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1. Epstein RM. Assessment in medical education. *N Engl J Med* 2007;356:387-96.
2. Norcini JJ, Lipner RS, Grosso LJ. Assessment in the context of licensure and certification. *Teach Learn Med* 2013;25:Suppl 1: S62-S67.
3. Reznick RK, MacRae H. Teaching surgical skills — changes in the wind. *N Engl J Med* 2006;355:2664-9.
4. Kogan JR, Holmboe ES, Hauer KE. Tools for direct observation and assessment of clinical skills of medical trainees: a systematic review. *JAMA* 2009;302:1316-26.
5. Saslow D, Hannan J, Osuch J, et al. Clinical breast examination: practical recommendations for optimizing performance and reporting. *CA Cancer J Clin* 2004;54:327-44.

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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 16,750 copies per milliliter; this was confirmed with repeat testing (Fig. 1A). The child did not have symptoms or signs of an acute retroviral syndrome or incident illnesses (including Epstein-Barr virus infection or cytomegalovirus infection) and had not received any vaccines. Epidemiologic risk factors for reinfection with HIV-1 such as through breast milk, pre-masticated food, or sexual abuse were not identified.

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

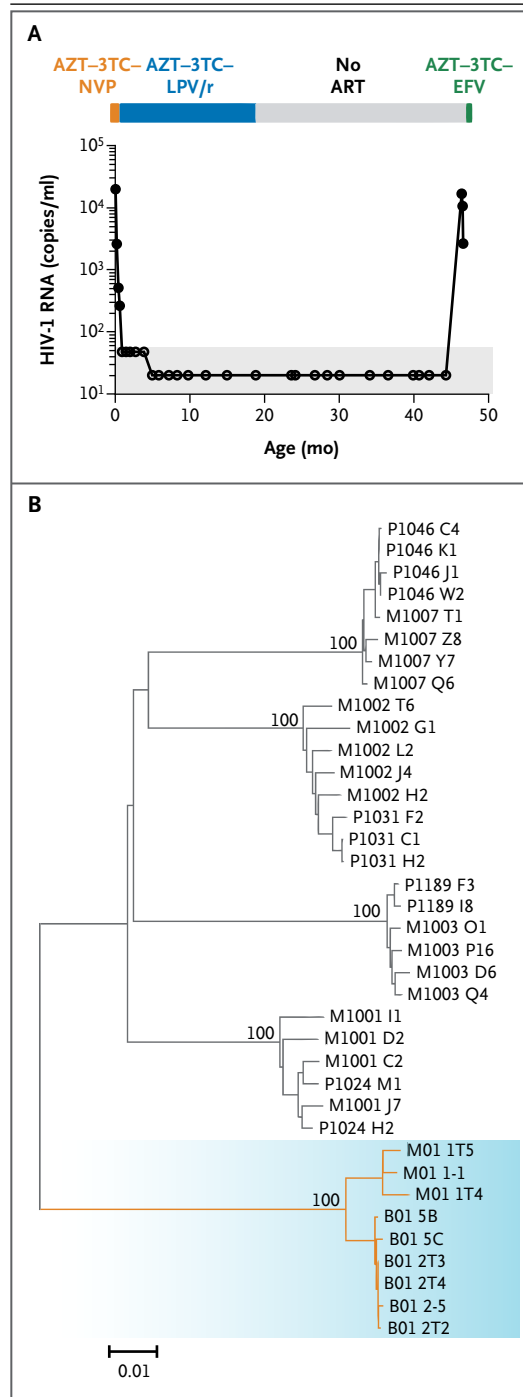
Figure 1. Plasma HIV-1 Load and Phylogenetic Analyses.

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 reinitiation 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.

(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

are completed, initiation of ART as early as possible in infants and continuation without interruption seem prudent.

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1. Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. *N Engl J Med* 2013;369:1828-35.
2. Kishko M, Somasundaran M, Brewster F, et al. Genotypic and functional properties of early infant HIV-1 envelopes. *Retrovirology* 2011;8:67.
3. Tomaras GD, Haynes BF. HIV-1-specific antibody responses during acute and chronic HIV-1 infection. *Curr Opin HIV AIDS* 2009;4:373-9.

4. Wolinsky SM, Wike CM, Korber BT, et al. Selective transmission of human immunodeficiency virus type-1 variants from mothers to infants. *Science* 1992;255:1134-7.

5. Rainwater-Lovett K, Luzuriaga K, Persaud D. Very early combination antiretroviral therapy in infants: prospects for cure. *Curr Opin HIV AIDS* 2015;10:4-11.

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