HIV/AIDS: More than 25 years later research advances but how close is a vaccine?

Q&A with Professor David A Cooper
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Epidemiology remains a politically sensitive area for any government. Has anything changed since AIDS first got the attention of public opinion in terms of the approach of worldwide decision makers?

The advent of the HIV AIDS pandemic was met with different responses in different countries. In Australia, for example, we had a bipartisan political response to HIV which ensured that 25 years later, we now have one of the lowest rates of transmission in the developed world.

Over time, most governments have come to understand that the lives of their citizens are more important than sensitive issues concerning behaviour, and we have seen a remarkable international effort to help developing countries get access to available treatments. For example, my organisation is active in South East Asia, particularly in Thailand and Cambodia, where we work with government and NGOs to roll out treatments, carry out relevant research and to help train local health workers.

Australia has a high rate of the HIV-positive population enrolled in clinical research. It seems to be quite an unusual achievement in the scientific community. How meaningful is such a factor to the defeat of the virus?

In the major Australian population centres such as Sydney and Melbourne, the affected community was quickly included in many aspects of the management of the epidemic. They were well organised and well educated, and they understood the importance of clinical research. This made recruiting for clinical trials more straightforward; also new studies were anticipated and welcomed by a community which understood the process and the future benefits for themselves and their friends. The gay community also helped in educating the sex worker and injecting drug communities, which meant that the benefits of prevention campaigns and treatment were quick to spread as far as possible.

The partnership approach which developed between researchers and the affected community was mutually beneficial and enduring. The community engaged with the science of HIV and its treatments, and community representation on scientific advisor groups at my organisation has been a feature of the response to HIV. Early community concerns -- that research studies
might delay access to urgently needed therapies -- encouraged us to find ways to allow the most desperately ill patients open access to new drugs as they became available.

What did we learn from the early HIV treatments? What are the areas of greatest significance that still need to be addressed?

The early HIV treatments seemed like a miracle after years of watching our patients suffer and die. Of course some of the early antiretrovirals had their limitations, in particular with side effects and viral resistance. But from them we learned the importance of rigorous monitoring, and we learned that the evaluation of new ARVs was essential for long-term management and viral control. We observed the importance of adherence, and this led directly to dialogue with the pharmaceutical companies to develop combination therapies, which in turn made dosing easier. For example, a single once-daily dose combining three or more drugs transformed the issue of patient adherence and lowered the risk of viral resistance.

Ahead of us lies the task of managing HIV as a chronic long-term condition. The cohort effect, in which we see long-term HIV patients, means that age-related conditions such as heart disease or cancer must be managed alongside their HIV disease and this is an area which will continue to present challenges.

Despite our advances, life expectancy is still not normal. Even in the best possible outcomes with combination therapy, about 10 years is lost from a normal lifespan. Death is now increasingly due to serious non-AIDS illnesses, such as cardiovascular disease, cancers, and end-stage liver and renal disease. The most reasonable explanation for the 10 to 20 year gap in life expectancy is the previously unrealised clinical effects of untreated HIV infection and this is likely to inform much of our future work.

In developing countries, the rollout of effective treatments brings with it an obligation to support the families who live with HIV disease. For example, we find in our clinics in Thailand and Cambodia that our work has expanded to include community outreach programs, promoting care in the community for children with HIV, not just medically but also with education and social and material support for their families.

Your contribution led the way in the global understanding of primary HIV infection and drug toxicity. Your team has also participated in most of the important strategic trials for HIV treatments. What is your opinion of current treatments?

It is true that our early work, in particular the identification of the seroconversion illness and the body’s immune response to its initial encounter with the virus was key in helping understand the early phase of disease, and we also have been involved in the development - at some stage - from phase one to phase four of every antiretroviral therapy that has been approved for use in HIV disease.

We are now in a different time and place with HIV treatments. There is a greatly increased range of drug therapies available with new modes of action, opening up different treatment options. We have five classes of drugs - non-nucleosides, nucleosides, protease inhibitors, integrase inhibitors and entry inhibitors - and these permit a large number of combinations to address resistance, toxicity, personal response to therapy and other factors arising from comorbid conditions such as heart or liver disease. Our work continues to improve therapeutic
regimens, to make them more easily tolerated, better employed and leading to improved outcomes.

*The quest to develop a vaccine has consumed the energy of scientists, the cash of drug companies, and funding agencies for 25 years. Do you expect any success in the near future in this field? HIV is very variable. Can aiming at searching for antibodies, the infection-fighting proteins that can neutralize strains of the virus, be of some help in developing a vaccine?*

The search for a vaccine - preventative or therapeutic - has been the Holy Grail for a long time in this field. Unfortunately, the pathogenesis of HIV has meant that a solution has eluded us so far. Many teams around the world continue to explore different options; for example, our group has one team looking at novel neutralising antibodies derived from brain isolates of the virus and isolates obtained pre-seroconversion. Recently results from a large vaccine trial in Thailand have been released showing that participants who received the trial vaccine had a 30% reduced risk of contracting HIV during the study period compared to controls. This is the first encouraging sign that a vaccine strategy may be effective in controlling the spread of HIV; however, further research is essential in developing a widely available and effective HIV vaccine.

Understanding immune responses and other factors capable of neutralising HIV is essential in developing treatments and future vaccine candidates. Improved knowledge of the interaction of HIV and the host immune system is essential in informing new treatments. All options, including the antibody pathway, are worth exploring until we find our way in; it's worth remembering that vaccine development is a long and complex process.

*Luc Montagnier, co-discoverer of the HIV virus and Nobel Prize-winning scientist, supported a dual-pronged approach after preventing infections in a trial in Thailand. The study coupled two vaccines, ALVAC, and AIDSVAX. Neither had stopped the AIDS-causing virus when tested separately in previous studies. Is combining shots the key to discovering a vaccine in the majority of HIV cases?*

We would never rule out combination vaccine approach. Knowledge and understanding of these vaccine candidates and how they work is presently incomplete but all approaches are worth exploring. Two or more candidates eliciting different host responses may well be the key to a viable vaccine. Watch this space!

**Do you see any other major breakthroughs coming along in the science of HIV?**

The time for major breakthroughs was when we were still establishing the early knowledge base. These days, HIV is one of the most intensively researched infectious diseases globally and our progress is measured these days in increments rather than breakthroughs. Other than vaccines, current research is focused on areas such as immune reconstitution and the potential for viral clearance.

In terms of eradication of the virus, there are several technologies that show promise in the laboratory, including gene therapy and small interfering RNAs. The major hurdle to these technologies being used in patients is in packaging and delivery, so that the therapy is delivered intact to specifically targeted cells in the body. Further research and development is required to identify and target all HIV-infected cells in the body in order to achieve
complete clearance of the virus from a patient.

_A partnership between a nonprofit treatment centre near Los Angeles and a California-based biotechnology company recently received U.S. $14.6 million to work on a new method for using stem cells to treat AIDS and HIV. Could this be a new frontier for clinical research?_

At present, there is no clear indication about where the cure or control for HIV will come from. Research into a wide number of fields is required, along with enormous investment, to expand our knowledge. No area of study can be dismissed without thorough investigation.

_Thank you very much for answering our questions Professor Cooper._