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Viremic Relapse after HIV-1 Remission in a Perinatally Infected Child

TO THE EDITOR: We previously reported1 the remission of human immunodeficiency virus type 1 (HIV-1) in a perinatally infected child — the “Mississippi Child.” After receiving antiretroviral therapy (ART) between 30 hours and 18 months of age, this child had persistently undetectable plasma HIV-1 viremia for 12 months in the absence of HIV-1–specific immune responses. At the time of the initial case report, it was uncertain whether HIV-1 reservoirs were established that could lead to rebound viremia.

After the first report, the child had persistently undetectable plasma HIV-1 RNA levels, as assessed by means of standard clinical assays, with normal CD4+ and CD8+ T-cell counts. Plasma viremia also remained undetectable through 21.9 months after the discontinuation of ART on ultrasensitive single-copy viral-load assays (<0.4 and <0.5 copies per milliliter).

During routine clinical follow-up at 46.4 months of age (27.6 months after the discontinuation of ART), the plasma viral load rebounded to 2658 copies per milliliter (Fig. 1A), circulating CD4+ T-cell levels increased to 43%, and the ratio of CD4+ T cells to CD8+ T cells normalized.

Within 72 hours after the reinitiation of ART, the plasma viral load dropped to 2658 copies per milliliter (Fig. 1A), circulating CD4+ T-cell levels increased to 43%, and the ratio of CD4+ T cells to CD8+ T cells normalized.

During the period of virologic remission, HIV-1 DNA was intermittently detected in circulating unfractionated peripheral-blood mononuclear cells (PBMCs) and cells enriched for resting and activated CD4+ T cells. HLA typing confirmed the patient identity of the cellular DNA used for HIV-1 DNA measurements. The median number of copies of HIV-1 DNA in unfractionated PBMCs and resting and activated CD4+ T cells before rebound viremia was 2.7 per million cells (interquartile range, 2.2 to 3.4), 3.5 per million cells (interquartile range, 2.1 to 4.4), and 3.3 per million cells (interquartile range, 1.8 to 5.5), respectively. However, replication-competent viral reservoirs remained undetectable throughout follow-up in a cumulative 64 million cultured resting CD4+ T cells.

HIV-1–specific antibody and cell-mediated immune responses were not detected through 21.9 months after the discontinuation of ART but were detected at viremic rebound by means of enzyme-linked immunosorbent assay. The findings were confirmed by Western blot testing (1:10 dilution), which revealed reactivity to HIV-1 Env (gp160) and Gag (p24); 72 hours later, Western blot testing revealed reactivity to HIV-1 Env.
(gp160, gp120, and gp41), Gag (p55, p24, and p17), and Pol (p66). The lack of detectable responses to p31 integrase was compatible with rebound viral replication of at least 1 month but less than 2 months.3

Before viremic rebound, sequencing attempts were unsuccessful. Single-genome amplification and sequencing of full-length HIV-1 Env directly from rebounding plasma virus revealed 98.6% sequence identity to maternal plasma viral sequences collected 24 months after delivery (Fig. 1B). Diversity was 0.1%, consistent with values seen in transmitted founder viruses in mother-to-child HIV-1 transmission4 and a lack of ongoing virus replication during the period of HIV-1 remission. Phenotypic and genotypic analysis of the HIV-1 Env sequence from rebounding virus showed R5 tropism.

In conclusion, the return of HIV-1 viremia after a substantial period of viral quiescence is consistent with the model of HIV-1 latency in which long-lived resting memory CD4+ T cells were generated during routine immunologic memory formation, though other reservoirs are also possible. To the best of our knowledge, this child received ART between 30 hours and 18 months of age. Whether earlier initiation or a longer duration of ART, alone or combined with immunotherapeutic strategies, would have affected the duration of remission is unknown. The findings in this case and others5 provide insight on how very early treatment may restrict but not eradicate HIV-1 reservoirs. Additional studies are under way to test this hypothesis and to determine whether ART alone will enable longer-term HIV-1 remission. Until these studies

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Figure 1. Plasma HIV-1 Load and Phylogenetic Analyses.
Panel A shows human immunodeficiency virus type 1 (HIV-1) RNA levels during antiretroviral treatment (ART), while the child was not receiving ART, and after the re-initiation of ART. Solid circles indicate detectable HIV-1 RNA, and open circles undetectable HIV-1 RNA; the shaded area indicates the limit of detection of the plasma viral-load assay. 3TC denotes lamivudine, AZT zidovudine, EFV efavirenz, LPV/r ritonavir-boosted lopinavir, and NVP nevirapine. Panel B shows phylogenetic analyses of maternal plasma viral sequences amplified from a maternal plasma sample collected 24 months after delivery of the infant (M01) and during viral rebound in the infant (B01) (shaded area). The neighbor-joining tree depicts full-length gp160 env sequences. Four previously described2 HIV-1 clade B–infected mother–infant pairs were included in the analysis for comparison of interpatient diversity and relatedness between mother and infant.
are completed, initiation of ART as early as possible in infants and continuation without interruption seem prudent.

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The content of this letter does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. government.

Supported by grants from the National Institutes of Health (RO1 HD080474, to Drs. Persaud and Luzuriaga; AI1097265, to Dr. Luzuriaga; and F32 AI108414, to Dr. Sanborn), the Johns Hopkins University Center for AIDS Research (P30AI094189, to Dr. Persaud), the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (UM1 AI106716, to Dr. Persaud), and the University of Massachusetts Center for Clinical and Translational Science (UL1TR000161, to Dr. Luzuriaga). Dr. Mellors is supported by a grant (UM1AI106701) from the AIDS Clinical Trials Group to the Pittsburgh Virology Specialty Laboratory and by a grant (contract 12XS547) from Leidos Biomedical Research through the National Cancer Institute.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.


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