

## Uncovering the cure

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'We're going to have a cure and it will happen on our lifetime.' So wrote the pioneer of HIV treatment activism, Martin Delaney, only months before he passed away from [liver](#) [1]A large organ, located in the upper right abdomen, which assists in digestion by metabolising carbohydrates, fats and proteins, stores vitamins and minerals, produces amino acids, bile and cholesterol, and removes toxins from the blood. cancer in January this year. David Menadue follows his dream.

The man who founded Project Inform in San Francisco in the early 1980s, will be sorely missed for the leading role he played in fighting HIV. Martin Delaney was a visionary. He was able to understand the complexities of the virus and propose invaluable insights on possible ways forward.[1](#)

One reason he believed that uncovering the cure is imperative is the unsustainable cost of providing a lifetime of [antiretrovirals](#) [2]A medication or other substance which is active against retroviruses such as HIV. to the millions of positive people in the world. The cost currently sits between US\$12,000 and \$25,000 per year per person. Some drug companies have recently reduced prices for developing countries and the US President's Emergency Plan for AIDS Relief (PEPFAR) did contribute a massive US\$15 billion last year, but still less than 30 percent of people with HIV worldwide are currently being treated. Billions more dollars are needed. One estimate puts it at US\$85 billion.

The other reason Delaney wanted a cure is so we can avoid the long-term use of multiple medications. We know some are highly toxic and already contribute to morbidity, but all side-effects will not be completely known for another twenty years.[3](#)

When current vaccine efforts 'hit the wall in the last year', Delaney noted that 'some of the world's experts are warning that a vaccine may never be possible due to HIV's unique properties.'

Similarly, the great hope invested in microbicides has yet to be fulfilled, although there are recent reports that a particular gel is showing promise in early [clinical](#) [3]Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. studies with women.

### Eradication theory

One of the big obstacles to curing HIV is the belief that it is necessary to completely eradicate it from the body. Post 1996, we heard that this might be possible by suppressing the virus to undetectable levels. Then we realised that HIV can hide in reservoirs which cannot be reached without first activating the virus – with damaging consequences.

Delaney challenged the view that the only way to cure HIV is to remove it from each and every cell in the body. Some [viruses](#) [4]A small infective organism which is incapable of reproducing outside a host cell. can exist in the body without being highly destructive. For example, many people carry the Cytomegalovirus (CMV) without it causing them harm.

There are people with HIV called non-progressors or elite controllers who sustain a level of HIV infection without illness. There are others who have been repeatedly exposed but have never seroconverted. These include those who lack the CCR5 receptor that HIV uses to enter the cell.

Delaney wondered whether the new CCR5 antagonists and integrase inhibitors will get the virus to such low levels that harmful HIV replication simply doesn't happen. [4](#)

### Shared optimism

Delaney's belief in the eventuality of a cure is shared by scientists such as Luc Montagnier, the French virologist who isolated HIV in 1983. Montagnier believes a therapeutic vaccine could well be discovered within five years, but

that it will take a different form to those currently being investigated and will probably be used in combination with other treatments to enhance the immune system. [5](#)

Professor Steven Deeks, from the University of California, is currently working with a group of elite controllers to see what they might bring to a potential cure. In talking with people who have had the virus for 15 years or so, Deeks has summarised that despite them having undetectable viral loads they continue to suffer from chronic inflammations, joint pain, weight loss, persistently low CD4 counts, and various other complications. He believes that the progresses made in treatment for rheumatoid arthritis and other autoimmune disorders may well have applicability to HIV.

Deeks also sees the possibility that CCR5 inhibitors (such as maraviroc) may work on the immune system as well as on the virus and so have a role as an immune-based therapy.

'I actually think immunopathogenesis-oriented work and immune-based therapeutics will lead to a cure,' he says.

## Gene therapy

The 2007 case of an HIV positive American man who was given a bone marrow transplant at Berlin's Charite Hospital after he developed leukemia, has renewed interest in gene therapy for HIV. The man was given bone marrow from a person with the CCR5 gene mutation and since the procedure no evidence of HIV has been found in any cells in his body. Scientists believe that as long as the virus remains undetectable this patient will not require treatment. [6](#)

It is the longest time someone who has had antiretroviral therapy and stopped has lasted without the virus rebounding. Normally it reappears within weeks. 'It is the closest we have come to a cure,' said Dr Gero Hutter from the hospital. [7](#) Others such as Professor Jay Levy from the University of California question whether these researchers have been premature in assuming that HIV is not still hiding somewhere in the patient's body. [8](#)

There are reasons why bone marrow transplants will not be used to treat HIV – including finding compatible donors (who are rare), the cost and the considerable risks to the person's health. However, this case does suggest that when viral levels are greatly reduced, the body alone seems able to keep HIV in check for long periods.

Several gene therapy trials and strategies have been initiated to mimic the effect of the bone marrow transplant. These involve making artificial versions of natural enzymes that disrupt the CCR5 gene so that it stops making the protein needed by HIV to enter the cell.

An Australian [Phase II](#) [5]A smaller clinical trial designed to establish whether a drug is effective. Phase II studies are conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks. If there is evidence that the drug is effective, a Phase III study is undertaken, with a larger number of participants, to confirm this. [9](#) involved 74 HIV positive people, half of whom had their stem cells manipulated through gene therapy. The trial did not use an enzyme to destroy CCR5, but one that cut up the gene sequence of another part of the HIV genome thus preventing replication. Unfortunately the proportion of cells with this 'modified gene' decreased over time (from 94 percent at four weeks to seven percent at 100 weeks). Though HIV replication was not controlled by the gene therapy after two years, it was found to be safe. So, now a way of sustaining the 'genetically modified' cells in the body needs to be found.

There are some trials being done at the University of California using stem cells to try to disable HIV's entry into the body. Stem cells are cells that can evolve into a number of different daughter cells (e.g. lymphocytes, monocytes, neutrophils) all with different roles in the immune system. Stem cells are taken from the patient's blood and treated in the laboratory. An enzyme is inserted into the cell that destroys their ability to express the CCR5 receptor on the cell surface. It is this receptor that HIV binds to, to gain entry to the cell. The 'genetically modified' patient stem cells (with the new enzyme inserted) are then infused back into the body, and the daughter cells will not express the CCR5 receptor.

Martin Delaney thought that while we needed to improve current treatments and reduce their toxicities, scientific and government circles needed to pay greater attention to finding a cure. Over the last two years The Foundation for AIDS Research (amfAR) has organised a series of meetings of scientists and community advocates from

around the world to look specifically at unravelling the challenges of HIV persistence and eradication. They are looking at new technologies that will delve into the mechanisms that allow HIV to persist despite an immune response and highly effective ART. They are also asking researchers to use existing drugs to reduce the virus to levels approaching zero and to create a regimen that might ultimately eradicate the virus.<sup>10</sup>

Unfortunately, Martin Delaney was not able to see the outcome he wished for in his lifetime. But hopefully it will occur within ours. If it does, it will be to his credit as well as other activists who maintained the pressure, and a testament to the hard work of those scientists and researchers who finally help deliver an end to HIV. And finally find the cure.

Thanks to Professor Jenny Hoy for her help with this article.

### Could mass treatment stop HIV?

It is widely accepted that effective treatment reduces the 'community viral load' and has a significant effect on limiting new transmissions. So, could mass testing and treatment eliminate the disease altogether?

The World Health Organisation (WHO) is currently debating whether to test this theory on the entire population of a resource-poor country. In 2008 it published a paper in *The Lancet* using South Africa as the case study, and calculated what would happen if everyone over the age of 15 were tested annually and all those who tested positive offered immediate free antiretroviral treatment, regardless of their CD4 count.

They found that within 10 years the scheme would slash new HIV infections from the current rate of 1 in 50 people to less than 1 in 1000. And within 50 years prevalence in the general population would fall from ten percent to less than one percent. <sup>11</sup>

One problem with this scheme is the cost. South Africa alone would need around US\$3.5 billion, but the money would be well-spent, WHO argues. They are currently calling for universal treatment for everyone with T-cell counts below 200. Not bad as a starter, but it will not eliminate HIV.

A country such as the United Kingdom might be more of a feasible option. It could probably afford to treat all of its estimated 73,000 positive population. But universal testing to find them all would have civil rights groups up in arms. And it would only work if everyone was immediately put on treatment and agreed to maintain therapy (when current guidelines recommend it only for CD4 counts approaching 350). Even then, HIV could still be imported from overseas.

This makes elimination on a country-by-country basis unfeasible.

'It's got to be done worldwide,' claims Brian Gazzard from the Chelsea and Westminster Hospital in London. 'A public debate on the issue would be wonderful,' he adds.

1. <sup>1</sup>. Delaney M. 'The Cure: Why, Whether, How and When' [www.theBody.com](http://www.theBody.com) [6], April 2008
2. <sup>2</sup>. 'New Hope over Elimination of AIDS', *New Scientist*, Issue 2696, page 5
3. <sup>3</sup>. *Op cit.* Delaney
4. <sup>4</sup>. 'Expert sees possible HIV cure in five years', Calgary Sun, [www.calsun.canoe.ca](http://www.calsun.canoe.ca) [7]
5. <sup>5</sup>. Jeffreys R, 'Palm Project Interview: A Talk with Steven Deeks', [www.thebody.com](http://www.thebody.com) [8]
6. <sup>6</sup>. Laurence J, 'Gene therapy offers hope of cure for HIV', [www.independent.co.uk](http://www.independent.co.uk) [9]
7. <sup>7</sup>. *Ibid.*
8. <sup>8</sup>. *Ibid.* Laurence
9. <sup>9</sup>. Mitsuyasu et al, 'Phase II Gene therapy trial of an anti HIV ribozyme in autologous CD34+cells', *Nature Medicine*, 15 February 2009
10. <sup>10</sup>. Johnston R and Laurence J, 'Imagine There's No HIV', [www.amfar.org](http://www.amfar.org) [10]
11. <sup>11</sup>. Wilson C, 'Are We About to Eliminate AIDS?', [www.newscientist.com](http://www.newscientist.com) [11]

[Treating HIV](#)  
[HIV research](#)

**Links:**

- [1] <http://www.napwa.org.au/glossary/term/102>
- [2] <http://www.napwa.org.au/glossary/term/122>
- [3] <http://www.napwa.org.au/glossary/term/475>
- [4] <http://www.napwa.org.au/glossary/term/125>
- [5] <http://www.napwa.org.au/glossary/term/91>
- [6] <http://www.theBody.com>
- [7] <http://www.calsun.canoe.ca>
- [8] <http://www.thebody.com>
- [9] <http://www.independent.co.uk>
- [10] <http://www.amfar.org>
- [11] <http://www.newscientist.com>