Can Doubling Dolutegravir Shrink the Viral Reservoir?

Unlike prior studies, new research finds antiretroviral intensification appears to reduce latent HIV in peripheral blood cells.

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Intensifying antiretroviral treatment by doubling the dose of dolutegravir may shrink the viral reservoir, though it did not appear to reduce inflammation, according to study results presented at the 2024 HIV Persistence During Therapy Workshop in Fort Lauderdale.

Antiretroviral therapy (ART) can keep HIV replication suppressed indefinitely, but the virus inserts its genetic blueprints into the DNA of human cells and establishes a long-lasting viral reservoir that the drugs can't reach. This integrated HIV DNA lies dormant in resting T cells during treatment, but it can start churning out new virus when antiretrovirals are stopped, making a cure nearly impossible.

People living with HIV are at higher risk for comorbidities despite antiretroviral treatment that suppresses viral load according to standard HIV RNA tests. This suggests that the drugs may allow residual low-level viral replication that leads to chronic immune activation and inflammation. Numerous studies over the years have explored whether ART intensification by adding more drugs can shrink the viral reservoir. These efforts have generally proved unsuccessful, but newer, more potent meds may offer more promise.

In the current study, Alexander Pasternak, PhD, of the Laboratory of Experimental Virology at Amsterdam University Medical Center, and colleagues investigated the impact of intensifying treatment by doubling the dose of dolutegravir, a second-generation integrase inhibitor with potent antiviral activity and a high barrier to resistance.

This Phase II trial included 20 HIV-positive adults who had been on standard antiretroviral regimen of 50 milligrams dolutegravir, 600 mg abacavir and 300 mg lamivudine (the drugs in the Triumeq combination pill) for at least the past six months. They were required to have viral suppression (HIV RNA below 20 copies) for at least one year prior to screening and a CD4 T cell count above 200.

The study participants were randomly assigned to either stay on the same regimen or add an extra 50 mg dolutegravir for 84 days. The investigators measured total and intact HIV DNA and

unspliced HIV RNA in peripheral blood cells and rectal tissue samples. They also analyzed biomarkers of immune cell activation (HLA-DR, CD38) and exhaustion (PD-1, TIGIT, LAG-3) on peripheral CD4 helper and CD8 killer T cells. Inflammation was assessed by measuring inflammatory cytokines including interleukin 1 (IL-1), IL-6, IL-17, interferon gamma and TNF-alpha in plasma and rectal tissue.

Dolutegravir concentrations in plasma and tissue significantly increased in the intensification group, the researchers reported in a poster. This group also saw significant declines in total HIV DNA, intact HIV DNA and unspliced HIV RNA in peripheral blood cells, as well as the ratio of unspliced RNA to total DNA. No such changes were seen in the control group that stayed on standard therapy. However, upping the dolutegravir dose did not affect total HIV DNA levels in rectal tissue.

Dolutegravir intensification was associated with changes in certain biomarkers of immune activation and exhaustion, but only the decrease in TIGIT expression was statistically significant. Intensification had no notable effect on systemic or rectal tissue inflammation. What's more, doubling dolutegravir did not lead to significant changes in CD4 or CD8 cell counts, though there was a temporary decrease in the CD4 to CD8 cell ratio that returned to near baseline by day 84.

"Our results strongly suggest that the pre-intensification ART regimen may not have been completely suppressive," the investigators concluded. "If confirmed in larger clinical trials, these results could have an impact on the clinical management of people with HIV and curative strategies."

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