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Finding a Cure for HIV: Much Work to Do

Antiretroviral therapy (ART) for HIV infection was one of the most spectacular scientific advances in recent decades. Patients who initiate ART at the right time can now have a normal life expectancy, and ART also dramatically reduces the risk for HIV transmission. However, treatment is not perfect. Lifelong ART is required, there are associated short- and long-term toxicities, and the drugs and health systems required to keep persons in long-term care come at a considerable cost (1). Therefore, there is a significantly renewed effort to find a cure for HIV (or a way to put HIV into remission) so patients can safely stop ART but keep their virus under control.

The reasons why ART cannot currently cure HIV are complex. The major barrier is the long-term persistence of latently infected resting T-cells, with virus integrated into the host genome but not actively replicating (2). Latently infected cells are established early after infection; are enriched in tissue sites, such as the gastrointestinal tract; and likely have preferential expansion or homeostatic proliferation leading to an extremely long half-life (3). Other long-lived infected cells, such as naive T-cells, astrocytes, or microglia, may also play a role.

In this issue, Henrich and colleagues (4) report an in-depth study of 2 patients with HIV who had "transient" HIV remission after stopping ART after hematopoietic stem cell transplantation (HSCT) for hematologic tumors. The patients were receiving suppressive ART and had HSCT with reduced-intensity irradiation and immunosuppression with tacrolimus, sirolimus, and methotrexate. Graft-versus-host disease developed in both patients, requiring additional treatment with prednisone. Nine months after HSCT, neither patient had detectable HIV DNA in his blood, a fairly crude measure of long-lived, latently infected resting T-cells that, if anything, overestimates the amount of residual infectious virus. HIV RNA and DNA were not detected in their blood in several subsequent tests, including using leukapharesis to collect many resting T-cells. In one patient, HIV DNA was not detected in rectal tissue. However, once ART was stopped 2 and 4 years after HSCT, the virus returned, albeit later than usual. Instead of the usual 1 to 4 weeks, it returned at 12 and 32 weeks. Viral rebound in blood was extremely rapid and was associated with classical symptoms of HIV seroconversion, and ART was reinstated, eventually resulting in effective virus control. Given that the patients had acquired a new "naive" immune system from a donor without HIV, there was no detectable HIV-specific T-cell response and waning HIV antibody levels before ART cessation.

There are some similarities but also many differences among these cases and the highly publicized "Berlin patient," Timothy Brown. The Berlin patient received an HSCT from a donor who did not express the key coreceptor for HIV (the chemokine receptor gene, CCR5) and was therefore naturally resistant to HIV (5), whereas the patients in Henrich and colleagues' study received stem cells from donors that expressed CCR5. The Berlin patient stopped ART soon after transplantation, whereas the patients in Henrich and colleagues' study received ART for a prolonged period to protect their new hematopoietic system from infection. There were differences in the conditioning regimens used, including the intensity of radiation and degree of immunosuppression, but importantly, the Berlin patient also had significant graft-versus-host disease. Finally and most significantly, the Berlin patient has not received ART for 6 years, has virtually no virus detected in blood or tissue (6), and remains the only patient truly cured of HIV.

There are also some similarities and differences among these cases and the highly publicized Mississippi baby (7). The Mississippi baby was infected with HIV at birth and received ART within 30 hours of delivery. Antiretroviral therapy was continued for 18 months and then stopped. Very low traces of the virus were detected in some cells, but the virus stayed at undetectable levels in plasma (for a remarkable 27 months) and then rebounded (7). As with the patients in Henrich and colleagues' study, viral rebound was significantly delayed compared with any previous reports, HIV DNA test results were largely negative after ART, and there was no detectable HIV-specific immune response, at least before rebound (neither antibodies nor HIV-specific T-cells).

However, despite these differences and the fact that HSCT will never be used as a strategy to cure HIV given toxicity and cost and very early ART after infection is not a feasible intervention for persons already infected with HIV, all 4 cases have much to teach us. These lessons are likely to significantly influence future avenues of research to find an HIV cure.

What did we learn from the patients in Henrich and colleagues' study? The good news is that it is possible to significantly reduce the number of long-lived, latently infected T-cells that persist in patients receiving ART and that this reduction was associated with a significant delay in viral rebound once ART was stopped. This was also demonstrated in the Mississippi baby.

The rest was not good news. We learned that the current assays we have to measure virus while patients are receiving ART are not sensitive enough to detect residual infectious virus and are not known to predict the critical clinical end point of when and whether virus rebounds after stopping ART. A robust biomarker that can predict viral rebound remains one of the most important currently unanswered questions in the field. We also learned that long-term remission of HIV will likely need more than just a decrease in the number of latently infected T-cells. Other

sources of virus and a boost or at least some level of effective immune control may also be important. The most sobering result was that these cases, along with the Mississippi baby, have raised the possibility that total elimination of every virus or infected cell simply may not be possible.

Which component of the regimen used in Henrich and colleagues' study so dramatically reduced HIV DNA? Bone marrow irradiation and chemotherapy alone have not previously been found to reduce long-lived, latently infected cells (8). Immunomodulatory drugs, such as sirolimus, may have played a role, as recently reported in a study of patients with HIV after kidney transplantation (9). However, the process of graft-versus-host disease or "graft-versus-leukemia" (or in this case, "graft–versus–latent reservoir") may have been critical. The expanding understanding of the immunology of the graft-versus-host response after transplantation (10), including the role of the innate immune response (specifically natural killer cells) and T-cells may be key in finding new ways to eliminate latency.

More tractable and scalable approaches than HSCT and very early ART are clearly needed for the 35 million persons already infected with HIV who will all eventually require lifelong treatment. One approach is to "purge" the virus from long-lived, latently infected T-cells. Several clinical trials of latency-reversing agents (including several histone deacetylase inhibitors and the antialcoholism drug, disulfiram) have recently been examined in patients with HIV receiving ART. Although each of these trials have shown some modest evidence of activation of virus from latency, no study has yet shown any change in the amount of residual infectious virus or HIV DNA (1). It is likely that purging alone will not be enough and a boost to the immune system may still be needed through either vaccination or immune modulation.

The modification of $CD4^+$ T-cells to make them resistant to HIV using gene therapy may be another promising yet invasive and expensive strategy. The elimination of CCR5 expression, a strategy inspired by the Berlin patient's success, using zinc-finger nuclease treatment of circulating T-cells has recently been shown to be feasible and safe in patients with HIV receiving ART (11). The challenge now will be to find ways to boost the numbers of modified cells. The even greater long-term challenge will be to ensure that any high-tech cure, such as gene therapy, is ultimately accessible, particularly in low-income countries.

In the early 1990s, Time Man of the Year and prominent HIV researcher David Ho paraphrased former U.S. president Bill Clinton when he said, "It's the virus, stupid," to emphasize the importance of understanding the virus's primary role in the pathogenesis of AIDS. However, in the case of finding a cure for HIV, it may not all be just about the virus. The amount of residual infectious virus left after ART and an effective immune response are both likely to be key in achieving HIV remission. The patients in Henrich and colleagues' study have demonstrated that we still have much work to do.

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