Curing HIV-1 Infection Remains an Elusive Goal

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Although current antiretroviral therapy (ART) for human immunodeficiency virus (HIV) successfully controls infection and reduces mortality, curing infection is an important goal. Long-term ART is associated with toxicities, costs, stigmatization, the burden of lifelong adherence, and the potential for disease transmission. Eradicating the virus via ART, vaccines, and immune-based interventions are under investigation. Researchers are also studying individuals whose immune systems appear to control their HIV infection or who have experienced remission related to hematopoietic stem cell transplantation (HSCT).

Daniel Kuritzkes, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, reviewed the cases of patients who might be appropriate candidates for an attempt at curing HIV infection. The so-called Berlin patient was an HIV-infected individual on ART who developed acute myelogenous leukemia for which he required allogeneic HSCT. A stem cell donor was selected who was human leukocyte antigen (HLA) compatible and homozygous for the CCR5 delta32 deletion and therefore intrinsically resistant to HIV infection. After more than 5 years of follow-up, the patient remains in long-term drug-free HIV and leukemia remission [Hutter G et al. *N Engl J Med*. 2009].

Several factors may have contributed to HIV remission in this patient: myeloablative chemotherapy or graft-versus-host disease reducing the viral reservoir, replacement of susceptible CCR5-positive cells with resistant CCR5-negative cells, or immunosuppressive therapy blunting activation of HIV-infected cells. To determine if these results could be replicated, pre- and posttransplant samples were examined from 2 other patients who had received HSCT. In both, HIV became undetectable after allogeneic HSCT; CD4-postive cells were present, suggesting that it might be appropriate for these patients to undergo an analytic treatment interruption (ATI) to confirm viral eradication. Unfortunately, both patients experienced relapses between 2 and 6 months after ATI; long-lived tissue reservoirs inaccessible to sampling might have contributed to viral rebound [Henrich TJ et al. *Ann Intern Med*. 2014].

The so-called Mississippi baby case involved a perinatally infected infant who was treated with ART within hours of birth [Persaud D et al. *N Engl J Med*. 2013]. ART stopped at age 18 months when the patient dropped out of treatment. HIV remained undetectable when off of ART, initially suggesting that very early treatment may have eradicated the infection; however, 27 months later, the infection rebounded. Long-lived latently infected cells appear to persist at levels or in reservoirs undetectable by current assays.

Olivier Lambotte, MD, PhD, CHU Bicêtre, Bicêtre, France, discussed elite controllers (ECs) as an example of patients experiencing a functional cure. ECs are defined in the United States as having ≥3 viral loads (VLs) <50 copies/mL for at least 12 months; in France, HIV controllers are defined as having a known HIV-1 infection for 10 or more years with ≥90% of the VLs <400 RNA copies/mL. Posttreatment controllers (PTCs) are formerly viremic patients having received ART and in whom the VL remains undetectable during a prolonged period after ART discontinuation. The existence of PTCs suggests that some type of intervention could result in remission. However, the mechanism of HIV control in PTCs is not known. Three nonmutually exclusive hypotheses include infection with attenuated virus, reduced genetic susceptibility to HIV (discussed by Dr Autran below), and an effective immune response.

The role of HIV reservoirs and how it might contribute to a cure was reviewed by Daniel Douek, MD, PhD, National Institutes of Health, Bethesda, Maryland, USA. Analysis of CD4 T-cell subsets from HIV controllers, according to the French definition, may provide information that is applicable to noncontrollers. Dr Douek presented unpublished data of viral quantification, CD4 T-cell subsets, and clonal sequencing from controllers with very low levels of virus. There was a higher frequency of infection in effector memory (EM) CD4 T cells than in central memory (CM) CD4 T cells. CM viruses

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resemble those in plasma, actively replicating, diversifying, and evolving over time, whereas EM cell-associated viruses are different; they represent highly repetitive clusters that are nonevolving. Therefore, a cure strategy in controllers should not target the more prevalent EM viruses but the more important CM subset to reduce the reservoir size of replicating virus.

Other patient cohorts were examined, including viremic noncontrollers, controllers, and suppressed viremic noncontrollers. CD4 T cells were sorted into multiple subsets; the amount of virus among subsets in noncontrollers was similar to that in controllers. There were no consistent differences among CD4 T-cell subsets when compartmentalization from plasma, distance from plasma sequence, diversity, or divergence from ancestral sequence was tested. Therefore, differences in reservoir among these CD4 T-cell subsets may relate more strongly to maintenance of, rather than susceptibility to, replication-competent HIV in vivo. Dr Douek suggested that looking at more strictly defined subsets and in cells in tissues might reveal important differences between controllers and noncontrollers.

Brigitte Autran, MD, PhD, University Pierre and Marie Curie, Paris, France, discussed the development of therapeutic vaccines to cure HIV infection. Efforts to develop HIV vaccines in the 2000–2010 period induced some immunity to HIV but did not control viral relapses. More recently, new vaccine efforts are targeting HIV reservoirs. Latently infected, dormant resting-memory CD4-positive T cells contribute to the reservoir but are not affected by immunity or ART. In untreated long-term nonprogressors (LTNPs) who had an asymptomatic HIV infection for at least 8 years and CD4 T-cell counts >600/mm^3, those who were HLA B27 or B57 positive had a lower reservoir of HIV DNA than did those without HLA B27 or B57 alleles [Descours B et al. *Clin Inf Dis.* 2012]. Long-lived CM CD4 T cells which are required for maintaining immune functions, are preserved in LTNPs and ECs. Strong anti-CD8 T-cell activity is correlated with protection of CM in LTNPs who were HLA B27 or B57 positive. Interestingly, PTCs do not share HLA types with controllers by the French definition, nor do they have as strong a CD8 T-cell response [Saez-Cirion A et al. *PLOS Pathogens*. 2013].

Dendritic cell– and peptide-based vaccines have resulted in only temporary virus control. Therefore, vaccines should be combined with other agents to control HIV reservoirs to target immune activation and residual replication.

Unique populations of HIV-infected patients, such as controllers and patients on long-term suppressive ART, may provide clues to developing cures. Surrogate markers are needed to help protect patients from relapse during ATI, which is essential to demonstrating eradication. Finally, a regulatory pathway for promising approaches

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