



Inaugural **Global Scientific Strategy** Towards an **HIV** Cure launched ahead of the XIX International AIDS Conference in Washington DC World's leading HIV/AIDS Scientists and Stakeholders to gather in Washington D.C. to discuss Global Alliance on HIV Cure research

Thursday, 19 July, 2012 (Washington D.C, US)--The Inaugural Global Scientific Strategy Towards an HIV Cure was launched today ahead of the XIX International AIDS Conference amid renewed optimism from the world's leading HIV/AIDS scientists that the future prospects for finding an HIV cure are increasing.

Over the past two years the International AIDS Society (IAS) has convened a group of international experts to develop a roadmap for research towards an HIV cure. Published online in an abridged form tomorrow, Friday July 20, in Nature Reviews Immunology, Towards an HIV Cure identifies seven important priority areas for basic, translational and clinical research and maps out a path for future research collaboration and funding opportunities.(1)

"The strategy is the result of a collaborative effort which has produced a roadmap that will constructively move HIV Cure research forward," said Françoise Barré-Sinoussi, the co-discoverer of HIV, Director of the Regulation of Retroviral Infections Unit at the Institut Pasteur in Paris and the IAS President-Elect. Barré-Sinoussi, together with Professor Steven Deeks, Professor of Medicine at the University of California, San Francisco, is co-chair of the group of 34 leading HIV scientists and clinicians who have developed the Global Scientific Strategy. Professor Barré-Sinoussi and Professor Deeks state the case for HIV cure research in a commentary piece published today in Nature. (2)

"The science has been telling us for some time now that achieving a cure for HIV infection could be a realistic possibility. The time is right to take the opportunity to try and develop an HIV cure – we might regret never having tried," concluded Barré-Sinoussi at the D.C. launch.

The vision for the IAS strategy for an HIV cure is very clear: a safe, affordable and scalable cure will improve the health and quality-of-life for those with established infection, reduce the risk of transmission of virus to those not infected, and ultimately allow resources to be shifted to other

needs.

"Finding a cure for AIDS is a critical innovation gap," said Michel Sidibé, Executive Director of UNAIDS at the launch in D.C. "A cure will bring new hope to people living with HIV and their loved ones and could end the cycle of stigma and discrimination."

Major investments in science have resulted in the worldwide availability of over 20 anti-HIV drugs. When used in combination, these drugs restore health, prolong life and reduce transmission of the virus. HIV-infected individuals who harbour drug-susceptible virus, who have access to antiretroviral drugs, who can tolerate the drug side effects, toxicities, and other complications, and who are able to adhere to therapy can maintain control of HIV infection indefinitely.

Despite these successes, these therapies have limitations. They do not eradicate HIV, requiring people to remain on expensive and potentially toxic drugs for life. They do not fully restore health as patients still experience co-morbidities such as increased cardiovascular disease, bone disorders or cognitive impairment. They are expensive and difficult to deliver to all in need.

Although the cost of delivering antiretroviral drugs to the more than 34 million people now living with HIV has decreased substantially, and the availability of these drugs in resource-poor settings has steadily increased, the costs associated with delivering antiretroviral drugs is overwhelming many organizations and public health systems. Estimates put the cost of the funding response to the HIV/AIDS epidemic by 2015 between US\$22-24 billion per year (3) and between US\$19-35 billion per year by 2031, with antiretroviral treatment accounting for up to 70 per cent of the total cost of care in the most affected countries. (4)

It is estimated that for every person starting treatment, two are newly infected, a path that is clearly unsustainable.

Given these limitations, there is growing recognition that the search for an HIV Cure is an imperative both in terms of the individual and public health benefits it would provide and also an opportunity to potentially avoid the long-term cumulative costs of ART. (5)

Also, an effective and scalable HIV cure will likely achieve what preventative approaches aim to do, which is to essentially stop transmission of HIV to those who are uninfected and restore the immunological function and normal health to those who are infected (6).

The renewed optimism in the search for an HIV Cure amongst scientists is based on a number of scientific advances that are helping to shed light on why it is that HIV remains persistent. Scientists have known for some time now that latent HIV reservoirs, where HIV hides and persists, are one of the main barriers to finding a cure. This is precisely why treatment does not eradicate HIV and why, when treatment is stopped, the virus rebounds.

“What we haven’t had until very recently is clear insights into why HIV persists during therapy,” said Steven Deeks, at the launch in Washington, D.C. “Our basic understanding of the mechanisms of HIV persistence in latent reservoirs is far superior than it was a decade ago. We are entering a stage in the epidemic in which we can seriously begin testing drugs that either prevent latency or which force the virus out of its hiding place, make it susceptible to our current drugs.” (7)

Why is an HIV Cure feasible?

Several recent observations make scientists enthusiastic about pursuing cure research.

For the first time ever there is now a “proof of concept,” as scientists like to call it, for an effective cure. The case of Timothy Brown, the so-called “Berlin Patient”, who received a stem-cell bone-marrow transplant in 2007 and is now considered to be cured of HIV, has proved that a cure is at least possible. This stem cell transplant worked because the donor was among the one percent of Northern Europeans who lack CCR5, the “doorway” through which HIV enters cells. While it is unrealistic to pursue this risky and costly therapeutic approach for most people, it has nevertheless got scientists thinking about the use of gene therapy to modify a

patient's own immune cells to make them resistant to HIV infection.(8)

The molecular biology regarding how HIV DNA becomes integrated in the chromosomes of infected people is the focus of intense research. This work has already led to a number of possible interventions, some of which are being tested in the clinic. Recently, in a test in HIV+ patients, David Margolis and colleagues showed that a dose of a drug that inhibits an enzyme involved in HIV silencing leads to rapid production of HIV RNA in the patient's latently infected cells. This could make such previously unreachable viral reservoirs susceptible to curative strategies. For example, in combination with treatments that enhance host immune defense, unmasking latent virus might allow clearance of infection (9).

Scientists have also been aware of a rare group of HIV infected people who appear to have naturally "cured" their own infection. These "elite controllers" are HIV positive but have no readily apparent virus in the blood. Scientists are gaining a better understanding of this group of patients.

There exists a unique cohort of patients in France who became HIV infected, started therapy early, and were able to successfully stop therapy without viral rebound (the "Visconti Cohort"). The study confirms the benefits of treating HIV at the very early stages of infection. There is an immensely valuable store of knowledge to be gained from analyzing the immunological characteristics that made therapy redundant for these patients. (10)

Understanding this group of people who efficiently control the virus replication and reservoirs, scientists believe, might lead to novel therapeutic interventions.

How can HIV be cured?

Currently, the following strategies are being investigated and it is expected that all of these

strategies will be more efficient in combination with each other, alongside the use of antiretroviral therapy to at least protect the immune system of patients to prepare them for a cure:

- Gene therapy
- Treatment Optimization and Intensification (eliminate all replication)
- Reversal of HIV latency (increase virus production)
- Immune-based Therapies (reverse pro-latency signaling)
- Therapeutic Vaccination (to enhance host-control)

What are the HIV Cure research priorities?

The Global Scientific Strategy Towards an HIV Cure identifies and recommends seven key priority research areas, as outlined in the table below.

Determine the cellular and viral mechanisms that maintain HIV persistence. This includes defining the role of mechanisms that contribute to the establishment and maintenance of latent infection, as well as defining the role of viral replication and or homeostatic proliferation.

Determine the tissue and cellular sources of persistent HIV in long term ART-treated individuals.

Determine the origins of immune activation and inflammation in the presence of ART and their consequences for HIV persistence.

Determine host and immune mechanisms that control infection but allow viral persistence.

Study, compare, and validate assays to measure persistent infection.

Develop and test therapeutic agents or immunological strategies to safely eliminate latent infection in individuals on ART. This includes strategies aimed at clearing latency.

Develop and test strategies to enhance the capacity of the host response to control active viral replication.

Funding and collaboration

The IAS and its partners will foster international research collaborations for an HIV cure and monitor progress made in the roll-out of the scientific strategy.

Addressing the scientific barriers will require substantial resources. NIH recently awarded the Martin Delaney Collaboratories, large grants for research toward a cure, as well as a series of targeted funding initiatives to support this area of research. These programs are in addition to the substantial portfolio of ongoing basic and clinical HIV research of research related to the elimination of viral reservoirs and other research toward a cure.

Other traditional government-based funders of biomedical research like the French National Agency for Research on AIDS and viral hepatitis (ANRS), the Canadian Institutes of Health Research (CIHR) and the Medical Research Council (MRC) in the United Kingdom are also increasing their commitment to cure research, and a number of non-government groups are raising and spending considerable amounts of money on cure research. Many of the pharmaceutical companies that invested heavily in antiretroviral drugs are now also allocating some of their resources to address this question.

The investment now going to cure research is substantial but almost certainly not sufficient. It is hoped that some of the emerging economies among countries heavily affected by the epidemic will take some ownership of this agenda.

“Under no circumstances should the inclusion of “cure” in the global response direct funding away from treatment, prevention and care programmes, or from biomedical research on HIV and its consequences, including vaccine and other prevention research,” said Barré-Sinoussi. “However, it is imperative that donors, governments and the AIDS community make viable economic investment in HIV cure research, and right now.”

Development and funding of a scientific agenda are needed but they are not sufficient. The Global Scientific Strategy Towards an HIV Cure has identified six key steps that need to be taken to enhance progress in HIV Cure research.

- The establishment of large, multinational collaborations involving experts from multiple disciplines (including those outside of the HIV arena) will likely be needed. The NIH-funded Martin Delaney Collaboratories were a first step in this direction;
- Translational research involving teams of basic and clinical scientists working side-by-side with knowledge flowing in both directions are needed;
- The optimization of relevant animal models for discovering and testing novel interventions is needed. The development of effective antiretroviral treatment for SIV in macaques has only recently been achieved; it is expected that this model will prove to be very important for future discovery when studies cannot be safely conducted in humans;
- Young researchers need to be mentored and supported, as they are likely to be the source of innovative, out-of-the-box thinking;
- 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 a regulatory pathway for advancing candidate therapies through the clinical trial process identified;
- Strong community support is needed to advocate against complacency and to ensure that patients and their communities are fully engaged and informed about the risks and benefits of curative studies.

Le plan stratégique international "Towards an HIV Cure" est lancé

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