Research priorities for an HIV cure: IAS Global Scientific Strategy 2021

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Pathways to an HIV Cure: Research and Advocacy Priorities
CHUM Montreal, Canada, July 28th, 2022
Investigator initiated industry funded research – Gilead, Viiv, Merck
Scientific advisory board (honoraria paid to me personally) – Gilead, Merck, Viiv, Esfam, Immunocore, Vaxxinity
Collaborative research (non funded) – Abbvie, Genentech, BMS
Online process: November 2020 - August 2021

Eight major topics and working groups formed

Steering committee (working group co-chairs, community member) generated draft

Draft strategy refined through an online stakeholder consultation (162 responses), and a review by experts and opinion leaders
Research priorities for an HIV cure: International AIDS Society Global Scientific Strategy 2021

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Despite the success of antiretroviral therapy (ART) for people living with HIV, lifelong treatment is required and there is no cure. HIV can integrate in the host genome and persist for the life span of the infected person. These latently infected cells are not recognized as foreign because they are largely transcriptionally silent, but contain replication-competent virus that drives resurgence of the infection once ART is stopped. With a combination of immune activators, neutralizing antibodies, and therapeutic vaccines, some nonhuman primate models have been cured, providing optimism for those approaches now being evaluated in human clinical trials. In vivo delivery of gene-editing tools to either target the virus, boost immunity or protect cells from infection, also holds promise for future HIV cure strategies. In this Review, we discuss advances related to HIV cure in the last 5 years, highlight remaining knowledge gaps and identify priority areas for research for the next 5 years.

Advances in the last 5 years

Remaining knowledge gaps

Research priority areas for next 5 years

Modern antiretroviral regimens can effectively block HIV replication in people with HIV for decades, but these regimens are not curative and must be taken for life. However, there is evidence that a cure can be achieved, initially, through treatment from a single-case study (Timothy Brown, a man living with HIV who became widely known as the “Berlin patient”) follow-

ing bone-marrow transplantation from a donor who was naturally resistant to HIV. On the basis of this inspiring development and the recognition that not everyone can access and/or adhere indefinitely to antiretroviral therapy (ART), a global consensus emerged approximately 10 years ago that a cureative intervention was a high priority for people with HIV and would be necessary to bring an end to the HIV pandemic. Since then, there has been a second case report of a cure following bone-marrow transplantation11 as well as evidence of persistence of only defective forms of the virus in certain patients and enhanced immune control of the virus by others after only a short time on ART.12–15 Further supporting the notion that a cure for HIV can be achieved.

An HIV cure includes both remission and eradication. Here, we define the term remission as durable control of virus in the absence of ongoing ART. Eradication is the complete removal of intact and rebound-competent virus. The minimal and optimal criteria for an acceptable target product profile for an HIV cure including the duration and level of virus control after ART has recently been developed and published by the International AIDS Society (IAS), following wide consultation with multiple stakeholders.

Characterization of the complete HIV reservoir. HIV DNA can be detected in CD4+ T cells in blood and lymphoid tissue in nearly all people with HIV on ART. Viral genomic sequences are mainly detectable in CD4+ T cells; it also includes tissue-resident
Definitions used

Remission: durable control of virus in the absence of ongoing ART

Eradication: the complete removal of intact and rebound-competent virus

Target product profile: the minimum and optimal characteristics of a cure

Main recommendations

1. Understanding HIV reservoirs
2. HIV reservoir measurement
3. Mechanisms of virus control
4. Targeting the provirus
5. Targeting the immune system
6. Cell and gene therapy

- 5. Pediatric remission and cure
- 6. Social, behavioral and ethical aspects of HIV cure
HIV reservoirs
Understanding HIV reservoirs: location
Understanding HIV reservoirs: biology

- Define and characterize the **sources of the rebound-competent** viruses
- Define the **phenotype** of infected cells
- Define the clinical significance of **defective** proviruses
- Define the mechanisms of **clonal proliferation**
- Determine if infected cells are **resistant to cell death**
- Define the impact of **sex and other factors** on the reservoir
HIV reservoir measurement

- Assays for rebound-competent reservoir, integration sites, stages of transcription, protein expression
- Extend modalities for in vivo imaging
- Point-of-care and eventually at home monitoring of viral load
Mechanisms of virus 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
Cure interventions
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
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
Cellular and gene therapy

**Ex vivo gene therapy**

- Gene modification of T cell (to target HIV envelope)
- PBMCs
- Leukapheresis
- PBMCs
- CD4+ enriched T cells
- CCR5 positive
- ZFN-cut CCR5 gene
- CCR5 negative
- Expansion of CAR T cells
- Re Infuse
- CAR T cell therapy
- Ex vivo gene editing

**In vivo gene therapy**

- AAV
- DNA
- mRNA-containing lipid nanoparticle
- Gene expression (such as CRISPR-Cas9 or bNAbs)
Cellular and gene therapy: priorities

• Define the level of **antigen expression** needed to enable direct targeting (CAR-T cells)
• Develop gene-editing strategies that **target the provirus**
• Develop strategies for **sustained production in vivo** of antiviral antibodies
• Leverage **advances** in other biomedical fields
Cross cutting priorities
• Characterize **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
Social, behavioral and ethical aspects of cure
HIV cure research in LMIC needs to be prioritised
Burden of disease
Issues related to HIV cure research in Africa

Implementation
- What do people want from a cure?
- What will it need to cost?
- What can be practically given in non-urban health care clinics?
- Acceptability of some interventions eg gene therapy

Scientific
- Will HIV subtype have an impact?
- Will host factors (genetics) unique to the dominant African population be important?
- Will common prevalent co-infections and chronic inflammation affect or preclude the use immunotherapy?

N’dungu et al., Nature 2018
Time to implementation of a product is long.

New Product Introduction

- Monitoring & Uptake
- Facility-Level Implementation
- Procurement Planning
- Stakeholder Engagement
- Registration
- Product Adoption & Decision-Making
- Planning & Budgeting
- Forecasting & Quantification

Clinton Health Access Initiative https://www.newhivdrugs.org/toolkit
HIV Cure Africa Acceleration project

HCAAP is a platform to promote dialogue among key stakeholders to accelerate the availability and delivery of an HIV cure.

- PLHIV and communities
- Community and NGOs
- African Union and African organisations
- International organisations
- Philanthropy
- Regulators
- Research
- Pharmaceutical companies (originators)
- Pharmaceutical companies (generics)

Izukanji Sikazwe
Mark Dybul

Dybul et al., Lancet HIV 2020
Cure: Iterative and incremental progress expected

The first generation of cures are expected to complex and difficult-to-scale, as were the initial antiretroviral regimens
Acknowledgements

Core Leadership Group: Steven Deeks, Sharon Lewin, Marein de Jong, Rosanne Lamplough and Simon Collins

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Working Group 2 (HIV reservoir measurement)
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Acknowledgements