Some Children Treated Very Early Have Sustained HIV Remission

Four of six children treated within 48 hours after birth maintained viral suppression for at least a year after stopping therapy.

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A small proportion of children who start HIV treatment within the first two days of life may achieve ongoing viral suppression after stopping antiretrovirals, according to study results presented this week at the Conference on Retroviruses and Opportunistic Infections (CROI 2024) in Denver. While these promising results hold clues for cure research, they do not reflect the realities of typical care for mothers and children living with HIV.

Among 54 children who acquired HIV during gestation and started combination antiretroviral therapy (ART) within 48 hours after birth, six met strict criteria for undetectable HIV and began a closely monitored treatment interruption. Four of them had sustained viral remission for at least a year, and one went 80 weeks before experiencing viral rebound, Deborah Persaud, MD, of Johns Hopkins University School of Medicine, reported.

Deborah Persaud presents at CROI 2024Liz Highleyman

“We think this is a really ground-breaking finding for the field of ART-free remission and cure for children,” Persaud said at a conference media briefing. But she added that the study results “point to the necessity of immediate neonatal testing and treatment initiation in health care settings for all infants potentially exposed to HIV in utero.”

Early Treatment for Babies

Pregnant women with HIV who are not on ART have a 15% to 45% chance of passing on the virus during pregnancy, childbirth or breastfeeding. Taking antiretrovirals reduces the risk to less than 1%, but many women living with HIV do not receive timely prenatal care or have access to treatment.

This was the case for the mother of the Mississippi Baby, who was not on treatment and had a detectable viral load at the time of delivery. Due to the high risk of exposure, the infant was started on a combination antiretroviral regimen 30 hours after birth, but testing revealed that she became infected despite treatment.

The child’s family stopped her antiretrovirals when she was 18 months old, but when she returned to care several months later, she still had viral suppression. This was surprising, as HIV inserts its genetic blueprints into the DNA of human cells soon after infection, establishing a long-lasting reservoir that is unreachable by antiretrovirals and usually invisible to the immune system. Most

people who interrupt treatment experience viral rebound within a few weeks.

Persaud described the case at CROI 2103 and in The New England Journal of Medicine, prompting global headlines about a possible cure. Extensive testing showed that the child's plasma HIV RNA, proviral HIV DNA in peripheral blood cells and HIV antibodies were undetectable. Unfortunately, though, the girl's viral load rebounded after just over two years off treatment.

While disappointing, the case added to the evidence that starting treatment very early might limit the size of the viral reservoir and spurred intensified research on viral persistence and a functional cure, or long-term remission without antiretrovirals. To this end, researchers launched a trial called IMPAACT P1115 (NCT02140255), funded by the National Institutes of Health.

The study enrolled infants at high risk for in utero HIV acquisition in Brazil, Haiti, Thailand, the United States and several counties in sub-Saharan Africa. Because diagnosis can take time, the babies preemptively started combination ART within 48 hours after birth.

In December 2023, Persaud and colleagues published findings from the study in The Lancet HIV; the results were previously reported in part at CROI 2022. This analysis included 54 children born during 2015-2017 who were confirmed to have acquired HIV during gestation. They initially started on a regimen of AZT (Retrovir) or abacavir (Ziagen), lamivudine (Epivir) and nevirapine (Viramune), with lopinavir/ritonavir (Kaletra) added later.

Most of the children did not maintain full viral suppression, likely due to inconsistent adherence. But those who had a stable undetectable plasma HIV RNA viral load from 48 weeks onward were eligible for an analytic treatment interruption (ATI) if they also met the following criteria:

- Not breastfeeding
- No detectable HIV DNA in peripheral blood cells (a measure of the viral reservoir)
- Two consecutive two negative HIV antibody tests (a measure of immune response)
- Normal CD4 count
- CD4 percentage of at least 25.

The eligible children had not yet stopped antiretroviral treatment at the time of publication, but Persaud presented updated results at CROI 2024.

Some advocates have raised questions about the ethics of treatment interruption for children, but Persaud explained that this is necessary because there are no known biomarkers that predict ART-free remission. She said that "mothers are very invested" in this research, and "this is something parents want for their children." She noted that the commitment of HIV-positive mothers and their communities enabled the research that proved antiretrovirals prevent mother-to-child transmission—studies some advocates opposed at the time.

Six children, all from sub-Saharan Africa, met the criteria and began a treatment interruption at median age of 5.5 years. The researchers initially planned to take eligible children off treatment around the age of 2 years, but this was delayed due to the COVID-19 pandemic. Four were girls and two were boys—an interesting finding, as recent research suggests that boys may be more likely than girls to maintain viral suppression off treatment.

Two of the six children had relatively rapid viral rebound at three and eight weeks after stopping treatment. But the other four achieved ART-free remission, defined as no detectable plasma HIV RNA for at least 48 weeks without antiretrovirals. Lopinavir plasma levels were measured retrospectively to ensure they were in fact off treatment. One of the girls maintained an undetectable viral load for 80 weeks before experiencing viral rebound. The others were still in remission at 48, 52 and 64 weeks.

All children who experienced viral rebound regained viral suppression after resuming treatment. Two developed acute retroviral syndrome—flu-like symptoms that arise as the immune system starts responding to the virus—and one had a low white blood cell count, but otherwise there were no clinical or immunological events of concern during or after treatment interruption.

“This is the first time we’ve been able to successfully recreate the case of the Mississippi baby—and in four children,” Persaud said in a Johns Hopkins news release. “These results are an important first step to understanding how to curtail HIV reservoirs in children toward ART-free remission and cure for more children living with HIV, ultimately changing the treatment paradigm for this infection that currently afflicts 1.7 million children around the world.”

Treatment in the Real World

While these results are promising, the study does not reflect real-world conditions for many mothers and infants with HIV. The study investigators were able to diagnose HIV within a strict time frame, start antiretrovirals hours after birth and monitor the infants frequently. In contrast, babies typically start treatment weeks or months after birth, especially in low- and middle-income countries where the burden of HIV is greatest.

The children in this study received older antiretrovirals that were approved for pediatric use at the time. As the trial continues, the researchers plan to evaluate newer, more potent regimens, potentially including integrase inhibitors and broadly neutralizing antibodies.

“If we can get the virus to such low levels that we might be able to use some newer, innovative treatments to keep them from needing to be on medication every day, then we’re setting them up for success for long-term virologic control,” trial protocol chair Ellen Chadwick, MD, of the Ann & Robert H. Lurie Children’s Hospital of Chicago, said in a news release.

The researchers also aim to identify biomarkers that could help predict the likelihood and timing of viral rebound after treatment interruption. Persaud noted that the criteria used for this analysis are not fully predictive of ART-free remission, as two children deemed eligible experienced early

viral rebound.

“These findings are clear evidence that very early treatment enables unique features of the neonatal immune system to limit HIV reservoir development, which increases the prospect of HIV remission,” commented National Institutes of Allergy and Infectious Diseases director Jeanne Marrazzo, MD, MPH. “The promising signals from this study are a beacon for future HIV remission science and underscore the indispensable roles of the global network of clinicians and study staff who implement pediatric HIV research with the utmost care.”

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