EDITORIAL COMMENT

Persistent HIV infection in newborns: how soon is soon enough?

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Over the last few years, attention has been drawn to efforts that seek to develop a cure for HIV infection. Investigators and scientists seek to completely eradicate HIV infection (called by some a sterilizing cure), or allow patients to interrupt antiretroviral therapy (ART) without the risk of viral rebound, viral transmission, or progressive disease (known as a functional cure). This wave of interest has been spurred by anecdotes of actual cure in real patients, first in Timothy Brown [1,2], and then more recently in two additional marrow transplant patients in Boston [3], and a newborn treated hours after birth – the 'Mississippi baby.' [4]. However, the relatively rapid return of viremia in the Boston patients is a sobering reminder of the challenges ahead.

In the latter case, a child born to an HIV-infected mother without prenatal care was treated as soon as possible within 30 h of birth with three-drug ART. Successful, suppressive therapy was administered until the child was withdrawn from medical care at 18 months of age. When the child returned to care at 26 months of age, plasma viremia was not detected. Numerous sensitive research assays were performed, without evidence thus far for the persistence of HIV infection [4].

The potential to eradicate infection by early treatment in newborns is particularly exciting as there are still many children across the world who are exposed to HIV during gestation and birth. The timely implementation of ART might result in eradication of HIV infection in some of these children. Alternatively or additionally, such early intervention could allow functional cure in some patients – durable and potent control of HIV infection, thereby avoiding the need for ART for a substantial period. A key missing piece of information in this regard is an understanding of how timely this intervention must be.

In this issue, Ananworanich and colleagues [5] provide important foundational information by presenting a study of 15 Thai children who initiated multidrug ART before 6 months of age, and then enjoyed sustained viral suppression. The children reported are now between 4 and 12 years old, and have been treated with standard ART for between 3.5 and nearly 12 years. The oldest was 6 months old at the time of ART initiation, and three of the children were – like the Mississippi baby – given ART continuously since birth.

Across all the children in this Thai cohort, nine out of 15 had extremely low integrated HIV DNA levels ($<$20 copies/10^6CD4$^+$ T cells), this form of HIV DNA being undetectable ($<$1 copy/10^6CD4$^+$ T cells) in two children. Although, the frequency of detection of HIV

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DNA generally reflects a broad distribution similar to the range of control of plasma viremia, it is surprising that the majority of children who received early ART had low levels of integrated proviral genomes. As the authors point out, conclusions about the frequency of latent, persistent infection in these children are limited by the inability thus far to directly measure this event through the use of a quantitative viral outgrowth assay (QVOA), as this requires a demanding apheresis procedure or a large volume blood draw. But the low levels of integrated virus suggest that cure or durable drug-free control of infection might be more easily achieved in HIV-infected children treated immediately after birth.

On the contrary, HIV-specific immune responses in these children were poor or rare. Only one of 15 patients detectable HIV-specific $CD4^+/CD8^+$ responses and most (47%) had nonreactive enzyme immunoassays. This deficiency suggests an intervention: future studies that seek to explore the safety of ART withdrawal in such populations might be well advised to consider employing immunotherapy such as an HIV vaccine prior to attempting a analytic interruption of ART. Given the developing state of the immune response, such immunotherapies will need to be carefully tested in children.

Most tantalizing are the three children described who, like the Mississippi baby, have been treated with fully suppressive triple-drug ART since the day of birth. These children are found to have among the lowest level of integrated HIV DNA. These patients are surely the best candidates for study to attempt to replicate the experience of the Mississippi baby. However, more definitive but invasive studies, such as the QVOA assay should document the presence or absence of replication HIV in such immediately treated children. The recovery of any replication-competent HIV should make any investigator reticent to stop ART, at least not until a potent anti-HIV immune response has been therapeutically put in place.

Nevertheless, these findings are impressive and exciting, and challenge us to redouble our efforts to provide better prenatal prophylaxis, and employ ART as soon as possible in the rare cases in which prophylaxis was not employed. The question of how soon is soon enough remains to be answered.

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Conflicts of interest

D.M. has consulted for Merck, GlaxoSmithKline and Chimerix, and holds common stock in Gilead.

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