Global Research Collaboration for an HIV CURE: The way forward

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IAS Webinar – Research Priorities for an HIV CURE: IAS Global Scientific Strategy
19th May 2022
Global North vs Global South

- Socio-economic status
- Disease prevalence
- Healthcare infrastructure
- National dedicated Research & Development support for Health
- Presence of major market players- Pharma and Funders for R&D
- HICs have supported LMICs to control the HIV epidemic this far
People estimated to be living with HIV

In millions

Total: **37.9 million**
34 Years after ART was developed, HIV/AIDS remains a leading cause of death

38M People living with HIV worldwide

North America and western and central Europe 2.2 million [1.9 million-2.4 million]
Caribbean 330,000 [260,000-390,000]
Latin America 2.1 million [1.4 million-2.7 million]
Middle East and North Africa 230,000 [190,000-310,000]
Western and central Africa 4.7 million [3.9 million-5.8 million]
Eastern Europe and central Asia 1.6 million [1.5 million-1.8 million]
Asia and the Pacific 5.8 million [4.3 million-7.6 million]

67% live in sub-Saharan Africa

47% of people living with HIV (17.8M) are unable to access effective antiretroviral therapy (ART)

... 11.6M live in sub-Saharan Africa

Hard-fought progress is threatened by stagnant funding and donor fatigue

A cure could benefit 38M people living with HIV today

Global rates are projected to remain steady through 2030¹

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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<tbody>
<tr>
<td>Curative</td>
<td>Acutely focused and locally targeted on the biology of the disease</td>
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<tr>
<td>One-time</td>
<td>Administered in just a single dose</td>
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<tr>
<td>Durable</td>
<td>Sustained, life-long benefits</td>
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<tr>
<td>Potent</td>
<td>Transformative efficacy improvements over standard of care</td>
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<tr>
<td>Safe</td>
<td>Improved safety profile, avoiding adverse events and challenging medical procedures</td>
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<td>Valuable</td>
<td>High impact on quantity and quality of life, with great clinical, economic, and social value</td>
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Global South is Currently Excluded from Gene Therapy Development

Kenneth Cornetta et al 2022
Gene Therapy Trials (accessed November 22, 2021 in ClinicalTrials.gov) by region

- United States and Canada: 418
- Europe: 131
- East Asia: 106
- Australia: 22
- Middle East: 21
- South America: 17
- Japan: 8
- Central America: 7
- Russia: 7
- Africa: 3
- And Canada: 2

Kenneth Cornetta et al, 2022
Gene Therapy Trials (accessed November 22, 2021 in ClinicalTrials.gov) by World Bank Income rating

Number of Sites

<table>
<thead>
<tr>
<th>Income Rating</th>
<th>Number of Sites</th>
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<tr>
<td>High</td>
<td>562</td>
</tr>
<tr>
<td>Upper middle</td>
<td>30</td>
</tr>
<tr>
<td>Lower middle</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
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Kenneth Cornetta et al, 2022
Gene Therapy Trials (accessed November 22, 2021 in ClinicalTrials.gov) by Upper Middle Income Countries

Number of sites

- China: 16
- Brazil: 6
- Turkey: 4
- Bulgaria: 1
- Columbia: 1
- Jamaica: 1
- South Africa: 1
WHAT IS THE WAY FORWARD?
The need to form partnerships

Existing

Basic research  Applied research  Product development  Validation and approval  Launch and ecosystem  LMIC scaled impact

$110M
HIV Frontiers
1/19

$100M
6/19

New Funding Announced: $200M

Gates and NIH join forces on HIV and sickle cell diseases
A unique marriage aims to speed development of simple DNA-based cures

By Jon Cohen and Jocelyn Kaiser

Design
Develop approaches for sustained viral suppression

Durability (Targeting & Editing)
Accelerate gene therapy for HIV
Develop engineered B cells for HIV

Detection
Discover HIV reservoir biomarkers

Internal foundation partners
DTS & HIV PST  HIV PST  Global Delivery & HIV PST
The need to form partnerships

Basic research
- Develop approaches for sustained viral suppression
- Accelerate gene therapy for HIV
- Develop engineered B cells for HIV
- Discover HIV reservoir biomarkers

Applied research
- $108M HIV Frontiers 1/19
- $40M IMMUNOCORE 9/19
- $16M BIONTech 10/19
- ~$210M 6/19

Product development
- $12.4M Novartis Institutes for BioMedical Research 11/20

Validation and approval

Launch and ecosystem
- Multi-national pharmaceutical company(s)

LMIC scaled impact

Internal foundation partners
- DTS & HIV PST
- HIV PST
- Global Delivery & HIV PST

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The HIV Frontiers program is laying the groundwork to reach a bold new goal

**THE GOAL**: In the next 10-15 years, achieve effective, long-lasting, and safe "single-shot" cures for HIV (i.e., durable ART-free suppression of viremia) that could ultimately be scaled and implemented globally, including in under-resourced parts of the world.

Two research platforms have emerged as frontrunners: gene therapy and therapeutic vaccination.

Either platform could lead to new treatments with a target product profile including:

- "Single-shot" (administered as an outpatient in a single encounter)
- Lowers the viral load to <50 copies/ml without ART, resulting in remission of disease and prevention of transmission
- Prevents or controls reinfection of the treated individual
- Safe
- Affordable: amortized cost including monitoring at $1-2k in sub-Saharan Africa, $50-100k in US/Europe, $25-50k in the rest of the world

1. Phillips et al., J Inf Dis 2016
The research platforms may provide “CURES” - not only for Hiv but FOR other diseases AS WELL

PLATFORM A: GENE THERAPY

Targeting and editing of long-lived cells *in vivo*, e.g., using viral or nonviral vectors to modify hematopoietic stem cells (HSCs), T stem central memory (TSCM) cells, and memory B cells

*Ex vivo* gene therapy can now cure sickle cell disease, but the technology is not accessible

Can the technology be adapted to develop an affordable *“in vivo”* approach to gene therapy to combat HIV?

Platform A will build on current *ex vivo* gene therapy approaches for sickle cell disease to develop single shot treatments that result in a “cure” for both HIV and sickle cell disease

PLATFORM B: THERAPEUTIC VACCINATION

Creation of a therapeutic vaccine against HIV by harnessing the “vaccinal effect” to generate durable T cell responses against HIV and/or by using an mRNA vaccine to induce T cell responses against highly-networked epitopes

A fraction (<1%) of people infected with HIV suppress virus in the bloodstream without ART. Could a treatment be developed that converts more people into this type of “elite virus controller”?

Could a vaccine given after a person is infected trigger an immune response that has a long-lasting, suppressive effect against HIV?

Platform B will leverage new technology in mRNA vaccines - developed for SARS-CoV-2, the virus that causes COVID-19 - to trigger a long-lasting immune response to suppress HIV in the body
Bringing curative interventions into sub-Saharan Africa

Sunnylands Summit: The Path Towards Ending HIV
February, 2019

Objective:
To consider what it will take to develop and ensure the widest possible access to a cure for HIV, specifically in sub-Saharan Africa

Goals:
• To align on a Target Product Profile for an HIV cure
• To agree what it will take to ensure that a cure with this profile is widely accessible to the largest number of people in sub-Saharan Africa

Multi-stakeholder Consensus on the Target Product Profile for an HIV Cure

HIV Cure Africa Acceleration Partnership (HCAAP):
The case for an HIV cure and how to get there

Dybul et al., Lancet HIV, 2020
Global Gene Therapy Initiative (GGTI) Working Group was formed in 2020 to work towards enabling access and implementation of gene therapies as curative medicines in LMICs initially focusing on HIV and SCD.

GGTI works by advocating for appropriate research, clinical development, capacity-building, training, community adoption, regulatory pathway approval and sustainability.
Cofounders of GGTI

Prof Jennifer Adair, FredHutch, Seattle

Dr Cissy Kityo Mutuluuza, Joint Clinical Research Centre, Uganda
Emphasis: patients and advocates at the table

Michael Louella
Community Engagement Project Manager, defeatHIV Community Advisory Board, Co-Chair, DARE CAB

Olabimpe Olayiwola
Research Assistant, NIH NHLBI Grant Recipient, Case Western Reserve University

Moses Supercharger
Chair, Joint Clinical Research Centre’s Community Advisory Board

Evelyn Harlow Mwesigwa
Program Officer, Uganda MoH; Director, Sickle Cell Network Uganda

Jeff Sheehy
Consultant
Former: CIRM Executive Board
District 8 Representative, San Francisco

Lynda Dee
Attorney
Founder: AIDS Action Baltimore
HOW ARE WE DOING IT?
Collaboration is integral to this project’s success

**Bolster transformative clinical gene therapy research,**
accelerating the development of curative therapies for SCD, β-Thalassemia, HIV, and other debilitating conditions.
Multispecific anti-HIV duoCAR-T cells display broad in vitro antiviral activity and potent in vivo elimination of HIV-infected cells in a humanized mouse model
A viral vector which delivers T cell gene therapies in peripheral blood.

Licensed to Sana Biotechnology


Founded a new biotech company in 2021 (Auraeda, Inc.)


A nanoparticle to deliver CRISPR gene edits to blood stem cells in the bone marrow.
Enable access to advanced therapies in LMIC, disrupting the current philosophy that access to advanced therapies in LMIC is a decade away from possible
Clinical trial design: Translating anti-HIV duoCAR-T cell therapy to PWH

- First-in-human phase I/II study to evaluate the **safety** and **efficacy** of duoCAR-T cell therapy in ART-suppressed PLWH (NCT04648046, PI: Dr. Steven Deeks)

**Study Design**

- **Cohort 1**: Lymphodepletion: NO
  - Dose: $3 \times 10^6$ cells/kg
  - 45 days

- **Cohort 2**: Lymphodepletion: YES
  - Dose: $3 \times 10^6$ cells/kg
  - 45 days

- **Cohort 3**: Lymphodepletion: YES
  - Dose: $1 \times 10^6$ cells/kg

**Time**

**Long term follow-up**

**Clinical Site (UCSF)**

ATI = Analytic Treatment Interruption
PLWH = people living with HIV
Collaboration is integral to this project’s success

Refine manufacturing processes involved in the production of advanced therapies, iterating over technology and driving down costs across the field.
Decentralized Manufacturing Container Facility  
cGMP Cell Therapy Processing Suite
Collaboration is integral to this project’s success

Develop infrastructure, institutional voids, and ecosystems, paving the path for large-scale international collaborations and similar projects.
Funding Success: Training the 1st Generation of Ugandan Gene Therapists

Dr. Lois Bayigga, JCRC as she learns the process of blood stem cell transduction in the Adair Lab.