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The cure conundrum

This summer, researchers launched a strategy to accelerate finding a cure for HIV. The effort aims to revolutionize treatment of the infection, but the inherent risks require that regulators ensure a measured approach.

Scientific narratives tend to center on a eureka moment. But few researchers have the great fortune of Archimedes to have a revelation spill forth quickly and clearly, particularly when it comes to modern biomedical research. Physiological insights can require time-consuming modeling, and trials to prove drug efficacy can take years. The need to exercise patience is therefore constant in medical research, and it is particularly important when hopes are high.

Nothing evokes more hope than the word 'cure', and this term was on the lips of many attendees of the XIX International AIDS Conference in Washington, DC this summer when a group of 34 scientists, brought together through the International AIDS Society (IAS), launched a scientific strategy to cure HIV (*Nat. Rev. Immunol.* **12**, 607–614, 2012). It is a noble and worthwhile goal given the estimated 34 million people living with the infection worldwide and the lack of an approved vaccine. Current antiretroviral drugs have turned what used to be a death sentence into a chronic illness, but these pills come with side effects ranging from diarrhea to nerve damage and fail to eliminate the virus.

Not surprisingly, patients seem eager to jump aboard the cure campaign. But there are hints that they strongly prefer that researchers deliver a 'sterilizing cure', which would completely rid the body of virus, rather than a 'functional cure', which would not clear the virus entirely but would keep viral load in check. In a survey of 458 HIV positive people in the Netherlands presented by HIV educator Fred Verdult at a symposium before the meeting, 95% of respondents felt a complete cure (in other words, a sterilizing cure) was very desirable, but only 19% found it very desirable to have a curative treatment that would involve regular clinical visits to ensure the virus was not circulating in the body.

It's understandable that people living with HIV would want a cure that truly frees them from the virus, given that they can already live healthy lives thanks to highly active antiretroviral therapy (HAART). Notably, the success of HAART raises the bar for clinical trials of potential 'cure' agents as well. The newly published cure strategy acknowledges that "the profound regulatory issues that surround the testing of novel drugs (many with high potential for toxicities) in a population that is generally doing well will need to be addressed," and to this end the IAS initiative has created a specific working group due to provide recommendations on these matters by the end of 2012.

This is an important discussion, given that the risk-benefit calculus for clinical trials is not an exact science, as a divergence in regulatory decisions illustrates. In a recent trial showing that the cancer drug vorinostat can reactivate latent HIV and bring the virus out of hiding, the US Food and Drug Administration had asked researchers to limit the delivery of the therapy to just a single dose because, as a relatively nonspecific histone deacetylase inhibitor, it has unknown long-term side effects (*Nature* **487**, 482–485, 2012). On the other side of the globe, a concurrent decision by the Therapeutic Goods Administration, Australia's drug regulator, allowed a similar trial of vorinostat in HIV-infected individuals to deliver daily doses of the drug for a full two weeks.

Regulators often lean on *in vivo* preclinical tests to guide decisions, as in most fields animal trials pave the way toward human studies. But HIV researchers regularly note that murine and simian models of HIV have their limitations. Even so, animal studies should be part of the process leading to clinical validation of potential cure compounds, lest speeding ahead results in failure.

There is a great need and momentum to find a cure for HIV and ideas continue to flourish. There is encouraging evidence for gene therapy and bone marrow transplant approaches, as well as proposals to combine agents that flush HIV out of the cell with therapeutic vaccines designed to kill infected cells. However, there needs to be continued frank discussion about the risks associated with putting these ideas to the test—particularly when it comes to combination trials where it might be wiser to first study each component individually, as they each carry their own risks. Patients signing up for cure trials will no doubt be hopeful; regulators and researchers need to temper that with the reality of the risks.