Studies Offer Insight Into HIV Reservoirs and Viral Rebound

A strong CD8 T-cell response may be a key to post-treatment viral control, and women may be better able to keep HIV suppressed than men.

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Several studies presented at the recent Conference on Retroviruses and Opportunistic Infections (CROI 2024) shed more light on persistent HIV, viral rebound and strategies to bring about long-term remission after stopping antiretroviral treatment.

Two studies analyzed post-treatment HIV control in a complex cure trial, one looked at sex-based differences in the viral reservoir and another provided an update on a case of sustained viral control that has lasted more than five years after stopping antiretrovirals.

Antiretroviral therapy (ART) can keep HIV replication suppressed as long as treatment continues, but the virus inserts its genetic blueprints (known as a provirus) into the DNA of human cells, establishing a long-lasting reservoir that is unreachable by antiretrovirals and usually invisible to the immune system. These proviruses can lie dormant in resting immune cells indefinitely, but they usually start churning out new virus when treatment stops, making a cure nearly impossible. Only a handful of people have been cured of HIV after stem cell transplants from donors with a mutation that blocks HIV from entering cells. In addition, a small number of people—known as elite controllers—appear to control the virus naturally, while a somewhat larger group of post-treatment controllers remain in remission after stopping antiretrovirals.

Post-Treatment Control

Researchers at the University of California San Francisco are conducting a complex combination cure trial that aims to induce post-treatment control in people living with HIV. The trial combines a therapeutic vaccine regimen, two broadly neutralizing antibodies, or bnAbs (10-1074 and VRC07-523LS), and a TLR9 agonist to coax HIV out of hiding. At last year's CROI, the investigators reported that seven of the 10 participants experienced delayed viral rebound to lower-than-expected levels after treatment interruption. Two of them maintained a viral load below 1,000, and one remained in remission for 18 months.

This year, the UCSF-amfAR study team presented results from further analyses of why this might have occurred. Amelia Deitchman, PharmD, PhD, Rachel Rutishauser, MD, PhD, and colleagues found that higher bNAb exposure was associated with more delayed viral rebound. Among those

with delayed rebound, however, post-treatment control was not consistently associated with bnAb exposure or viral susceptibility to the antibodies, "suggesting significant contribution of changes in anti-HIV immune function."

In a second analysis, Demi Sandel, Rachel Rutishauser, MD, PhD, and colleagues found that people who maintained partial control of HIV after interruption of a standard antiretroviral regimen or the combination intervention showed stronger CD8 killer T-cell responses to reactivating or rebounding virus. In other studies, a strong HIV-specific CD8 T-cell response was also a hallmark of elite controllers.

"Our data suggest that individuals who go on to achieve partial control of HIV post-ART or post-intervention have an early, robust, memory-like proliferative CD8+ T cell response to HIV reactivation in vivo," they concluded. "These results support continued focus on developing HIV cure strategies that enhance HIV-specific CD8+ T cell proliferative capacity."

"We found an immunologic correlate of viral load control after the intervention—that CD8 T cells are responding more robustly as virus rebounds in people who are able to control," study coauthor Michael Peluso, MD, told POZ. "This suggests a possible mechanism for why control was achieved. We think this has been one of the most informative cure studies in the last year."

Reservoir Sex Differences

Prior studies and anecdotal reports suggest that women may be more likely to be elite controllers or experience post-treatment control, perhaps due to differences in immune response or the nature of the viral reservoir. On the other hand, there is also some evidence that boys exposed to HIV before birth may be more likely than girls to control HIV after stopping antiretrovirals.

Toong Seng Tan, MD, of the Ragon Institute, and colleagues sought to better understand these potential differences by comparing the viral reservoir in 34 men and 30 cisgender women (all post-menopausal) who had been on continuous suppressive ART for a median of 20 years.

After analyzing more than 4,000 viral genomes, they found that the frequency of intact and defective HIV genomes did not differ between males and females, but women were more likely to have intact proviruses inserted in transcriptionally silent parts of their chromosomes where they were unable to reactivate. This suggests that women might be better candidates for "block and lock" cure strategies that aim to keep latent virus from rebounding.

"[O]ur results suggest a sex-based difference in host immune-driven proviral landscape evolution during long-term suppressive ART," the researchers concluded. "The HIV reservoir in women is associated with features of deeper latency; therefore, women may be primed to achieve a state of HIV control, and the inclusion of women in cure studies should be a priority."

Long-Term Remission

Finally, Leah Carrere of the Ragon Institute, PhD, Ole Søgaard, MD, of Aarhus University in Denmark, and colleagues presented in-depth follow-up results from a man who has maintained

post-treatment viral control for more than five years.

The man was a participant in the eCLEAR trial, a “kick and kill” cure strategy study that tested ART plus a bnAb (3BNC117) and the latency-reversing drug romidepsin, which is used to flush dormant HIV out of hiding and make it susceptible to antiretrovirals.

The trial enrolled 59 participants, mostly white men, who were starting HIV treatment for the first time. About half had acquired the virus within the past six months while the rest had chronic HIV. They were randomly assigned to receive ART alone, ART plus the bnAb, ART plus romidepsin or all three therapies. After a year on treatment, 20 people opted to undergo a closely monitored treatment interruption.

At CROI 2022, Søgaard reported that most participants experienced viral rebound after stopping treatment. However, four of the five people whose HIV was fully sensitive to the bnAb maintained a viral load below 5,000 copies during the planned 12-week interruption. One participant who received all three therapies still had an undetectable viral load at that point and stayed off antiretrovirals. At the time of that report, he had maintained viral suppression off ART for 3.7 years.

This year, the researchers reported that the man has now maintained viral control for 5.3 years following treatment discontinuation. Further analysis showed that he has no known protective HLA alleles associated with natural control of HIV. During the treatment interruption, he maintained strong effector CD4 T cell responses and HIV-specific CD8 T cell responses, especially against HIV’s gag protein.

Replication-competent proviruses were detected in the man’s CD4 T cells during the treatment interruption, though they declined over time. “Post-treatment control in this individual is associated with replication-competent HIV-1 proviruses that are detectable in in vitro assays but are not rebound-competent in vivo,” the researchers reported.

What’s more, the man had a higher proportion of intact proviruses integrated into regions of heterochromatin, or densely packed DNA that is usually transcriptionally silent, as seen in elite controllers.

“This post-treatment controller likely has a strong immune-mediated selection of intact proviruses in heterochromatin locations that may have a weaker ability to drive rebound in vivo,” they wrote. “Future research into the phenotypic profiles of HIV-1 infected CD4 T cells of this post-treatment controller could provide deeper understanding of the reservoir’s persistence and overall viral control.”

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