IAS TOWARDS AN 
HIV CURE:
A GLOBAL STRATEGIC APPROACH
The groundbreaking first IAS Towards an HIV Cure Global Scientific Strategy, published in 2012, presented the first global overview of, and strategic plan for, HIV cure research. That initial strategy galvanized the interest and enthusiasm of researchers, funders and advocates worldwide in a scientific challenge to which few had given serious consideration before – the development of a safe and effective cure for HIV infection.

Since the publication of the original IAS Global Scientific Strategy: Towards an HIV Cure, significant scientific advances, often guided by and aligned with the recommendations of that initial cure research plan, have helped to transform the HIV cure research field. Among these, researchers have:

- Significantly expanded our scientific understanding of HIV reservoirs and of latency, the process by which HIV infection remains in the body despite the use of antiretroviral therapy.
- Initiated studies to determine whether early HIV suppression by ART is associated with significantly smaller HIV reservoirs and virologic control in adults and infants.
- Built the clinical evidence that sustained, albeit temporary, periods of aviremia in HIV-infected individuals can be achieved.
- Continued progress in understanding how broadly neutralizing antibodies could be used in combination approaches to HIV cure.
- Proven the safety and potential efficacy of novel strategies, including encouraging results in gene therapy, towards HIV remission or cure.
- Produced new data on latency reversing agents in clinical trials.
- Produced promising results from monkey studies of a toll like receptor, TLR7-agonist, designed to stimulate and eliminate latent virus.
- Advanced efforts to use CRISPR technology to create HIV immunity in cells.
- Deepened our understanding of how to utilize the innate immune systems of people living with HIV.
- Developed new tools to quantify replication-competent virus.

In recent years, HIV cure research has come into its own as an expanding multi-disciplinary field of inquiry, marked by growing scientific interest, the study of increasing numbers of promising scientific approaches towards a cure, including strategies from other fields of biomedical research, more cure research-focused collaborations, and a growing sense that a cure or sustainable remission for HIV is feasible.

A NEW SCIENTIFIC STRATEGY TOWARDS AN HIV CURE 2016

Because both challenges and opportunities in HIV cure research continue to evolve rapidly, the International AIDS Society (IAS) convened a multi-disciplinary, 59-member International Scientific Working Group of leading basic, clinical, and social scientists, ethicists, and global stakeholders to develop this second Global Scientific Strategy for HIV cure research. This new strategy, developed over a two-year period and released at AIDS 2016, incorporates the contributions of that working group, as well as the input of scores of community leaders, industry representatives, funders, regulatory agency representatives, and HIV researchers from around the world, collected through hundreds of hours of online and in-person consultations. The IAS Global Scientific Strategy: Towards an HIV Cure 2016 is a comprehensive roadmap identifying the most pressing gaps in HIV cure research, with recommendations to overcome them for researchers, donors, and other stakeholders. The strategy analyzes current progress and makes concrete recommendations to advance the search for HIV cures in these seven focal areas.

SCIENTIFIC FOCAL AREAS OF THE 2016 GLOBAL SCIENTIFIC STRATEGY

This second Global Scientific Strategy also includes a more concentrated focus on the importance of social and behavioural science and the ethical aspects of HIV cure research, and on HIV cure research in resource-limited settings.

The Global Scientific Strategy serves as:

A A guide for scientific research, to address the most critical knowledge gaps and outstanding questions in the field.

B A tool for funders and policy-makers, to guide their support for the most effective and efficient research to advance the HIV cure agenda.

C A framework for advocates, to support high quality, ethical, and cost-effective research that can lead to a cure for HIV.
WHY DO WE NEED A CURE FOR HIV?

While HIV antiretroviral therapy (ART) can control the virus and improve the lives of people living with HIV, treatment requires lifelong adherence, which is challenging for many. Individuals who receive ART can experience serious side effects, including immune system dysfunctions, chronic inflammation, and drug toxicities.

Beyond the challenges for individuals, however, are the challenges for health systems as a whole. Delivering HIV testing, treatment, and retention services to the 37 million people living with HIV today, and the millions more who will need it in the future, will be extremely challenging to achieve. According to UNAIDS, the cost of providing ART to 90% of people in need in low- and middle-income countries will reach US$19.3 billion in 2017, or nearly ¾ of every dollar invested in the HIV response.

Progress in the effort to address the persistence of HIV has given researchers increasing hope that a cure is possible, and may one day be globally scalable. Interest in cure research is growing not only in more developed settings, but also in low- and middle-income countries, which shoulder the highest HIV burden, and have the potential to benefit most from a cure.

PRE-REQUISITES FOR AN HIV CURE

Outstanding progress has been made since the launch of the 2012 IAS Global Scientific Strategy: Towards an HIV Cure, in efforts to foster a multidisciplinary international research alliance in HIV cure research. Building on the recommendations from the initial 2012 strategy, researchers, funders, and advocates have come together to:

- Improve international scientific collaborative research on cure strategies; engage and ensure cross-fertilization between different research disciplines, in particular between basic and clinical researchers
- Coordinate investments to pursue the most promising HIV cure research approaches
- Promote the involvement of young researchers and researchers from other fields to the effort to develop HIV cure or remission strategies
- Strengthen communication and information exchange between public and private sector researchers working on HIV cures
- Strengthen community engagement in HIV cure research efforts, especially in public awareness and ethical trial design

Moving forward, to ensure the successful implementation of the IAS Global Scientific Strategy: Towards an HIV Cure 2016, it is imperative that all stakeholders in HIV cure research:

- Build upon the scientific collaborations and partnerships developed at the international level to ensure transfer of knowledge and continue to maximize the value of cure research resources
- Strengthen the cross-fertilisation of disciplines between clinical, basic, and social sciences to ensure a well-informed and ethical responses to HIV cure research
- Build capacity for and understanding of HIV cure research in different populations and settings, including in resource-limited countries
- Enhance platforms to facilitate data exchange between early phase clinical trials, and standardization of experimentation in primate models
- Further invest in training and research financing programmes to encourage novel and innovative research strategies, in line with the priorities outlined in the Global Scientific Strategy, from young researchers and researchers from outside of the HIV field
- Foster public-private partnerships to alleviate the regulatory and logistical challenges associated with drug development
- Empower the community of people affected by HIV, through knowledge dissemination, capacity building, and effective community-engagement strategies, to represent their interests and participate knowledgeably in HIV cure research
- Boost research on the psychosocial and ethical implications of participating in HIV cure clinical research, to ensure that both patients and clinical trial designers are well-informed and prepared.

Reference:
**MOLECULAR BIOLOGY OF HIV LATENCY AND REVERSAL STRATEGIES**
- Develop refined cell models to further decipher the molecular mechanism of HIV latency.
- Characterize the distribution of the replication-competent virus.
- Establish the ethical balance in research between scientific gain and participants' interests.
- Improve understanding of the development of the innate and adaptive immune system.
- Explore the potential of engineered T-cells to target HIV-infected cells.
- Determine the performance characteristics of all assays of putative biomarkers.
- Develop methods to deliver gene therapies to reservoir cells.
- Develop an operational definition for HIV remission, to facilitate communications across disciplines and with a broader audience.

**VIRAL RESERVOIRS, IMMUNOLOGY OF HIV PERSISTENCE AND ‘KILL’ STRATEGIES**
- Characterize the impact of host immune environment on size, distribution and inducibility of the reservoir.
- Develop animal and clinical studies to understand the anatomic and cellular components of reservoirs, responses to novel interventions and the utility of candidate biomarkers for predicting viral reactivation.
- Understand latent reservoir dynamics and factors associated with establishing and maintaining latency, including the role of the central nervous system as a reservoir.
- Develop methods to deliver gene therapies to reservoir cells.
- Develop a non-human primate and human sample repositories and clinical databases to validate single or composite biomarkers of the duration of ART-free remission.
- Measure and promote stakeholder engagement in HIV cure research.

**MODELS FOR HIV CURE OR SUSTAINABLE REMISSION**
- Establish the impact of timing of ART on HIV persistence and remission.
- Further explore pre-existing immune responses against HIV and the role of immunotherapeutics.
- Develop methods to boost immune responses in combination with gene/cell therapies.
- Assess biomarkers of HIV persistence in different populations, including children, adolescents, the elderly, women, and transgender populations.
- Use decision analysis and related modelling to optimize trials, enhance cure strategies, and demonstrate budget impact.

**RESEARCH IN NEONATES, INFANTS AND CHILDREN**
- Better understand the role of HIV restriction factors in controlling the establishment and maintenance of HIV latency.
- Determine the impact of immune-modifying drugs on latency reversal in animal models, and ultimately in humans.
- Understand the impact of timing of ART on HIV persistence and remission.
- Further explore pre-existing immune responses against HIV and the role of immunotherapeutics.
- Develop methods to boost immune responses in combination with gene/cell therapies.
- Assess biomarkers of HIV persistence in different populations, including children, adolescents, the elderly, women, and transgender populations.
- Use decision analysis and related modelling to optimize trials, enhance cure strategies, and demonstrate budget impact.

**GENE AND CELL THERAPY**
- Identify medically and ethically appropriate ways to conduct HIV cure research in children.
- Understand the consequences of and develop alternative approaches to chemokine to enhance hematopoietic stem cell (HSC) engraftment.
- Identify potential biomarkers of the persistence of replication-competent proviruses.
- Identify potential biomarkers of the persistence of replication-competent proviruses.
- Determine optimal health systems and policy strategies to promote HIV cure research.

**NOVEL BIOMARKERS AND TECHNOLOGIES TO QUANTIFY HIV RESERVOIRS**
- Identify potential biomarkers of the persistence of replication-competent proviruses.
- Determine optimal health systems and policy strategies to promote HIV cure research.

**SOCIAL SCIENCES AND HEALTH SYSTEMS RESEARCH**
- Promote patient-focused research to understand perceptions, attitudes, and beliefs towards HIV cure.
- Measure and promote stakeholder engagement in HIV cure research.
- Use decision analysis and related modelling to optimize trials, enhance cure strategies, and demonstrate budget impact.

**THE GLOBAL SCIENTIFIC STRATEGY CALLS FOR...**

Key recommendations of The IAS Global Scientific Strategy: Towards an HIV Cure 2016 include the following:

- Develop cell assay systems to assess key responses: latency enforcement, RNA expression, antigen expression, and virion production.
- Develop therapies to enhance immune system capacity to target and eliminate virus-producing cells during ART, and control residual HIV in its absence.
- Develop an operational definition for HIV remission, to facilitate communications across disciplines and with a broader audience.
- Identify medically and ethically appropriate ways to conduct HIV cure research in children.
- Understand the consequences of and develop alternative approaches to chemokine to enhance hematopoietic stem cell (HSC) engraftment.
- Identify potential biomarkers of the persistence of replication-competent proviruses.
- Determine optimal health systems and policy strategies to promote HIV cure research.