

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

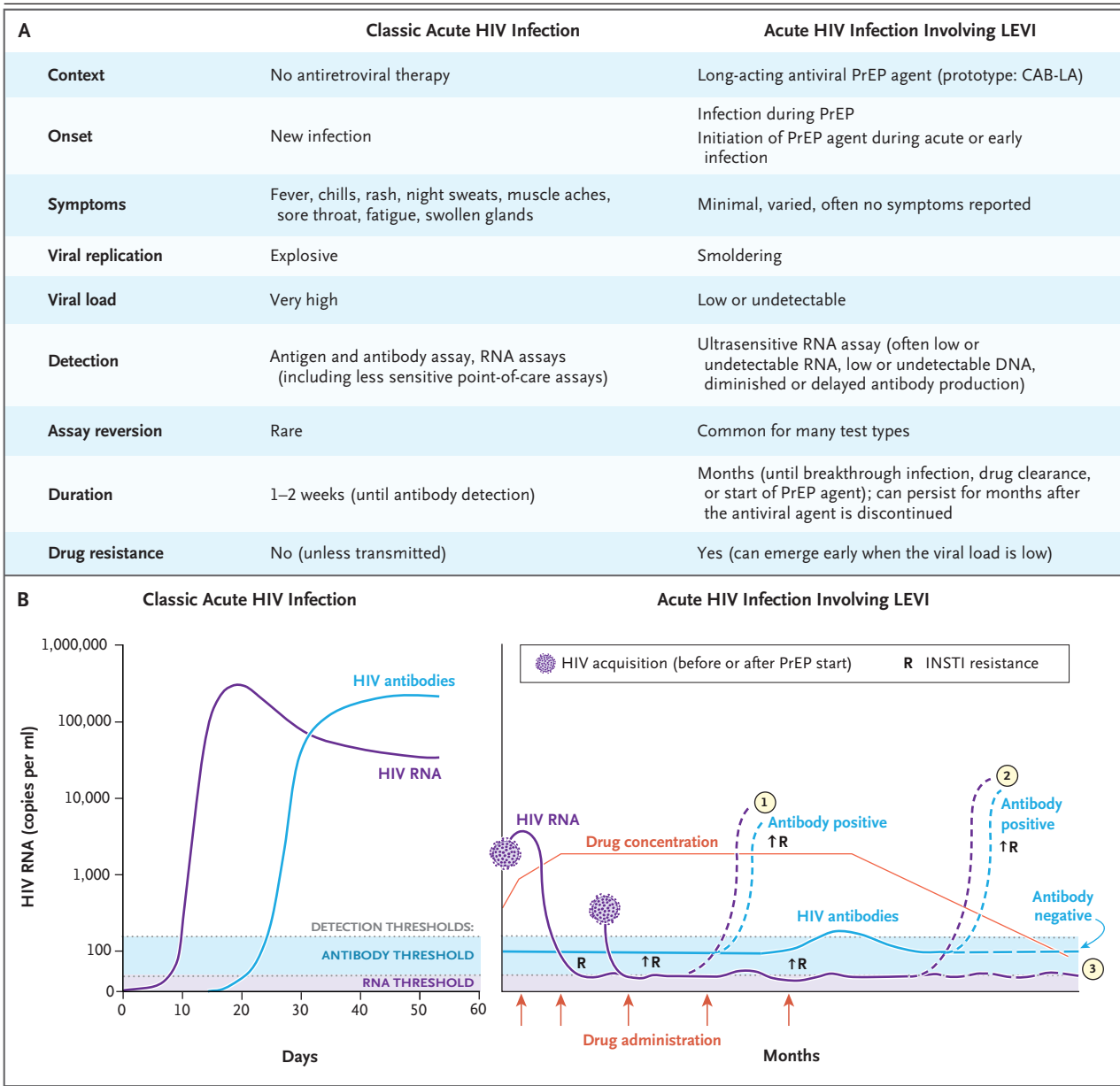
In the HPTN 083 and 084 trials, 41 HIV infections were identified among 3446 participants who had been randomly assigned to receive CAB-LA. In 17 of the 41 participants (41%), detection of infection was delayed when an HIV rapid test and an HIV antigen and antibody test were used for screening. In total, 14 of these 17 participants had had at least one CAB-LA injection and had had the last CAB-LA injection within 6 months before the first visit at which they had a positive HIV test (see the Supplementary Appendix). A total of 10 the 14 participants had integrase strand transfer-inhibitor (INSTI) resistance, in-

cluding 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 after the last 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 in persons in whom LEVI is present, and such findings can complicate clinical management. False positive results can create confusion and distress for patients and providers in the presence of LEVI, since it may be difficult to determine 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 in participants receiving CAB-LA PrEP in the open-label extensions of the HPTN 083 and 084 trials, 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 bicitegravir. Further research is needed to identify 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.

Raphael J. Landovitz, M.D.
University of California, Los Angeles
Los Angeles, CA
rlandovitz@mednet.ucla.edu

Sinead Delany-Moretlwe, M.B., B.Ch., Ph.D.
University of the Witwatersrand
Johannesburg, South Africa

Jessica M. Fogel, Ph.D.
Susan H. Eshleman, M.D., Ph.D.
Mark A. Marzinke, Ph.D.
Estelle Piwowar-Manning, B.S.
Paul Richardson, M.Sc.
Johns Hopkins University
Baltimore, MD

Figure 1 (facing page). Key Features of Classic Acute HIV Infection and Acute HIV Infection Involving 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 acute HIV infection involving 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"). In some participants in the two trials, breakthrough infection was not observed, even after drug concentrations dropped below detectable 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.

Elias K. Halvas, Ph.D.

John W. Mellors, M.D.

University of Pittsburgh
Pittsburgh, PA

Deborah Persaud, M.D.

Johns Hopkins University
Baltimore, MD

Ryan Kofron, M.S.

University of California, Los Angeles
Los Angeles, CA

Marybeth McCauley, M.P.H.

Scott Rose, B.S.

FHI 360
Durham, NC

Alex R. Rinehart, Ph.D.

ViiV Healthcare
Research Triangle Park, NC

James F. Rooney, M.D.

Gilead Sciences
Foster City, CA

Adeola Adeyeye, M.D.

National Institutes of Health
Bethesda, MD

Myron S. Cohen, M.D.

University of North Carolina at Chapel Hill
Chapel Hill, NC

Deborah Donnell, Ph.D.

Fred Hutchinson Cancer Center
Seattle, WA

Mina C. Hosseinipour, M.D., M.P.H.

University of North Carolina at Chapel Hill
Chapel Hill, NC

Beatriz Grinsztejn, M.D., Ph.D.

Instituto de Pesquisa Clinica Evandro Chagas-Fiocruz
Rio de Janeiro, Brazil

for the HPTN 083 and 084 Study Teams

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