from a logistics point of view, but can be done among high-risk populations, usually in the context of research. For infants, HIV infection is acquired during the perinatal period, and the exact timing of infection is more difficult to pin down. Those who test positive on diagnostic nucleic acid amplification tests within the first 48 hours of life are generally

assumed to have acquired infection at some unknown point during gestation in utero. Those who test negative within the first 48 hours of life and who test positive within the next few weeks are assumed to have acquired infection intrapartum or via early breastfeeding. Thus, starting ART in a newborn hours from birth is not necessarily hours from infection. Nevertheless, soon after birth is as still close as we can get, and age at starting ART in infants has proved to be an excellent predictor of the size of the peripheral blood viral reservoir in children living with HIV with sustained viral suppression on ART [3, 4].

Enthusiasm for the possibility that very early ART in newborns may lead to posttreatment control or remission was at its peak after the first report of the “Mississippi baby” [5]. This infant, diagnosed with HIV and started on ART within 30 hours of birth, maintained viral suppression for about 18 months after ART was interrupted [5]. Soon after this report, several observational studies were set up to investigate the effects of starting ART in newborns with HIV as early as possible in the settings in sub-Saharan Africa where the HIV epidemic predominates. One of these studies was the Early Infant Treatment (EIT) study conducted in Botswana and reported by Maswabi and colleagues in this issue of *Clinical Infectious Diseases*.

At large clinical sites in and around Gaborone and Francistown in Botswana, comprehensive programs to screen newborns born to women living with HIV

were established. Screening was done with a combination of point-of-care diagnostics and laboratory-based nucleic acid amplification diagnostic tests with rapid turnaround time. Over > 3 years, 10 622 HIV-exposed newborns were screened and 42 (0.4%) were confirmed to be HIV infected. Almost all of these (40/42) were enrolled into the study and started on ART at a median of 2 days after birth. While certainly a challenge for enrollment, it is a remarkable success that this almost nationwide effort yielded so few infants with HIV. The low transmission rate highlights the strengths of the Botswana programs that provide ART for adults living with HIV.

Finding infants with HIV early enough, and rapidly starting ART in these infants, is a challenging undertaking on its own. But overcoming this initial hurdle is only the first step. The next obstacle is choice of a suitable drug regimen. Unlike the wide range of choices of antiretrovirals available for adults, there are limited drug options available in appropriate formulations and with adequate data on dosing for infants, particularly neonates. Ritonavir-boosted lopinavir is generally recommended as part of first-line regimens in infancy [6]. However, a black box warning advises against its use in preterm infants and in the first 2 weeks of life. Maswabi and colleagues opted to use nevirapine (NVP) as part of the initial regimen for the neonates along with lamivudine and zidovudine. Nevirapine, however, may seem to be a poor choice

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for this population as efavirenz was widely used in this setting for maternal treatment. Hence, we can predict that pre-ART viral mutations conferring resistance to NVP are likely to be common in this population of infants. Despite this concern, almost all infants responded with viral decline to their (on average) 3 weeks of NVP-based ART. These results are encouraging as NVP is widely available and there are a great deal of data on the safety of this drug in this age group.

Maswabi and colleagues also conducted a nested NVP pharmacokinetic substudy. To date, neonatal treatment doses of NVP have had to be inferred from modeling studies in the absence of direct data. EIT found a high degree of variability in NVP concentrations at weeks 1 and 2, with almost 50% of neonates having concentrations below the predicted ideal therapeutic target of 3000 ng/mL. Interestingly, there was no correlation between NVP concentrations below this target and viral response. The authors conclude that the 3000 ng/mL target may be unnecessarily high and that the current recommended 6 mg/kg twice-daily dosing is most likely adequate.

Ritonavir-boosted lopinavir was substituted for NVP once the infants reached ages considered safe for the use of this drug and, coincident with this switch, 22% of infants experienced viral rebound. The most likely explanation for this pattern is the foul taste of the ritonavir-boosted lopinavir syrup. Fortunately, mothers appeared to have been able to convince their infants to swallow sufficient quantities of this liquid and viral load resumed its decline. By 24 weeks, 71% of infants had attained a viral load < 40 copies/mL.

Maswabi and colleagues present the results of 71% suppression by 24 weeks as a success and indeed it is, given the many challenges involved in identifying and treating infants such as these. However, despite quite low pretreatment viral loads (median of 11 220 copies/mL), viral decline was not particularly rapid, with only 20% at 4 weeks and 55% at 12 weeks after ART starting to achieve viral load < 40 copies/mL. Data on long-term sustainability of viral suppression on ART and on immune recovery are not presented. A comparable study in South Africa reported highly similar rates of initial viral suppression, but < 50% of early treated infants sustained suppression through 72 weeks [7]. In addition, a surprisingly high proportion of children with sustained viral suppression on ART had CD4 T-cell parameters below the expected normal range for age [7].

We have come a long way in prevention of HIV transmission from women to their offspring. The EIT study highlights just how far, with tremendous success in achieving very low HIV transmission rates in a well-functioning program as that in Botswana. However, for those infants who acquire infection despite this, we still have a long way to go in terms of learning how best to treat them, and even farther to go to learn how to steer a course toward attaining remission. Maswabi and colleagues provide encouraging new data supporting the efficacy of the initial use of NVP in ART regimens for neonates as well as encouraging results that reasonable viral suppression rates can be attained. But the study also highlights critical gaps. One of these gaps is the need for drug regimens suitable for this age group that are more adherence-friendly.

It is only once we can utilize antiretroviral regimens that can rapidly suppress virus and keep it down with adequate immune recovery and that are realistic for mothers to fully adhere to will we be able to determine if very early ART in infants with HIV may indeed be a stepping stone to achieve HIV remission.

Notes

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