

CORRESPONDENCE



Features of HIV Infection in the Context of Long-Acting Cabotegravir Preexposure Prophylaxis

TO THE EDITOR: The results of the HIV Prevention Trials Network (HPTN) 083 and 084 trials (ClinicalTrials.gov numbers, NCT02720094 and NCT03164564, respectively) showed that long-acting injectable cabotegravir (CAB-LA) was superior to daily oral tenofovir disoproxil fumarate–emtricitabine in the prevention of sexual transmission of human immunodeficiency virus (HIV). In these trials, we observed an altered presentation of acute HIV infection in the context of CAB-LA preexposure prophylaxis (PrEP), which we term “long-acting early viral inhibition (LEVI).”¹⁻⁵

Emerging data suggest that the laboratory and clinical presentations of HIV infection involving LEVI may be different from those of classic acute HIV infection (Fig. 1; see also the Supplementary Appendix, available with the full text of this letter at NEJM.org). Cases involving LEVI are characterized by a low or undetectable HIV viral load and diminished or delayed antibody production and are usually clinically silent. Levels of HIV antigens, antibodies, RNA, and DNA are often near the level of detection of available assays; these assays may revert from reactive, indeterminate, or positive to nonreactive or negative — findings that make the confirmation of HIV infection challenging.⁵

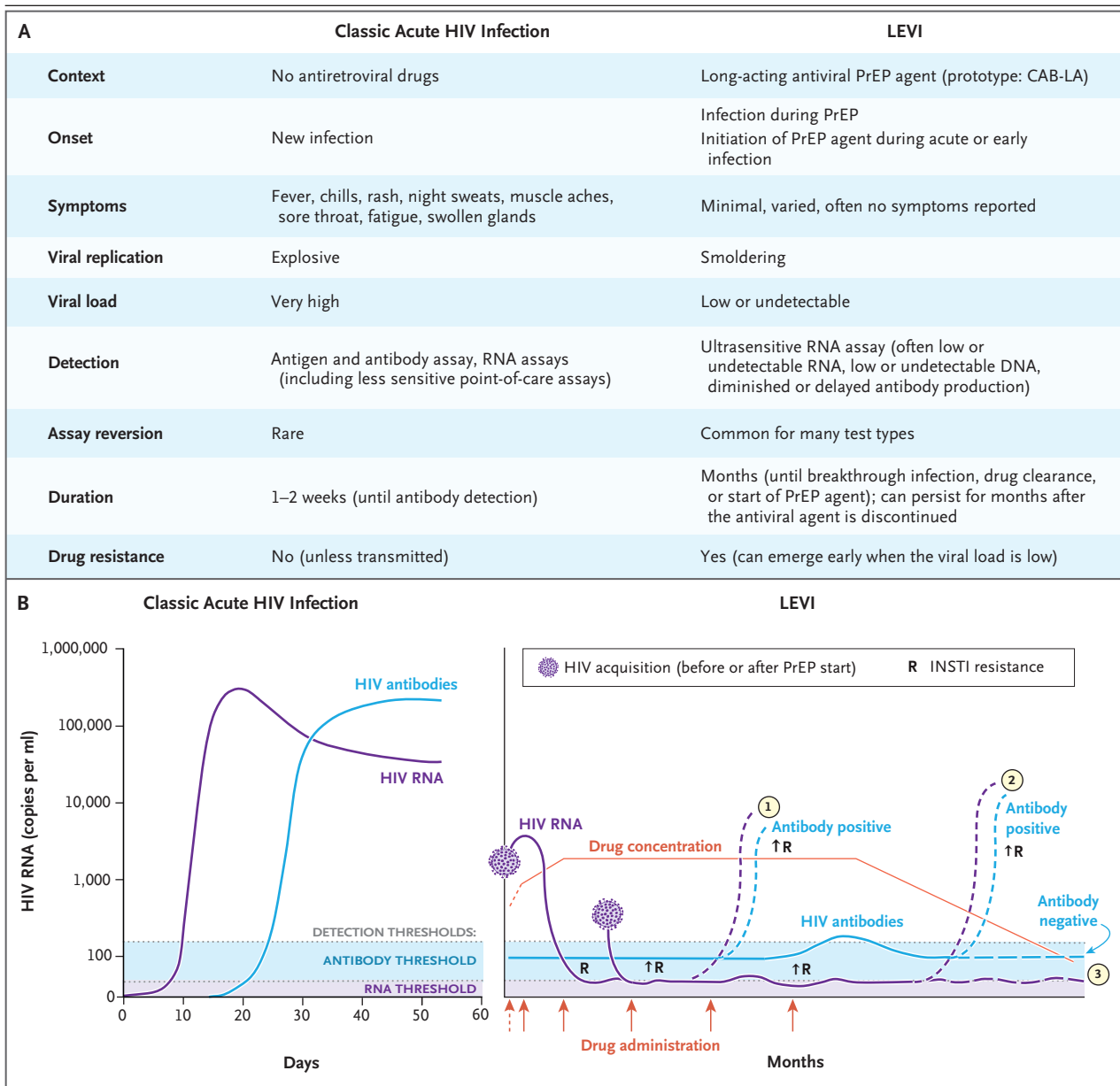
In the HPTN 083 and 084 trials, 41 HIV infections were identified among 3446 participants who had been randomly assigned to receive CAB-LA. In 17 of the 41 participants (41%), detection of infection was delayed when an HIV rapid test and an HIV antigen and antibody test were used for screening. In total, 14 of these 17 participants had received at least one CAB-LA injection and received an injection within 6 months before or after the first visit at which they had a positive HIV test (see the Supplementary Ap-

pendix). A total of 10 of the 14 participants had integrase strand transfer-inhibitor (INSTI) resistance, including all 6 participants with incident HIV infection that occurred with on-time injections.

INSTI resistance often emerges early in the course of LEVI.³ Among the participants who had been designated as male at birth, INSTI resistance was observed only in those in whom HIV infection occurred within 6 months before or after a CAB-LA injection⁴; these intervals may be longer in persons designated as female at birth. In patients in whom LEVI has occurred, HIV RNA testing detects infection earlier than standard HIV screening assays and often detects infection before INSTI resistance emerges.³ However, false positive HIV RNA tests may also occur when HIV RNA testing is used to screen for HIV infection, and such findings can complicate clinical management. False positive results can create confusion and distress for patients and providers when this testing is used to screen for HIV infection, since it may be difficult to deter-

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mine whether HIV infection has occurred. False positive results may also lead to unnecessary cessation of CAB-LA PrEP and unnecessary initiation of HIV treatment.

Current guidelines from the Centers for Disease Control and Prevention recommend that HIV RNA testing be performed in persons receiving CAB-LA PrEP. We are evaluating the use of RNA testing to screen for HIV infection in participants receiving CAB-LA PrEP in the open-label extensions of the HPTN 083 and 084 tri-

als, in which RNA testing is performed as part of the HIV testing algorithm at all scheduled trial visits.

When interpreting HIV test results in persons who are receiving CAB-LA PrEP, providers should recognize that a prolonged period of observation with frequent retesting may be needed before infection can be confirmed or ruled out and that delays in diagnosis may be associated with INSTI resistance, including resistance to dolutegravir and bictegravir. Further research is needed to identify

Figure 1 (facing page). Key Features of Classic Acute HIV Infection and LEVI.

Panel A lists the key laboratory and clinical presentations of classic acute human immunodeficiency virus (HIV) infection as compared with those of acute HIV infection involving long-acting early viral inhibition (LEVI). Panel B shows HIV viral load over time relative to acquisition of HIV infection and administration of preexposure prophylaxis (PrEP) in the absence and presence of LEVI. In the absence of antiretroviral drugs, classic acute HIV infection usually involves unconstrained, explosive viral replication after infection, with peak viremia occurring 7 to 14 days after infection. Classic acute HIV infection can be detected in the first days of infection with the use of an RNA assay. Antigen and antibody assays usually become reactive 12 to 15 days after infection. Antibody-based confirmatory and discriminatory assays usually become positive approximately 1 month after infection. Antibody expression is associated with a rapid decline in viral load, followed by establishment of a viral load set point. With LEVI, HIV acquisition may occur before or after the initiation of PrEP. HIV drug resistance (i.e., integrase strand transfer-inhibitor [INSTI] resistance) often emerges early in the course of LEVI, when viral loads are low; additional resistance-associated mutations may emerge over time before breakthrough infection occurs. Further details regarding patterns of resistance are provided in the Supplementary Appendix. As shown in Panel B, breakthrough infection can occur with on-time PrEP administration and with expected drug concentrations (circled "1"), or it can occur after drug administration stops and drug concentrations decline (circled "2"). Drug can be detected after oral doses (dashed arrow) or injections (solid arrows). In some cases, breakthrough infection may not be observed even when drug concentrations reach low levels (circled "3"). Antibody-based confirmatory and discriminatory assays often remain negative or indeterminate for long periods and may still not be positive even 1 year after HIV infection. CAB-LA denotes long-acting injectable cabotegravir.

the most effective treatment regimen in persons with breakthrough infection who are receiving CAB-LA PrEP, to identify improved HIV screening assays and algorithms for use in persons who are receiving CAB-LA PrEP, and to determine whether LEVI occurs with other long-acting PrEP agents.

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Newborn Screening and Presymptomatic Treatment of Metachromatic Leukodystrophy

TO THE EDITOR: Metachromatic leukodystrophy (MLD) is a lysosomal storage disorder characterized by progressive neurodegeneration due to a deficiency in the enzyme arylsulfatase A (ARSA). This deficiency leads to the accumulation of toxic sulfatides, primarily in the nervous system.¹ The age at symptom onset and the severity of neurodegeneration in patients with MLD are related to the level of residual enzyme activity.² Presymptomatic treatment with autologous hematopoietic stem-cell gene therapy (atidarsa-gene autotemcel [arsa-cel]) for early-onset subtypes and allogeneic hematopoietic stem-cell transplantation (HSCT) for late-onset subtypes are effective.^{3,4} Therefore, early detection and intervention are critical for improving clinical outcomes in patients with MLD, and newborn screening could play an important role in management of the condition.

We report on screening, diagnostic testing, and treatment decisions from a prospective study, conducted from October 2021 through July 2023, in which newborn infants were screened for MLD. This cohort study was performed in hospitals affiliated with the newborn screening laboratory in Hannover, Germany, and the University Children's Hospital Tübingen served as the qualified treatment center (i.e., a medical facility that has been certified as being able to administer both types of MLD treatment).

Dried blood-spot samples from 109,259 newborns were obtained as part of the existing German newborn screening program. A three-

tiered screening strategy was used, with analysis of C16:0 and C16:1-OH sulfatide species as the first tier. Samples with elevated sulfatide levels underwent measurement of ARSA activity (the second tier) and genetic sequencing (the third tier) (see the Supplementary Methods section in the Supplementary Appendix, available with the full text of this letter at NEJM.org).⁵

Elevated sulfatide levels were detected in 381 newborns. Second- and third-tier testing showed abnormally low ARSA activity and two pathogenic ARSA variants (with presumed compound heterozygosity) in each of three newborns (Fig. S1 and Table S1 in the Supplementary Appendix). These three newborns were classified as screen-positive and were confirmed to have MLD. They underwent clinical assessment and received treatment at the qualified treatment center in accordance with the proposed care pathway (Fig. 1). Prediction of the MLD subtype on the basis of genotype and enzyme activity informed the treatment plans (Table S2). The two infants with predicted early-onset MLD received arsa-cel therapy at the age of 12 months, and the infant with predicted late-onset MLD was under medical surveillance at the time of this report and was scheduled to undergo allogeneic HSCT at a later age (see Supplementary Results). At the time of this report, all three children identified by newborn screening had reached all developmental milestones appropriate for their age (see Supplementary Results and Table S3).