HIV Cure – Basic Facts
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1. What is the difference between a vaccine against HIV/AIDS and a cure?

A cure and a vaccine are two different things; scientists are working to develop a vaccine against HIV/AIDS, whilst also working on research towards an HIV cure in parallel.

A preventive HIV vaccine would contribute to protecting people who are not infected with HIV, by inducing protective immune responses against the virus. Although vaccines are generally preventive, it is important to note that a therapeutic vaccine for HIV could induce immune responses to help control the virus in people who are already infected by HIV. A therapeutic vaccine could ultimately be a component of a cure approach.

An HIV cure would help those who are already infected to control or eliminate the virus, in the absence of anti-retroviral therapy (ART).

2. What is the difference between a functional and sterilizing cure?

There are two types of broadly defined approaches to curing HIV infection:

- elimination of all HIV-infected cells (a sterilizing cure)
- life-long control of virus in the absence of ART without achieving complete eradication of HIV (a functional cure)

3. Living with HIV is no longer a death sentence so why do we need a cure?

(i) Many HIV positive people can now live to full life expectancy on a regimen of anti-retroviral drugs. The development and rollout of antiretroviral therapy is one of the major successes in the fight against HIV/AIDS, saving millions of lives. However, after more than 30 years of the AIDS epidemic only half of the 14 million people eligible for treatment are currently receiving it (close to 26 million are eligible for antiretroviral therapy, under WHO 2013 consolidated ARV guidelines- and only 10 million of those are on treatment).

(ii) Despite the successes, anti-retroviral therapies do have limitations. As they do not eradicate HIV from the body, a daily regimen of medications is required, which can have significant side effects and may not fully restore function of the immune system. As HIV+ patients age, some still experience co-morbidities such as increased risks of cardiovascular disease, bone density loss, cancer or neurocognitive impairment.

(iii) Although the cost of delivering antiretroviral drugs has decreased substantially, and the availability of these drugs in resource-poor settings has steadily increased,
the costs associated with delivering antiretroviral drugs is not sustainable for many organizations and public health systems.

(iv) The input from scientists, clinicians and activists in the search for alternatives to lifelong treatment will benefit the patients, the health systems and the economy.

(v) There is always a danger of development of drug resistance in long term therapy, especially when there is poor adherence to treatment.

4. Haven’t scientists always been looking for a cure for AIDS?

(i) The search for a cure for HIV/AIDS began in the early 90’s when mortality rates among HIV+ people were much higher. Research and trials have provided essential insight into the immune system and contributed to the accumulated knowledge over the years, however the search still continues. When the first triple combination antiretroviral therapy came on the market in 1996 there was great excitement and an accompanying level of expectation amongst researchers that this new class of drugs might actually eliminate HIV from the body and “cure” people. A number of high-profile curative approaches were conducted following the development of combination therapy, but these were unfortunately unsuccessful in eradicating HIV, and the field shifted towards optimizing therapy.

(ii) Researchers discovered however that HIV hides in so-called reservoirs despite anti-retroviral treatment. Continued research on latent HIV has been necessary to gain the knowledge about reservoirs to develop strategies towards eradication.

5. Why now?

(i) Scientific evidence is steadily accumulating:

- **Elite controllers**

  Scientists have been aware that the so called “elite controllers” — those very few people who are infected with HIV for at least a decade, and yet are able to control viral replication despite the absence of antiretroviral treatment — were always going to be a vital part of future cure research, and are now gaining a better understanding of this unique group of patients.

  Some of the more recent science indicates that the elite controller status is related to the host genetics permitting robust cell mediated immunity and/or restricting an infection in their CD4 lymphocytes and macrophages.

  Understanding this group of people who efficiently and spontaneously control the virus replication and typically present smaller reservoirs may be key in the search to attaining a “functional” cure that would allow long-term remission of infected individuals.

- **The Berlin patient.**
The case of the Berlin patient, Timothy Brown, provided a proof of concept. Timothy Brown, a patient with leukaemia and HIV, received a stem-cell bone-marrow transplant in 2007 from a donor with a gene mutation (CCR5Δ32) which provides natural resistance to HIV, leading to the remission of his leukaemia and he is now considered to be cured of HIV.

Although this approach is too elaborate, risky and specific to serve as a universally applicable HIV cure strategy, the case of the Berlin patient stimulated new interest among the international scientific research community.

- **Post-treatment controllers – The VISCONTI Cohort and the Mississippi Baby**

  - **VISCONTI Cohort**: In France, researchers have identified a unique group of 14 patients, the ANRS VISCONTI cohort, that have been treated very early after infection for a mean duration of three years before stopping their treatment. Since then, they have been able to control their virus replication without the need for ART. Understanding the immune mechanisms involved in these rare post-treatment controllers is of great interest to cure research.

  - **Mississippi Baby**: Early in 2013, researchers led by Deborah Persaud at Johns Hopkins University announced that a Mississippi baby born with HIV was started on antiretroviral treatment about 30 hours after birth. The unidentified child has now been “functionally cured” and has not received medication for about a year, with no signs of viral rebound. The case indicates again a correlation between early suppression of HIV to undetectable viral loads and the size of latent HIV reservoirs. The result still needs to be confirmed by further analysis but it further confirms the benefits related to early therapeutic intervention.

- **Latency reactivation studies: Proof of concept**. Current treatments are effective at reducing the levels of the virus in the bloodstream, but a drug which can ‘knock out’ HIV when it lies dormant is thought to be the key to a cure. Scientists have found that Vorinostat, a drug used to treat lymphoma, can reactivate HIV out of hiding. While other chemicals have disrupted dormant HIV in vitro, this is the first time that any substance has done the same thing in people.

  On-going studies provide encouraging results that other molecules in this class of drugs (HDAC inhibitors) may also prove successful in reactivating latent HIV. At this stage, these studies only provide proof of concept that disrupting HIV dormancy is possible, but further investigation is necessary to gain insight into the mechanisms that will follow HIV reactivation. The idea is
that the awakened viruses would either kill the cell, or alert the immune system to do the job. Drugs could then stop the new viruses from infecting healthy cells. If all the hidden viruses could be activated, it should be possible to completely drain the reservoir.

6. Which clinical approaches are currently being investigated?

- **Testing eradication at acute HIV infection**

  Early antiretroviral therapy initiated at acute HIV infection is believed to decrease the reservoir size. The ANRS Visconti cohort and the Mississippi baby case suggest that post-treatment control may be possible for some patients.

- **Antiretroviral intensification**

  This approach aims to investigate whether enhanced anti-retroviral treatment above the standard 3-drug regimen may show additional benefits in reducing viral markers, such as plasma viremia and/or integrated proviral DNA (a hallmark of reservoirs).

- ** Reactivation strategies**

  A class of drugs called HDAC (histone deacetylase) inhibitors is being investigated to reactivate HIV expression in latently infected cells. Encouraging results show that HDAC inhibitors are able to “wake up” the dormant HIV. Researchers now need to investigate how the immune system, antiretroviral drugs or immune-based treatments could kill the reactivated virus.

- **Gene therapy approaches**

  Gene therapy approaches may provide exciting novel mechanisms towards an HIV cure, however, it is important to state that these approaches are still in infancy. Gene therapy approaches include the strategy to modify the CCR5 receptor of HIV, protecting cells against HIV infection. Another strategy investigated is that of modifying cells to express anti-HIV genes.

- **Therapeutic immunization**

  A therapeutic vaccine aims to boost the immune system of HIV+ infected people to create strong, specific anti-HIV immune responses to better fight the virus and reduce the viral load.

It is important to note that it is unlikely that a single approach will be successful to cure HIV infection. To obtain a decrease in viral reservoirs and a potential eradication of the virus, combination therapeutic approaches will most likely need to be investigated.
7. Understanding HIV reservoirs

With the extremely efficient combination of medications that are available today, the amount of HIV in the blood reaches undetectable levels in most successfully treated patients. Still, these treatments do not completely eradicate HIV from the body, and if patients stop therapy, the virus rebounds from the reservoirs. Nevertheless, exceptions have been identified: residual replication, latently infected cells in which the virus DNA is integrated but not expressed as HIV virions, and several compartments such as the brain called sanctuaries where HIV stays out of reach from both current drugs and the immune system. It is important to develop new strategies targeting those reservoirs specifically.

HIV antiretroviral (ARV) therapy cannot cure HIV mainly because the virus can become “latent” by integrating its DNA into cells which prevents the immune system from recognizing and clearing these cells. Determining how this ‘latency’ works, where infected cells reside and how latent infection could be reversed are the focal points of most on-going cure research.

Such work is based on the assumption that if all latently infected cells could be identified and HIV is forced out of them while ARV’s inhibit that virus from infecting new cells, then the person’s immune system could identify and kill all infected cells, thereby achieving a cure. Yet, it is unclear whether the immune system has the capacity to kill infected cells, even if they could be forced to start making virus. It is also unclear which specific cell types contain HIV reservoirs during long-term therapy.

8. The seven scientific research priorities of the Global Scientific Strategy Towards an HIV Cure include:

1. Cellular and viral mechanisms involved in HIV persistence at a molecular level
2. Anatomical compartments and cellular sources of HIV reservoirs
3. Immune activation and dysfunction in the presence of ART
4. Natural models of HIV/SIV control
5. Assays to measure persistent infection
6. Therapeutic and immunological approaches for eliminating persistent HIV infection
7. Enhancement of immune responses to control viral replication.

9. Six Prerequisites in the search for an HIV Cure

(i) The establishment of large, multinational collaborations involving experts from multiple disciplines (including those outside of the HIV arena). The NIH-funded Martin Delaney collaboratories were a first step in this direction which now need to be duplicated in an international effort;
(ii) Multidisciplinary research involving teams of basic and clinical scientists working side-by-side with knowledge flowing in both directions;

(iii) The optimization of relevant animal models for discovering and testing novel interventions. The development of effective antiretroviral treatment for SIV (simian immunodeficiency virus – the monkey counterpart of HIV) 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.

(iv) Young researchers should be mentored and supported, as they are likely to be the source of innovative, out-of-the-box thinking;

(v) Address the profound ethical and regulatory issues that surround testing of novel drugs (many with high potential for toxicities) in patients who are doing relatively well with long term ARV therapy, while providing an effective regulatory pathway for advancing candidate therapies through clinical trials;

(vi) Strong community support to advocate against complacency and to ensure that patients and their communities are fully engaged and informed about expectations, risks and benefits of cure-related studies.

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The International AIDS Society (IAS) is the world's leading independent association of HIV professionals, with over 16,000 members from more than 196 countries working at all levels of the global response to HIV. Our members include researchers from all disciplines, clinicians, public health and community practitioners on the frontlines of the epidemic, as well as policy and programme planners. The IAS is the custodian of the biennial International AIDS Conference, and lead organizer of the IAS Conference on HIV Pathogenesis, Treatment and Prevention. Under the auspices of the International AIDS Society, an international working group of researchers developed a Global Scientific Strategy: Towards an HIV Cure, which was launched at a scientific symposium immediately preceding the XIX International AIDS Conference in Washington, DC in July 2012. HIV cure remains a key priority for the IAS and the IAS will organize a new edition of the HIV cure symposium in Melbourne on 19&20 July 2014.

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