Clinical Infectious Diseases

EDITORIAL COMMENTARY

Capitalizing on Postexposure Antiretroviral Prophylaxis to Restrict Seeding of the Human Immunodeficiency Virus Reservoir

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(See the Major Article by Massanella et al on pages 427–38.)

Keywords. HIV; antiretroviral prophylaxis; reservoir seeding.

It is estimated that 1.7 million children < 15 years of age were living with human immunodeficiency virus (HIV) in 2018 [1]. As in infected adults, antiretroviral therapy (ART) in these children is lifelong due to early establishment of stable HIV reservoirs that preclude ART-free remission and cure. However, despite tremendous progress in strategies to prevent perinatal HIV transmission, new HIV infections continue, with an estimated 160 000 infections in children in 2018 [1]. It is thought that limiting the size of HIV reservoirs through early ART is a key first step toward ART-free remission and cure, for which perinatal HIV infection is especially suited due to knowledge of timing of HIV exposure.

In this study, Massanella et al [2] provide key evidence that uninterrupted administration of antiretroviral (ARV) prophylaxis until ART initiation has the potential to durably limit seeding of HIV reservoirs in perinatal infections. The authors examined the effects of directly transitioning Thai infants with confirmed perinatal HIV infection from their prophylactic ARV regimen to an ART regimen on biomarkers of the HIV reservoir, compared with HIV-infected infants who either received no ARV prophylaxis or who completed their ARV prophylactic regimen but were not receiving any ARVs at ART initiation. The longitudinal study was performed on children enrolled in the RV475/HIVNAT209 study of early treatment of perinatal HIV infection; the study included 31 children at the pre-ART timepoint (11 with continuous prophylaxis prior to ART), 45 children with 1 year on ART (17 with continuous prophylaxis), and 85 children with 3 years on ART (34 with continuous prophylaxis). The authors also examined the HIV reservoir in 37 older children from the RV474/HIVNAT194 study, of whom 6 had directly transitioned from prophylaxis to ART, 10 had received ARV prophylaxis that was discontinued for several weeks before ART initiation, and 21 had received no ARV prophylaxis. Biomarkers of HIV infection included pre- and post-ART plasma viral loads, cell-associated total and integrated HIV DNA, and transcriptional competence of the proviral reservoirs using the Tat/rev induced limiting dilution assay (TILDA).

It is important to note that the study findings are based on a small subset of study participants from 2 different cohort studies, in whom ARV prophylactic regimens varied from single to dual and triple ARV prophylaxis, reflecting the evolving changes in infant prophylactic regimens to prevent perinatal HIV transmission. In addition, there was a predominance (68% in RV475/HIVNAT209 and 73% in RV474/HIVNAT194) of in utero–infected infants in the continuous ARV arm, whose infection was therefore already established at the time of initiation of ARV prophylaxis at birth, representing suboptimal ARV treatment.

Nonetheless, study findings showed that infants who directly transitioned from ARV prophylaxis to ART had significantly lower pre-ART plasma viral loads, total and integrated HIV DNA, and inducible proviruses compared with infants who received discontinuous or no ARV prophylaxis. Continuous ARV from birth was also correlated with lower reservoir size, including inducible reservoirs, at years 1 and 3 of ART, supporting the notion that direct transition to ART from prophylactic ARV reduced initial seeding of the reservoir. Notably, proviral reservoir decay dynamics, including the inducible proviral reservoir, were similar between the 2 groups, with both groups exhibiting biphasic decay dynamics with a faster first-phase decay followed by stabilization after 2–3 years of ART. This confirms the contribution of short- and long-lived cells to the total HIV-infected

Received 20 May 2020; editorial decision 21 May 2020; published online 5 June 2020.

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Clinical Infectious Diseases® 2021;73(3):439–40

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DOI: 10.1093/cid/ciaa715

cell pool pre-ART, and the stability of the reservoir, even with direct transition from a triple ARV prophylactic regimen initiated at birth to ART. A critical observation is the rapidity and high concentrations at which HIV-infected cells are generated in untreated perinatal HIV infection in infancy, highlighting the importance of earlier identification and treatment of perinatal HIV infection.

Total and integrated DNA at the pre-ART timepoint were significantly correlated with plasma viral loads. Importantly, the lower viral loads associated with direct transition from continuous ARV prophylaxis to ART were also associated with a higher proportion of infants (63%) achieving undetectable plasma viral loads by 6 months of age (compared with 31% in infants who discontinued or received no prophylaxis), highlighting the contribution of longer-lived cells to plasma viremia during ART. HIV reservoir size at start of ART was highly correlated with the size of the reservoir at 1 and 3 years of ART, which has been observed previously [3]. The length of time without ARV in the discontinuous ARV prophylactic group was also significantly correlated with the size of the reservoir at 1 and 3 years of age.

Altogether, these results indicate that ARV prophylaxis administered from birth leads to partial suppression of HIV replication among in utero– and peripartum-infected infants, and that this suppression is sufficient to limit seeding of HIV reservoirs when infants are directly transitioned to a protease inhibitor–based regimen—an effect that is sustained through 3 years of ART. These findings have implications for strategies aimed at limiting the HIV reservoir toward ART-free remission and cure.

It is important to underscore that the continuous ARV group was predominantly infected in utero, which enables direct transitioning from ARV prophylaxis to ART as HIV infection can be identified in these infants from blood samples collected within the first 48 hours of life. However, almost all infants in the continuous ARV group had detectable viremia before transitioning to the ART regimen, which emphasizes the nonsuppressive effects of triple ARV regimens when administered at prophylactic dosage. This approach can be optimized with the use of treatment, rather than prophylactic, dosages of ARV, which would provide an ART regimen that could effectively control rather than partially suppress HIV replication, while averting ARV drug resistance. Indeed, recent studies have shown that initiating a 3-drug treatment regimen from birth in a therapeutic rather than prophylactic regimen in in utero–infected infants leads to faster decay of HIV-infected cells in the first year of life [4, 5].

A major limitation to widespread implementation of a strategy of direct transition from the ARV prophylactic regimen to ART is the limitation in sensitivity of infant HIV diagnostic tests, especially for peripartum or early breast-milk transmission; prophylactic regimens reduce the amount of detectable HIV RNA and DNA, complicating identification of HIV infection in infants. Such an approach will require frequent testing with more sensitive assays in the first 6 weeks of life, when the infant is still receiving the ARV prophylactic regimen. This is not feasible with the existing testing algorithm for HIV-exposed infants, where most are tested around 6 weeks of age when the prophylactic ARV regimen has been discontinued, and it is also challenging to implement for breast-milk HIV transmission.

The study by Massanella et al once again emphasizes the importance of initiating ARVs or novel therapeutic approaches as early as from birth to limit HIV reservoirs in perinatal infection. Indeed, the capacity of very early and early ART to afford ART-free remission has been illustrated in both perinatal [6] and adult [7] infections. However, this will require investments in earlier and more frequent testing of HIV-exposed infants, and in administration of combination regimens for infant prophylaxis.

Notes

Financial support. This research was supported by the National Institutes of Health (grant numbers R01 HD080474 and PO1 AI131365 to D. P.); and the BELIEVE Martin Delaney Collaboratory (grant number 1UM1AI26617).

Potential conflicts of interest. D. P. reports grants from the National Institute of Allergy and Infectious Diseases and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and advisory board fees for Merck, outside the submitted work. A. D. reports no potential conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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