Tentative first steps to eradicate latent HIV

Purging latent HIV with reactivating drugs is one of the most promising approaches to curing HIV infection. In *The Lancet HIV*, Thomas Rasmussen and colleagues report results of a phase 1/2 trial of panobinostat, a histone deacetylase inhibitor, to reactivate latent HIV. They show that the drug was well tolerated in the short term and the treatment increased both the amount of cell-associated HIV RNA and low-level transient HIV viraemia. There was, however, no overall change in measurements of the HIV reservoir after 8 weeks of panobinostat treatment. A subset of patients had a planned interruption in antiretroviral therapy, all of whom had rapid rebound of viraemia, although there was a post-hoc correlation between changes in HIV DNA on panobinostat and the time to re-emergence of viraemia. Although this study shows the most robust reactivation of HIV reported to date, it also shows the difficulty of affecting a well established HIV reservoir.

Why was there no effect on the HIV reservoir despite clear evidence of reactivating HIV? Unfortunately, the total number of cells reactivated during panobinostat treatment was probably extremely low. Plasma HIV RNA was barely detectable. Although cell-associated unspliced HIV RNA increased (presumably from reactivated latently infected cells), it was only a two- to three-fold increase from the baseline level. If reactivation contributes to the normal rate of decay of the latent reservoir, then the increase in reactivation caused by panobinostat might only be two to three times faster than normal decay of the reservoir. The half-life of the reservoir in patients taking antiretroviral treatment is roughly 4 years.1 Speeding up this half-life by several-fold during the short period of the intervention is likely to have a negligible effect on reservoir size, as Rasmussen and colleagues noted.

A second difficulty with reactivation strategies such as panobinostat treatment is that the drug might not truly purge the reservoir because the cells from which HIV is reactivated might return to a latent state. Immune responses might need to be boosted with therapeutic vaccines to assist in the killing of virus-expressing cells.1 In this context, it will be interesting to assess whether the low-level reactivation reported by Rasmussen and colleagues stimulated HIV-specific immunity itself.

A third issue with attempting to reactivate HIV after long-term antiretroviral therapy initiated during chronic HIV infection is that this might not be the optimum timing of the intervention. Studies of SIV-infected macaques5–8 suggest that the reservoir might be more susceptible to reactivation and purging at the initiation of antiretroviral therapy than after long-term treatment. Such a strategy also leaves little time for virus-specific immunity to fall. Studies of very early initiation of antiretroviral therapy during acute infection show that the residual reservoir is much smaller, and purging studies might be more successful in that setting.9

Indeed, antiretroviral therapy was initiated within a day of diagnosis for two of the four participants whose HIV DNA decreased during panobinostat treatment. One of these patients also had an antiretroviral therapy interruption and this patient also had the longest time until HIV rebound (around 40 days). Purging strategies might, therefore, be more successful in some subsets of patients than in others.

The results of this study confirm that the latent reservoir can be stimulated into low-level virus replication, an important step. A concern with the safety of histone deacetylase inhibitors is their ability to induce long-term changes in gene expression profiles.10 Long-term safety should be carefully monitored. More specific and effective drugs to reactivate the latent reservoir are in development.11 Modelling studies12 suggest that the reservoir would need to be reduced by more than 1000-fold to enable a durable interruption of antiretroviral therapy. Although Rasmussen and colleagues’ results are promising, much work is left to do.

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We declare no competing interests.


12 Hill AL, Rosenbloom DJ, Fu F, Nowak MA, Siliciano RF. Predicting the outcomes of treatment to eradicate the latent reservoir for HIV-1. Proc Natl Acad Sci USA 2014; published online Aug 5. DOI:10.1073/pnas.1406663111.