Towards a cure for HIV—are we making progress?

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Until recently, no-one dared to discuss a cure when it came to HIV. There had been a general consensus among experts that the best we would ever achieve would be durable control of the infection with antiretroviral therapy (ART). And, in this regard, we have been tremendously successful. ART is often given as only one tablet a day with minimal toxicity, leads to normal life expectancy, and reduces viral transmission. But therapy clearly has its limitations. It must be administered daily for life, remains expensive for the most affected countries in the world, and is not completely benign in terms of short-term and long-term toxic effects.[1] These limitations have motivated the field to revisit the idea that we indeed need a cure.

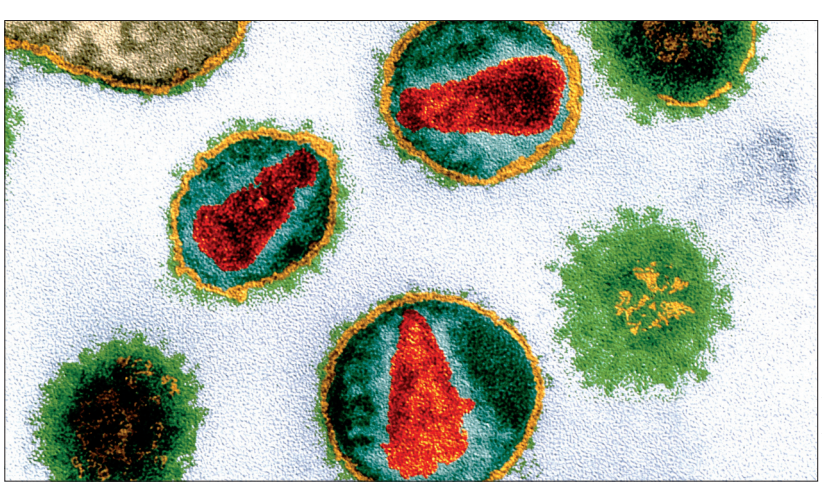
So how far have we come towards finding a cure? And how much further will we need to go? The past year has yielded some encouraging advances, together with a very clear reminder that the challenge of finding a cure for HIV was never easy, and is unlikely to get any easier.

Cure means different things to different people. Putting HIV into remission—meaning viral suppression once ART is stopped, at least for a defined period—might be the most realistic target for the cure effort. Certainly, early initiation of ART, within weeks or even months of infection, can substantially reduce the amount of long-lived latently infected memory CD4+ T cells—the major source of persistent infectious virus on ART. In 5–15% of adults, early initiation of ART could potentially lead to remission—but of unknown duration and through an unknown mechanism.[2] By contrast, it is hoped that extremely early initiation of ART—within hours to days—can actually prevent establishment of a long-term latent infection. The widely publicised infant from Mississippi,[3] an HIV-infected baby who received ART within 30 h of delivery, stayed on ART for 18 months and seemed to be cured, eventually experienced viral rebound after a remarkable 27 months off ART.[4] This sobering news—that HIV can remain hidden for years and eventually rebound—has implications for how we define a cure, and how we will monitor those who are thought to be in remission.

Currently, one of the most important limitations in the field is the lack of a reliable biomarker for the total body burden of replication-competent HIV that persists in people on ART. This was central to the case of the infant from Mississippi,[3,4] as well as for two patients infected with HIV in Boston, MA, USA, who received a stem-cell transplant for lymphoma.[5] In each of these cases, the currently available assays failed to detect evidence of HIV while the patients were still on ART. But once these patients stopped ART, the virus returned, albeit later than the usual 1–4 weeks: 12 and 32 weeks for the patients from Boston[6] and 27 months for the child from Mississippi.[4] So although transient remission was achieved in all the patients, no tests predicted if, and when, the virus was to return. We have much work to do to identify a robust biomarker—virological, immunological, or even genetic—that will predict time to viral rebound once ART is stopped.

These three patients—the child from Mississippi and the two patients from Boston—illustrate that substantial reductions in the amount of residual infectious virus may be possible but that this might never be enough to lead to long-term remission. In these three patients, at least before cessation of ART, there were no detectable HIV-specific T cells and waning or no detectable antibodies to HIV.[3,5,6] This complete lack of an immune response to the virus might have allowed the virus to rebound. Maintaining or boosting some HIV-specific immunity might be key to keeping even a very small level of persistent virus under control in the long term.

Very early initiation of ART and bone-marrow transplantation are never going to be treatment options for most people who live with HIV infection, or will become infected in the future. Are there other more tractable and scalable approaches? One approach is to "purge" the virus from long-lived latently infected



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memory CD4+ T cells. The finding that the histone deacetylase inhibitor vorinostat can activate HIV transcription in latently infected cells in patients on ART was an important first step to show that latency was not completely irreversible.[7] Recent work, however, has raised important questions: are histone deacetylase inhibitors able to activate a sufficient proportion of latently infected cells; is true virus produced; and, more importantly, does the recently activated cell indeed die?[8,9] Given the differences and limitations of currently available laboratory models of HIV latency,[10] the true answers to these questions lie with the results of clinical trials of latency reversing agents in patients with HIV infection on ART, which are critical to advancing the field. Results from a study of the potent histone deacetylase inhibitor romidepsin will be presented in Melbourne, Australia, at the 20th International AIDS Conference (AIDS 2014) on July 20–25, 2014.[11]

Ultimately, purging HIV will probably need a combination approach both for activation of the virus and for clearance, what is now referred to as "shock and kill". As with activation of HIV, the "kill" might also be a challenge. Therapeutic vaccines for HIV have had limited success to date, although cytomegalovirus as a novel persistent vector to deliver HIV antigens[12] and highly active broadly neutralising antibodies[13] might both have potential in eliminating latently infected cells. Work in cancer immunology might also deliver new ways to "kill", through immune modulatory therapies that can activate antigen specific T cells, such as anti-programmed death 1 (PD1) and anti-programmed death-ligand 1 (PDL1).[14] Studies of anti-PDL1 in HIV infection are now underway (eg, safety and immune response of BMS-936559 in HIV-infected people taking combination antiretroviral therapy, ClinicalTrials.gov identifier NCT02028403).

Finally, some success has recently been achieved in making cells "resistant" to HIV, using gene therapy to eliminate the main receptor for HIV entry, CCR5, ex vivo. In a recent clinical trial of 12 patients with HIV infection on ART, CCR5 negative gene modified T cells were safely transferred and persisted in blood and tissue.[15] Six of the 12 patients stopped ART and virus rebounded in all, although encouragingly the CCR5 negative gene modified T cells survived longer in the presence of active virus replication than non-modified CD4+ T cells.[15]

On July 19–20, 2014, in Melbourne, Australia, the International AIDS Society will once again bring together the world's top researchers to present the latest findings on strategies toward an HIV cure at a preconference symposium. This workshop will address greater engagement of low-income countries in the cure effort; current steps towards development of a public–private partnership for HIV cure; and ethical and logistical issues related to treatment interruptions as a clinical endpoint for cure-related trials. The programme will also include experts in graft-versus-host disease and epigenetic modification in the management of malignant disease, which will reinforce the growing belief that learning from related disciplines could accelerate current efforts.

When HIV was discovered 31 years ago we could never have imagined the great successes possible with ART. The scientific and operational challenges were immense but innovation, investment, and collaboration delivered. Let us hope we can achieve the same success in the coming decades in the search for that elusive cure for HIV.

Sharon R Lewin, Steven G Deeks, Françoise Barré-Sinoussi
Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, VIC 3004, Australia (SRL); Centre for Biomedical Research, Burnet Institute, Melbourne, VIC, Australia (SRL); Department of Medicine, San Francisco General Hospital, University California, San Francisco, San Francisco, CA, USA (SGD); and Inserm and Unit of Regulation of Retroviral Infections, Department of Virology, Institut Pasteur, Paris, France (FB-S)
sharon.lewin@monash.edu

SRL and SGD declare no competing interests. FB-S holds the following patents with colleagues: number 5 610 035 (Sept 27, 1994) on methods for the preparation of hybridomas producing lymphadenopathy-associated virus (LAV) gp110-specific monoclonal antibodies and methods for the purification of gp110 employing said monoclonal antibodies; number 97-20 (May 16, 1997) on anticorps et peptide dérivé. Applications à la thérapie SIDA; number 96 15 087 (Dec 8, 1997) on variant HIV-1 non-M non-O fragments et applications; number EP1810032 (2009) on CD85j receptor ligand and use thereof; and number 13305654.9-1464 (2013) on metabolic pathways inhibiting HIV_1 replication. FB-S is the President of the International AIDS Society and chairs the Towards an HIV Cure initiative. SRL, SGD, and FB-S are Co-Chairs for the International AIDS Society Workshop on Strategies Towards an HIV Cure, July 19–20, 2014, in Melbourne, Australia. SRL and FB-S are Co-Chairs of the 20th International AIDS Conference.

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