

## Closing in on HIV Eradication

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*December 1, 2017*

Nearly 35 years after the discovery of HIV, we have evolved from no understanding of how the virus was transmitted, how it attacked the immune system, or how to manage it, to highly effective treatment regimens, stellar prevention interventions, and a near-normal life span. But the most desired outcome of all research and care remains elusive - a cure. The tides, however, may even be turning there.

An article published in a special November 2017 edition <sup>[1]</sup> of the open access journal PLOS Medicine, exclusively dedicated to HIV, showcases a team of UCSF doctors who revealed further evidence <sup>[2]</sup> that timing may be everything when it comes to initiating antiretroviral therapy (ART) in the hopes of eradicating the virus. Previous studies have led researchers to wonder if very early treatment initiation could be the key to long-term ART-free HIV remission, a cure, or at the very least limit the total viral burden of HIV in an individual.

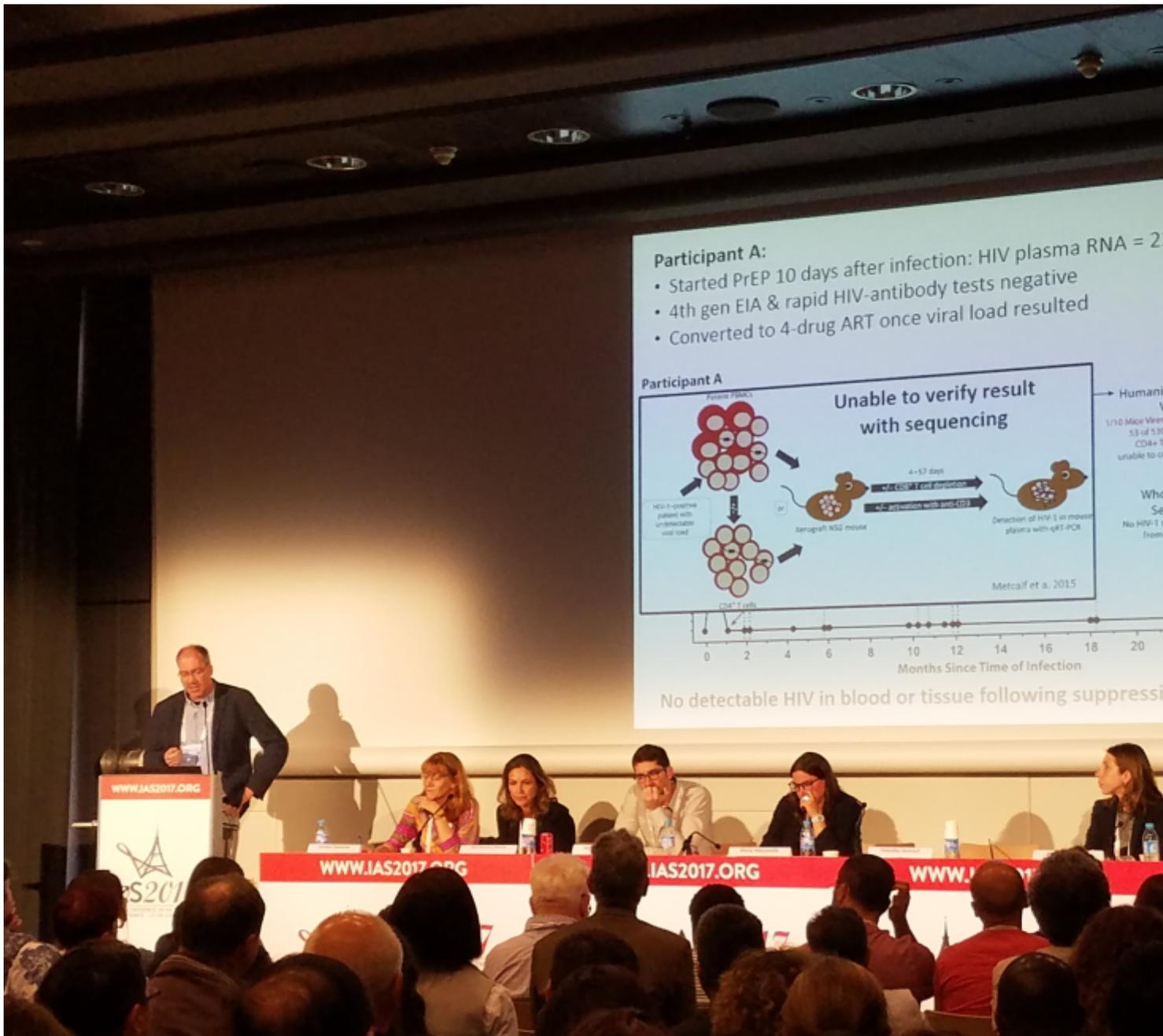
Of course, early treatment requires regular testing. One way clinicians can ensure routine HIV screening is by helping individuals access the HIV prevention drug PrEP <sup>[3]</sup>.

Since its approval by the FDA in 2012, pre-exposure prophylaxis (PrEP) has been gaining popularity among those at higher risk for HIV-infection. At UCSF's Ward 86 PrEP clinic <sup>[4]</sup>, physicians aim to get interested individuals on PrEP in a swift, informed way ? which includes initial HIV testing. If the test is negative, individuals can initiate PrEP; if the test is positive, they initiate a more comprehensive course of ART. With individuals looking to access PrEP receiving regular HIV screenings, clinicians now have an effective way to find and then treat during this early infection phase.

The timing of the HIV test is key. A ?window period? ? a few days after immediate infection ? when the virus is not detected by a screening, may result in a negative test result even if the individual does in fact have the virus ? meaning he or she may begin PrEP despite already having acquired HIV. This was the case with one of two individuals in a groundbreaking story spearheaded by former UCSF physician Hiroyu Hatano and a team currently led by Drs. Steve Deeks and Tim Henrich.

The doctors studied two individuals who began ART at an estimated 10 (Participant A) and 12 (Participant B) days after HIV infection. Presenting as a unique and important case, Participant A had received negative results on HIV tests that were performed when he was seeking to start a PrEP regimen ? though seven days after beginning the prophylactic

treatment, HIV RNA was detected in a routine screening, prompting his enrollment in ART as opposed to PrEP.



Dr. Timothy Henrich at IAS 2017

Both individuals had extremely low viral load measurements at the onset of ART, and blood and tissue tests were performed to determine if HIV was persisting. While very low, intermittent levels of HIV were detected in blood (but not tissue) in Participant B, no HIV could be definitively detected in Participant A ? the individual who had begun ART after just a week of PrEP.

After 34 months of being on ART, Participant A decided to interrupt his treatment, while being carefully monitored by physicians. For 225 days, his virus remained undetectable without ART.

But then it jumped.

After an initial test showed evidence of the virus, he was screened again 6 days later ? with a staggering increase in viral load. Participant A went back on treatment.

Though promising for almost 8 months, this near complete lack of detectable virus for the duration of infection did not lead to sustained therapy-free remission. And it seems that it may all boil down to when Participant A began his antiretroviral medication.

The researchers, explained Dr. Henrich, aimed to ?look at the impact of extremely early initiation of ART on the size of the HIV reservoir.? This initiation happens during a time known as ?hyperacute infection? ? the earliest stage of detectable HIV-infection. This is when that permanent reservoir of the virus is established in a person's blood and tissue, but when a protective immune response to fight the virus may not have been generated. The hope is that this early initiation keeps the reservoir low and the viral burden minimal; alternatively, lack of treatment allows the reservoir to grow.

But that exact timing of beginning treatment is difficult to pinpoint. If a person recently infected with HIV begins ART after that reservoir has begun to establish itself but before the immune system has recognized it has something to fight, as what happened with Participant A, it can ?[freeze] everything in place for a few years,? said Dr. Deeks.

?In this case,? he continued, ?PrEP was given to a person on what may literally [have been] Day 1 of his systemic infection. The day before he would have not had any detectable evidence of HIV. I doubt we could ever treat an adult any earlier.?

It was during that time when Participant A had no detectable evidence of HIV that his permanent reservoir of the virus was seeding ? but not quite enough time for that protective immune response to activate before he started treatment. Subsequently, when he decided to stop his ART, Deeks explained, ?and one of the few remaining viruses [from that reservoir] took off, the immune system was completely unprepared. The virus had nothing to stop it from replication.?

This poses challenges moving forward. The precipitous balance of time between initial infection, establishment of the reservoir, and mounting of an immune response is delicate, but there is promise. As Dr. Deeks noted, ?once we get people on therapy, we [can] work to build up some immune response such that when treatment is stopped, [there will be] something able to keep any residual virus under control.?

Can we work with those who began treatment during early infection in other ways in search of eradication? Dr. Henrich says yes. ?We can take individuals who were treated in this hyperacute stage and artificially boost their immune system to recognize HIV ? for example, with vaccines.?

Of course, there is no HIV vaccine yet; though there are trials underway. But perhaps we've been testing vaccines on the wrong cohort, Henrich says, as most trials work with HIV-negative volunteers. ?Maybe what we need to do is ?boost? HIV [allowing the immune system to recognize it] to develop HIV immunity in individuals with extremely low levels of an HIV reservoir.?

Might that bring us to the end of lifelong ART? Perhaps, Deeks admits. ?We are working on

such studies now.?

*This research was supported as part of the amfAR Institute for HIV Cure Research, the Delaney AIDS Research Enterprise, Collaboratory for AIDS Research on Eradication, BEAT-HIV Delaney Collaboratory, and by the Department of Veterans Affairs, the James B. Pendleton Charitable Trust, Leidos Biomedical Research, Inc., and the NIH.*

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