

# HIV Integration and the Persistence of HIV Infection

*During antiretroviral therapy, propagation and persistence of cells harboring HIV can depend on the DNA site of viral integration.*

Combination antiretroviral therapy (cART), which can completely block viral replication, is now used to control HIV in millions of patients worldwide. However, during infection, a DNA copy of the HIV genome is inserted into the cells it infects, which persists as long as the host cell lives, and can initiate an active infection if therapy is discontinued. This makes curing HIV a daunting task.

In untreated patients infected for a few years, the viruses in the blood differ from one another. By contrast, in many of the patients treated with cART for long periods, identical strains emerge in the blood. In a recent paper in *Science*, Stephen Hughes, Ph.D., Director of CCR's HIV Drug Resistance Program, and his colleagues proposed that the identical viruses are the result of clonal expansion of infected host cells, and that, in some cases, this expansion is driven or facilitated by HIV DNA

integration in genes that promote the growth of the infected cell.

Hughes and colleagues sequenced the HIV DNA integration sites in peripheral blood mononuclear cells (PBMCs) or CD4+ T cells from the blood of five patients treated with long-term cART. Of the 2,410 integration sites they identified, approximately 40 percent were found multiple times, showing that these sites came from cells that had clonally expanded after infection. In one striking example, more than 50 percent of the infected cells in a patient were from a single clone. Moreover, some of the clones of HIV-infected cells were shown to persist in patients for more than a decade.

Among the patients studied, there were three or more independent integration sites in 29 different genes. Most of these genes (21/29) are known to be directly involved in cell growth. In two of the genes, *MKL2*

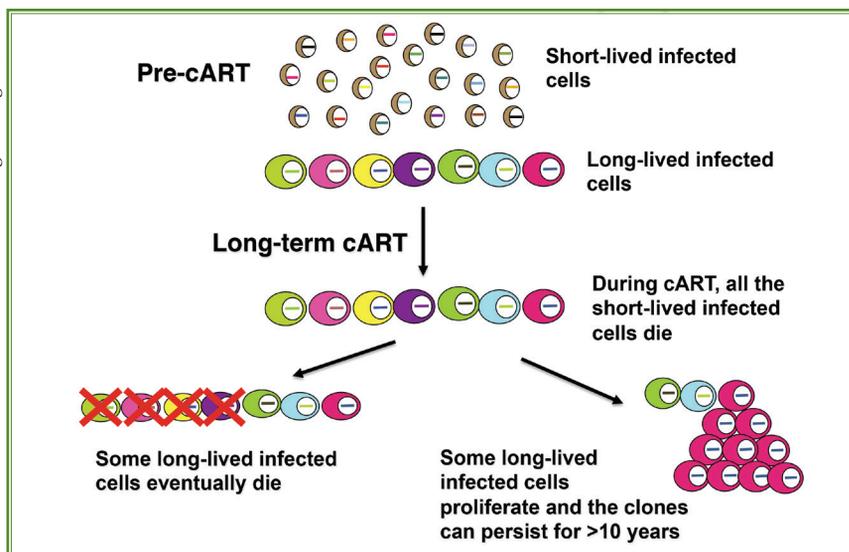
and *BACH2*, there were, respectively, 16 and 17 independent integrations. The sites and orientations of the integrations in *MKL2* and *BACH2* suggested that cells carrying these integrations were selected because they altered the expression or the protein products produced by these two genes.

From these data, the researchers proposed that HIV persists, in part, because infected cells can divide and grow clonally. In some cases, the clonal growth of the infected cells depends on where HIV integrates into the human genome. More research is needed to determine what fraction of the clonally expanded cells carry intact copies of the HIV genome that can give rise to infectious virus. However, the researchers did identify one expanded clone that produced the majority of the virus in the blood of a patient.

"If we are going to achieve a cure for HIV, we will need not only to suppress the replication of the virus, but also to block the expansion of infected cells," said Hughes. "Our research also suggests that gene-therapy patients who are treated with HIV-based vectors should be carefully monitored for the development of malignancies. We may also need to reexamine the question of whether HIV DNA integration may play a role in the development of some HIV-related malignancies."

*To learn more about Dr. Hughes's research, please visit his CCR website at <https://ccr.cancer.gov/stephen-h-hughes>.*

Image: S. Hughes, CCR



Some long-lived HIV-infected cells persist in patients who are treated with combination antiretroviral therapy (cART), preventing them from being cured. Some infected cells can grow and divide, and these expanded clones can persist for more than 10 years in patients.