Towards
an HIV Cure
IAS

Research Priorities for an HIV Cure: IAS Global Scientific Strategy 2021

The science in context

International AIDS Society

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A new scientific strategy towards an HIV cure

Research Priorities for an HIV Cure: IAS Global Scientific Strategy 2021, published in Nature Medicine, highlights critical gaps and promising progress in HIV cure research, providing strategic recommendations to researchers, donors, advocates and other stakeholders for the next five years. IAS – the International AIDS Society – through its Towards an HIV Cure programme convened a 68-member International Scientific Working Group of leading researchers, ethicists, industry representatives and community advocates to develop this third Global Scientific Strategy. The groundbreaking first IAS Global Scientific Strategy: Towards an HIV Cure was published in 2012 and updated in 2016. The strategy incorporates reviews of over 150 studies and input from stakeholders globally through online consultations and a survey.

Research Priorities for an HIV Cure: IAS Global Scientific Strategy 2021 makes concrete recommendations for cure research priorities in basic, translational, clinical and behavioural and social sciences. It emphasizes the importance of ethical implications, strengthening cure research in low- and middle-income settings, and meaningful engagement of communities affected by HIV, who are central to the success of any cure.

The Global Scientific Strategy serves as:

- A guide for scientific research, to address the most critical knowledge gaps and outstanding questions in the field
- A tool for funders and policy makers, to guide their support for the most effective and efficient research towards an HIV cure
- A framework for advocates, to support high-quality, ethical and cost-effective research that can lead to a cure for HIV

The need for an HIV cure

While antiretroviral therapy (ART) can control the virus and improve the lives of people with HIV, treatment requires life-long adherence, which is challenging for many due to a host of factors that may prevent or hinder access. Individuals who receive ART may also experience side-effects or drug toxicities, including immune system dysfunction and chronic inflammation.

There are also challenges for health systems to deliver HIV prevention and testing services to people at risk of HIV, as well as treatment, care and retention services for people living with HIV today and the millions more who will need these in the future.

Ten years ago, a global consensus emerged that a curative intervention was a high priority for people living with HIV and would be necessary to help control the HIV epidemic. A cure could overcome the limitations of ART, limit new HIV transmissions, reduce stigma and discrimination, and provide a sustainable financial solution for epidemic control.

2020 key facts supporting HIV cure research

37.7 million
people globally living with HIV

1.5 million
people newly acquired HIV

680 000
people died from AIDS-related illness

27.5 million
people were accessing ART

US$26 billion
was required for the AIDS response in low- and middle-income countries

Funding for HIV/AIDS programmes was **insufficient** to achieve **UNAIDS 95-95-95 goals**

HIV cure definitions

To impact the global HIV epidemic, curative interventions must ultimately prove to be safe and effective, provide protection against reinfection, be affordable in developing countries, and be scalable to address the epidemic. The minimal and optimal criteria for various HIV cure strategies, including acceptability, were defined following a 2020 IAS consultation.

Eradication

A classic cure works to eliminate HIV from the body completely, including from hidden reservoirs.

Remission

A sustained ART-free HIV remission would reduce the amount of HIV in the body to levels where it cannot be detected, cause illness or be transmitted – but it would not completely remove the virus from the body.

Research Priorities for an HIV Cure: IAS Global Scientific Strategy 2021 focuses on both remission and eradication.

Progress in HIV cure research raises hope for a cure

- Research on "HIV controllers", people who naturally control HIV without ART or after a cure-related intervention, has provided new information and directions for cure research.
- HIV reservoirs (cells that are the source of HIV once ART is stopped) are now seen as evolving rather than static sources of HIV not reached by ART. Important differences among people with HIV have been identified, such as biological sex, which affect reservoir location and dynamics.
- Technological developments allow for a better understanding of how HIV latency is established and how the virus is reactivated after an analytical treatment interruption (conducted in the context of HIV cure research); this allows for the identification of new targets for HIV cures.
- New drugs and interventions are being developed and have started to show success in animal (preclinical) models.

Several cases of remission and eradication have been recorded. Research towards an HIV cure is drawing on these real-world cases, as well as on HIV controllers, to better understand how a cure could work and help identify targets for HIV cure-related interventions. Examples include:

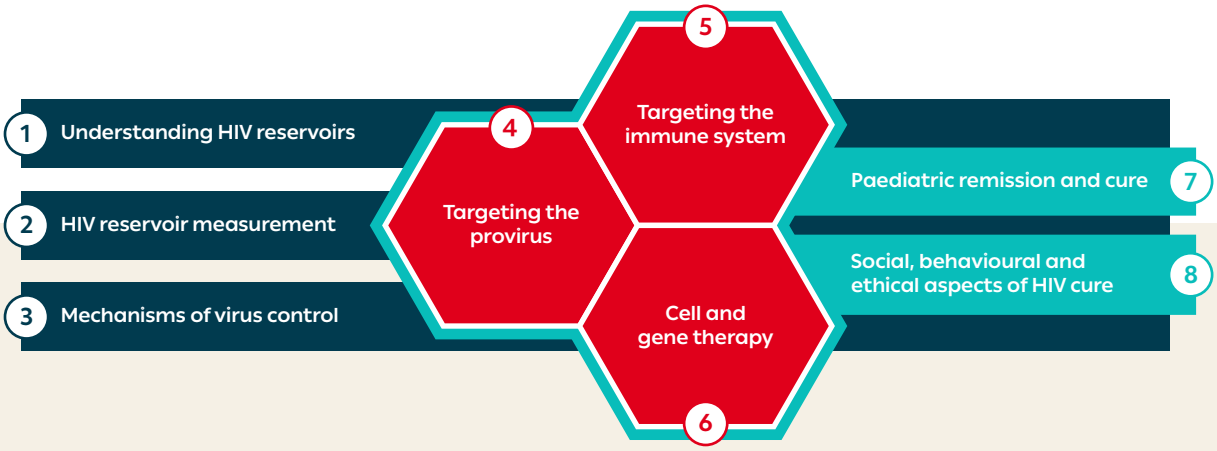
- Timothy Ray Brown, the "Berlin patient" (2008), and Adam Castillejo, the "London patient" (2019), remained virus-free while off ART following a complex stem-cell transplant.
- The VISCONTI cohort (2013) of 14 people who initiated ART soon after acquiring HIV and remained on treatment for a minimum of three years have controlled their HIV since stopping ART.
- The "South African child" (2017) received ART treatment for 40 weeks shortly after birth and was able to suppress the virus without medication after stopping treatment.
- Loreen Willenberg (2020) and the "Esperanza patient", named after the Argentinian town she was born in, (2021), are known as "HIV exceptional controllers" due to their immune systems natural ability to clear the virus to an undetectable level.

Prerequisites for an HIV cure: Beyond the science

- Coordinating investments to pursue the most promising HIV cure research approaches
- Strengthening international collaborations to ensure a multidisciplinary approach for the development of a cure that is accessible and scalable in diverse settings
- Promoting the involvement of early-career researchers and researchers from countries most affected by HIV
- Supporting communication and information exchange between public and private sector researchers working on HIV cure research to alleviate the regulatory and logistical challenges associated with drug development
- Building HIV cure research capacity among different populations and settings to generate increased HIV cure research and advocacy globally
- Enhancing community engagement in HIV cure research through knowledge dissemination and capacity building for advocacy and effective engagement to represent their interests
- Boosting research on the psychosocial and ethical implications of participating in HIV cure clinical research to ensure that both participants and clinical trial designers are well-informed and prepared

Recommendations of the 2021 strategy

This third IAS Global Scientific Strategy is a comprehensive roadmap featuring the most pressing gaps in HIV cure research and research priorities to guide the field toward a widely accessible, acceptable and affordable cure. The strategy outlines the recommendations in eight focal areas.



Research requires a better understanding of the HIV reservoirs ①, in particular how the virus integrates its genetic material into the human genome, and how to measure the reservoir size ②, as well as identifying the sources of viral rebound when ART is stopped and the mechanisms of cellular expansion that follows.

Understanding the mechanisms of virus control ③, particularly HIV controllers' natural control of HIV in the absence of ART, will provide clues to design curative interventions, especially interventions targeting the host immune system.

To support curative interventions, tools building on innovative technologies will have to be developed to better understand HIV biology, identify new targets and measure the success of curative interventions. Discovering biological markers will help with unambiguously identifying and targeting HIV-infected cells, as well as optimizing, standardizing and validating animal models, such as humanized mouse models.

Curative interventions will focus on targeting the provirus ④ and the immune system ⑤ and also leverage cell and gene therapies ⑥.

Successful cure research will require integration of behavioural and social sciences and ethical aspects of cure research ⑧ and not be limited to adults; it will include HIV cure research for children ⑦.

Research tools often rely on complex technologies not easily accessible or available in all research contexts and settings. Identifying biological markers and developing point-of-care tests are important to facilitate our understanding of the HIV reservoir and measure the impact of cure interventions. These tools should be scalable and accessible in various settings.

Preclinical research relies on animal models, especially in situations where it would be unethical or impractical to use humans. Animal research provides crucial information and knowledge that underpins scientific advances and can provide insights into how cure interventions affect the reservoir, viral reactivation during ART, or viral recrudescence after ART interruption.

Research priorities for an HIV cure

Targeting the provirus

The HIV reservoir remains the main target for an HIV cure. The following three approaches to target the reservoir are identified as priority areas.

- "Poke and clear" (previously "shock and kill") involves drugs called latency-reversing agents (LRAs) to awaken the dormant virus in HIV-infected cells. Following activation, the virus-producing cells are eliminated by a second intervention.
- "Block and lock" is a strategy on the opposite side of the spectrum that, instead of awakening the HIV reservoir, drives the reservoir into a deeper permanent resting state.
- "Reduce and control" attempts to reduce the size of the reservoir and help the immune system control viral replication without the need for long-term ART.

These approaches may use one or more agents, including broadly neutralizing antibodies (bNAbs), various killer cells, therapeutic vaccines, and cell and gene therapies.

The effort to target the HIV reservoir will have to account for differences observed between people and the development of more potent LRAs, with less off-target effects and improved safety profiles.

To evaluate the impact of these approaches, the strategy emphasizes the need to find biomarkers and develop better tools to detect, measure and understand the HIV reservoir.

Challenges of targeting the HIV reservoir

- Understanding the viral landscape: location, state and ability of the virus to become active and produce more copies of virus
- Mitigating the risk of off-target effects of drugs and approaches used
- Improving accuracy, specificity and sensitivity of tests for different parts of the virus (DNA, RNA, proteins) and types of viruses circulating in different populations
- Harmonizing tests across laboratories

Targeting the immune system

Recognition of infected cells by the human immune system may contribute to sustained ART-free HIV remission. There is a robust and growing range of immune therapies based on vaccines and immune stimulators and modulators that holds promise and might advance to proof-of-concept testing.

Research into the development and use of broadly neutralizing antibodies alone or in combination with other approaches, including therapeutic vaccines, immunomodulators and/or LRAs, is recommended.

These studies will be intensive and complex. Biomarkers will be needed to assess their efficacy as they have yet to be used in humans. They present multiple challenges from methodological and regulatory perspectives.

Broadly neutralizing antibodies are originally obtained from a person with HIV who has particularly good immune responses against the virus. They can be modified to increase their potency and half-life, and can be combined with other broadly neutralizing antibodies or other interventions.

Cell and gene therapies

Inspired by the elimination of HIV in Timothy Ray Brown and Adam Castillejo, the strategy endorses further research based on cell and gene therapies. This includes gene editing with CRISPR/Cas9 (or related) technology and cell-based therapies using chimeric antigen receptor (CAR)-T cells.

Cell and gene therapies can also be used to deliver antibody-like molecules that could mimic natural immune control of the virus.

Delivering these interventions into the body is challenging, and progress will be needed to overcome these obstacles, as well as to ensure that they can be deployed in low- and middle-income settings.

Cell and gene therapies for HIV cure

Several innovative approaches based on genome editing have been developed as cure strategies. These approaches can be delivered **in vivo** (using nanotechnology to deliver the HIV therapeutic to target cells in the body) or **ex vivo** (cells are taken from the patient, modified in a laboratory, and reintroduced in the patient).

CRISPR-Cas9 (or similar) genome editing technology

First identified in bacteria, CRISPR technology uses an enzyme capable of editing out genetic material in human cells. The approach could be used to remove HIV hidden in reservoir cells or to remove the protein on the surface of human cells used by HIV to enter and infect the cells. Zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) are two other genome editing technologies developed for an HIV cure.

Chimeric antigen receptor (CAR)-T cells

Clinical applications in humans of CAR-T cells began 25-30 years ago. CAR-T cells can recognize and eliminate HIV-infected cells. T cells are taken from a patient's blood, modified in a laboratory, and given back to the patient by infusion.

Human studies of cell and gene therapies remain small and have shown limited success so far. Research still has to overcome some challenges, notably the diversity of location of the reservoir cells and the risk of off-target effects.

Paediatric remission and cure

Globally, during 2020, an estimated 160,000 children acquired HIV, far from the global UNAIDS 2020 target of 20,000. In 2019, only 58% of pregnant women with HIV in western and central Africa received ART to prevent perinatal transmission. The unique context of perinatal HIV acquisition necessitates paediatric-specific strategies to achieve sustained ART-free remission in children.

Early antiviral therapy alone (for example, the "Mississippi baby") will not be enough to reach a cure. It is necessary to include infants and children along with adults in the advances of HIV cure research.

Research goals over the next five years include studying differences in the dynamics of the HIV reservoir of children and adults and developing non-invasive research tools and methodologies specifically for studies with children.

Key differences between adults and children relevant to HIV cure research

- Children born with HIV have immune systems that have always been exposed to HIV. This differs from adults who acquired HIV after their immune systems were already developed.
- Infants and children have the prospect of needing ART for decades longer than most adults with HIV. This suggests that their need for a cure is more important.
- Early ART after birth might make the HIV reservoir smaller and potentially easier to eliminate than in adults, who are diagnosed later in infection.

Cure research in context

Research directed towards an HIV cure intertwines critical social, behavioural, ethical and community and stakeholder engagement aspects that must be incorporated in the scientific research agenda. Research Priorities for an HIV Cure: IAS Global Scientific Strategy 2021 advocates for:

- The meaningful engagement of communities living with and affected by HIV in all stages of cure research, including educational efforts by researchers, supported with adequate funding
- Broadening the representation and diversity of stakeholders during the development of HIV cure research interventions
- Nesting social, behavioural and ethics research into trials to gain a better understanding of how gender, race and other characteristics shape and enhance participation in research
- Assessing the social impact of the research at community and individual levels to ensure feasibility, acceptability and appropriateness of HIV cure research interventions
- Boosting the understanding of the research in both participants and their partners
- Factoring equity and justice in the design and development of effective strategies to ensure acceptability, scalability and cost effectiveness of HIV cure research interventions

The establishment of the HIV Cure Africa Acceleration Partnership (HCAAP) is expected to enable broader engagement and facilitate rapid implementation of any successful strategy in low- and middle-income settings.

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Key recommendations of Research Priorities for an HIV Cure: IAS Global Scientific Strategy 2021

① Understanding HIV reservoirs

Define and characterize the sources of the replication- and rebound-competent viruses during ART.

Define the phenotype of cells harbouring intact HIV genomes.

Define the clinical significance of defective yet inducible proviruses.

Define the mechanisms of clonal proliferation.

Determine if infected cells that persist on ART are resistant to cell death.

Define the impact of sex and other factors on the reservoir and virus-specific therapies.

② HIV reservoir measurement

Develop and validate a high-throughput assay to quantify the rebound-competent reservoir.

Develop assays that quantify integration sites.

Develop assays that account for key qualitative differences in viral transcripts.

Develop methods to quantify HIV protein expression in cells and tissues.

Develop imaging modalities that quantify the size, distribution and activity of the reservoir in tissues.

Define the link between the cellular reservoirs, residual plasma viremia and the rebounding virus.

Develop assays for point-of-care and eventually at-home viral load monitoring.

③ Mechanisms of virus control

Identify the mechanisms that contribute to SIV/HIV control.

Define the role of HIV-specific antibodies, B cells and the innate immune response in virus elimination or control.

Define the viral dynamics and biomarkers associated with post-treatment control.

Optimize human organoid models, as well as mouse and nonhuman primate models for cure- and remission-related studies.

④ Targeting the provirus

Develop improved strategies to reverse latency.

Develop strategies to permanently silence the provirus.

Determine the impact of targeting the provirus at the time of initiation of ART.

Define the role of viral subtype on the effectiveness of interventions that target the provirus.

⑤ Targeting the immune system

Develop "reduce and control" approaches.

Develop immune modulators.

Conduct clinical trials to determine whether combination immunotherapies will result in safe and durable HIV remission.

⑥ Cell and gene therapy

Define the level of antigen expression needed to enable recognition of infected cells by immunotherapies.

Develop gene editing strategies that target the provirus.

Develop strategies for sustained production in vivo of antiviral antibodies.

Leverage advances in other biomedical fields to develop safer and more scalable approaches.

⑦ Paediatric remission and cure

Characterize the establishment, persistence and potential for preventing or reversing HIV latency in infants and children on ART.

Develop assays to monitor and identify biomarkers to predict the efficacy of HIV-1 cure therapeutics.

Test HIV immunotherapies and other strategies in infants and children.

⑧ Social, behavioural and ethical aspects of cure

Expand community/stakeholder engagement and capacity building.

Develop HIV cure research with equity, representation and scalability considerations.

Establish standards for the safe conduct of clinical research.

Integrate social, behavioural and ethics research as part of HIV cure trials.

Build capacity for basic discovery research and clinical trials in high-burden settings where HIV resources are limited.