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Viremic relapse after HIV-1 remission in a perinatally infected child

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

TO THE EDITOR: We previously reported 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 reintiation 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

![Figure 1. Plasma HIV-1 Load and Phylogenetic Analyses.](image-url)
are completed, initiation of ART as early as possible in infants and continuation without interruption seem prudent.

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