Could Very Early Treatment Cure Babies Born With HIV?

Infants treated within the first days of life can have a very low viral reservoir, but most don't receive antivirals so soon in the real world.

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Infants born with HIV who start antiretroviral therapy (ART) within two days after birth may be able to maintain viral suppression after stopping treatment, according to study results published in The Lancet HIV.

These findings confirm prior research suggesting that very early treatment limits the size of the viral reservoir, potentially enabling a functional cure. These children have not yet stopped antiretrovirals to see whether their viral load will rebound, but a treatment interruption is planned for a later stage of the study.

Taking antiretrovirals during pregnancy can suppress the virus and prevent mother-to-child transmission, but some women living with HIV do not receive timely prenatal care and have a detectable virus at the time of delivery. A pregnant person with HIV who is not receiving ART has a 15% to 45% chance of passing on the virus during pregnancy, childbirth or breastfeeding, according to the World Health Organization.

At the 2013 Conference on Retroviruses and Opportunistic Infections, Deborah Persaud, MD, of Johns Hopkins University School of Medicine reported the case of the Mississippi Baby, an infant born to a mother who was not on treatment and had a detectable HIV viral load at the time of delivery. Due to the high risk of exposure, the girl was started on a three-drug antiretroviral regimen 30 hours after birth.

Early testing revealed that the child was infected despite treatment. She continued on antiretrovirals and achieved an undetectable viral load within a month. The child's caretaker stopped her treatment when she was 18 months old, but the girl nonetheless maintained viral suppression without ART. As described in The New England Journal of Medicine, extensive testing showed that her plasma HIV RNA viral load, proviral HIV DNA in peripheral blood cells and HIV antibodies were undetectable.

News of the Mississippi Baby garnered global headlines and raised hopes that very early treatment might lead to a functional cure. But unfortunately, as Persaud reported the following year, after

more than two years off ART, the girl's viral load ultimately rebounded, and her CD4 T-cell count started to decline, at which point she resumed antiretroviral therapy.

Though disappointing, the case spurred intensified research on persistent virus and the effects of very early treatment. While ART can suppress HIV replication indefinitely, the virus inserts its genetic blueprints into the DNA of human cells during the early stages of infection and establishes a long-lasting reservoir that is unreachable by antiretrovirals and usually invisible to the immune system.

Now, Persaud and her team have published findings from IMPAACT P1115 (NCT02140255), an ongoing study of more than 50 children, suggesting that starting antiretrovirals within the first days after birth may indeed lead to viral suppression that could potentially be maintained even after interrupting treatment. The results were previously presented in part at the 2022 Conference on Retroviruses and Opportunistic Infections.

"We sought proof of the concept that if you can safely treat babies with a three-drug regimen within 48 hours of life, you can limit the buildup of these reservoirs and get them to very low levels that may lead to ART-free remission, where the virus doesn't come back quickly if the ART is stopped," Persaud said in a Johns Hopkins news release.

This analysis included 54 children born to HIV-positive mothers in sub-Saharan Africa, Brazil, Haiti, Thailand and the United States between January 2015 and December 2017. The infants were confirmed to have acquired HIV during gestation.

One group of 34 infants (23 girls and 11 boys) born to mothers who were not on ART during pregnancy were started on a three-drug regimen of AZT (Retrovir) or abacavir (Ziagen), lamivudine (Epivir) and nevirapine (Viramune) within two days after birth. A second group of 20 infants (10 girls and 10 boys) born to mothers who were on treatment during pregnancy started a similar regimen shortly after birth. A fourth drug, boosted lopinavir (Kaletra), was added for all babies who tested HIV positive at around 14 days old. Infants with two consecutive undetectable viral loads stopped nevirapine.

While these are not the most potent antiretrovirals, they were the only drugs approved for newborns at the time of the study, Persaud noted. As the trial continues, the researchers plan to evaluate newer more effective and better-tolerated regimens, potentially including integrase inhibitors and broadly neutralizing antibodies.

Treatment side effects for infants are a concern. In this study, 44% of babies in the first group and 35% in the second group experienced severe, albeit reversible, adverse events.

The researchers estimated that infants in the first group had a 33% chance of achieving and maintaining an undetectable HIV RNA plasma viral load through the age of 2 years, while those in the second group had a 57% chance of doing so.

Among the children who did maintain an undetectable plasma viral load at age 2, 64% in the first

group and 71% in the second group had no detectable HIV DNA, indicating a very small or nonexistent viral reservoir. What's more, 83% and 100%, respectively, tested negative for HIV antibodies, suggesting that there may be no persistent virus to trigger an ongoing immune response. They also had normal CD4 counts and CD4 percentages.

A majority of the children did not maintain full viral suppression, likely due to inconsistent daily adherence to treatment. Of the 54 babies in the study, 19% (six in the first group and four in the second group) met all the criteria to be eligible for a carefully monitored treatment interruption in a later portion of the study. But caution is warranted, as the Mississippi Baby eventually experienced viral rebound despite meeting similar criteria.

"The obvious clinical benefits in terms of morbidity and mortality of super early initiation of ART can no longer be ignored," Philippe Van de Perre, MD, PhD, of the University of Montpelier in France, and Penny Moore, PhD, of the University of the Witwatersrand in Johannesburg, wrote in an accompanying commentary. "Guidelines for pediatric HIV care should urgently include super early diagnosis of neonates infected with HIV in utero and prompt initiation of ART during the window when mother-neonate pairs are still in the maternity ward. Implementation of such policies has the potential to spare some of these children from lifelong ART therapy."

While these initial results are promising, Persaud stressed that this study does not reflect real-world conditions. The researchers were able to diagnose HIV within a strict time frame, start antiretrovirals very early and monitor the infants frequently. In contrast, standard treatment for babies typically starts at 2 to 3 months of age, often due to delayed test results, particularly outside of the United States.

"If you treat at 2 to 3 months of age, when most children start a regimen, very, very, very few kids would actually get to this undetectable stage by 2 years of age," Persaud said. "It would actually take them until 5 years of age and older to get to a low HIV DNA level, and it's never to this undetectable level."

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