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Drugs that flush out HIV may impair killer T cells, possibly hindering HIV eradication

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Histone deacetylase (HDAC) inhibitors have shown promise in "flushing out" HIV from latently infected cells, potentially exposing the reservoirs available for elimination by cytotoxic T lymphocytes (CTL), also called killer T cells. However, findings published on August 14th in *PLOS Pathogens* now suggest that treatment with HDAC inhibitors might suppress CTL activity and therefore compromise the "kill" part of a two-pronged "flush-and-kill" HIV eradication strategy.

At least three different HDAC inhibitors, romidepsin, panobinostat, and SAHA, are under investigation as flushing agents. The individual drugs differ somewhat in their specificity for the 18 known human HDACs, and are also known to interact with other cellular factors and to alter the function of immune cells. Arguing that "this high degree of complexity both in terms of immunological outcomes and underlying mechanisms, necessitates that HDAC inhibitors be studied in a context that is matched to their intended utility", Brad Jones, from the Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology and Harvard, Boston, USA, and colleagues set out to test whether the three drugs affected the ability of CTL to eliminate HIV-infected target cells.

While the individual effects of the drugs on virus-specific CTL differ somewhat depending on specific assays, schedules, and doses, treatment with any of the three HDAC inhibitors impaired the ability of CTL to kill HIV-infected immune cells. All three drugs also rapidly suppressed CTL production of the key immune mediator interferon gamma.

Discussing the limitations of the study, the researchers state that, because their assays all involve drug treatment of CTL in cell culture settings, the extent to which HDAC inhibitors impact CTL function in HIV infected patients remains unknown. Consequently, they hope that their results will "motivate the incorporation of assays measuring ex-vivo T-cell function into ongoing and planned clinical trials of HDAC inhibitors, and that immunosuppression will be considered as a potential factor limiting the effectiveness of any observed outcomes". They also highlight the potential broader risk of treating HIV-positive individuals—whose immune systems remain compromised even on antiretroviral therapy—with HDAC inhibitors that have shown immunosuppressive activity in several studies, including this one.

More information: Jones RB, O'Connor R, Mueller S, Foley M, Szeto GL, et al. (2014) Histone Deacetylase Inhibitors Impair the Elimination of HIV-Infected Cells by Cytotoxic T-Lymphocytes. *PLoS Pathog* 10(8): e1004287. DOI: 10.1371/journal.ppat.1004287

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