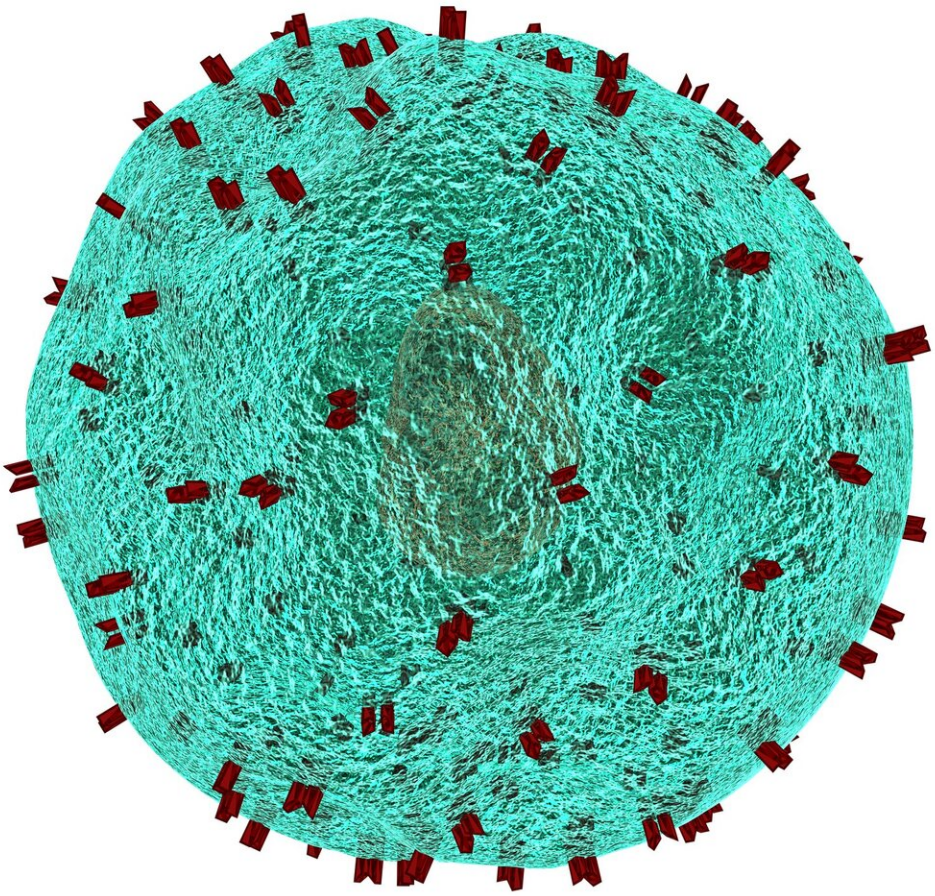
Children surpass a year of HIV remission after treatment pause

March 6 2024



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Four children have remained free of detectable HIV for more than one year after their antiretroviral therapy (ART) was paused to see if they could achieve HIV remission, according to a presentation today at the 2024 Conference on Retroviruses and Opportunistic Infections (CROI) in Denver.

The children who acquired HIV before birth were enrolled in a clinical trial in which an ART regimen was started within 48 hours of birth and then closely monitored for drug safety and HIV viral suppression. The outcomes reported today follow planned ART interruptions once the children met predefined virological and immunological criteria.

"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," said NIAID Director Jeanne Marrazzo, M.D., M.P.H. "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."

Advances in ART have significantly reduced perinatal HIV transmission when a child acquires HIV while in the uterus, during birth, or through the consumption of milk from a lactating person. If transmission does occur, children must take lifelong ART to control the replication of the virus and protect their immune systems from life-threatening complications. Typically, interruption in treatment will lead to rapid resumption of HIV replication and detectable virus in the blood within weeks.

However, in 2013, a case report described an infant born with HIV in Mississippi who initiated treatment at 30 hours of life, was taken off ART at 18 months of age, and remained in remission with no evidence of detectable HIV for 27 months.

Building on the observation that very early ART initiation may limit HIV's ability to establish reservoirs of dormant virus in infants, researchers began an early-stage proof-of-concept study of very early ART in infants conducted in Brazil, Haiti, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, the United States, Zambia, and Zimbabwe.

Previous publications from the clinical study showed that ART initiated within hours of birth was safe and effective at achieving and maintaining HIV suppression. A small subset of children achieved sustained HIV suppression and met other predefined study criteria for interrupting ART.

These criteria include a durable absence of HIV replication from 48 weeks of ART initiation onward, no detectable antibodies near the time of ART interruption, and having a $CD4^+$ T-cell count (the main immune cell target of HIV) similar to those of a child without HIV. Children who met these criteria were older than 2 years, and had stopped consuming human milk were eligible to interrupt ART.

Data presented at CROI summarized the experience of six children, all aged 5 years, who were eligible for ART interruption with close health and safety monitoring. Four of the six children experienced HIV remission, defined as the absence of replicating virus for at least 48 weeks off ART. One of them experienced remission for 80 weeks, but then their HIV rebounded to detectable levels.

Three others have been and remain in remission for 48, 52, and 64 weeks, respectively. However, two children did not experience

remission, and their HIV became detectable within three and eight weeks after ART interruption, respectively. The two children whose HIV returned at eight and 80 weeks experienced mild acute retroviral syndrome (ARS) with symptoms including headache, fever, rash, swollen lymph nodes, tonsillitis, diarrhea, nausea and vomiting.

One child had markedly low white blood cells, which are a type of immune cell. Both the ARS and white blood deficiency resolved either prior to or soon after restarting ART. The three children who experienced viral rebound resumed HIV suppression within six, eight, and 20 weeks of restarting ART.

"This is the first study to rigorously replicate and expand upon the outcomes observed in the Mississippi case report," said lead study virologist Deborah Persaud, M.D., professor of pediatrics at the Johns Hopkins University School of Medicine and director of the Division of Pediatric Infectious Diseases at Johns Hopkins Children's Center, Baltimore.

"These results are groundbreaking for HIV remission and cure research, and they also point to the necessity of immediate neonatal testing and treatment initiation in health care settings for all infants potentially exposed to HIV in utero."

The latest findings show that very early ART initiation has varying but favorable outcomes on the control of HIV. While ARS was generally mild and resolved in both cases, the authors cautioned that close monitoring for this potential event is needed in ongoing and future HIV remission research involving ART interruption.

The children participating in this study took ART regimens with medicines that have been part of standard first-line therapy for decades. Further research is planned or underway to understand how these

observations could differ in children receiving newer, more potent generations of antiretroviral drugs and to identify biomarkers to predict the likelihood of HIV remission or rebound following ART interruption.

Additional studies are also needed to understand the mechanisms by which neonatal immunity and very early ART initiation limited the formation of HIV reservoirs and contributed to the remission observed in this study.

"ART shifted the HIV care paradigm, but treatment is a long road, especially for children as lifetime HIV survivors," said Adeodata Kekitiinwa, MBChB, MMed, emeritus clinical associate professor in the Department of Pediatrics at Baylor College of Medicine, study investigator of record and clinical research site leader in Kampala, Uganda.

"This trial takes us a step closer to realizing another paradigm shift in which our approach to ART could be so effective that it might be used for a season of life, rather than its entirety."

More information: Persaud et al. ART-Free HIV-1 Remission in Very Early Treated Children: Results from IMPAACT P1115. Conference on Retroviruses and Opportunistic Infections in Denver, Colorado. Wednesday, March 6, 2024.

Provided by National Institutes of Health