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Pathways to an HIV Cure: Research and Advocacy Priorities

CHUM Montreal, Canada, July 28th., 2022

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

AIDS 2022

Conflict of interest disclosure

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

IAS Global Scientific Strategy 2021: process

- 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

nature medicine REVIEW ARTICLE
https://doi.org/10.1038/s41591-021-01590-5

Research priorities for an HIV cure: International AIDS Society Global Scientific Strategy 2021

Steven G. Deeks[1], Nancie Archin[2], Paula Cannon[3], Simon Collins[4], R. Brad Jones[5], Marein A. W. P. de Jong[6], Olivier Lambotte[7], Rosanne Lamplough[8], Thumbi Ndung'u[9,10,11], Jeremy Sugarman[12], Caroline T. Tiemessen[13], Linos Vandekerckhove[14], Sharon R. Lewin[15,16,17] and The International AIDS Society (IAS) Global Scientific Strategy working group*

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 cell. 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 these 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.

Modern antiretroviral regimens can effectively block HIV replication in people with HIV for decades, but these therapies are not curative and must be taken for life. However, there is evidence that a cure can be achieved; initially, this came from a single case study (Timothy Brown, a man living with HIV who became widely known as the 'Berlin patient') following bone-marrow transplantation from a donor who was naturally resistant to HIV[1]. 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 curative 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 transplantation[2] as well as evidence of persistence of only defective forms of the virus in certain patients[3] and enhanced immune control of the virus by others after only a short time on ART[4]—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 any 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 off ART, has recently been developed and published by the International AIDS Society (IAS), following wide consultation with multiple stakeholders[5].

In 2011 and 2016, the IAS convened expert working groups to outline a strategy for developing an effective and scalable cure[6,7]. Since then, significant progress has been made, and the overall agenda has evolved. Here, we assembled a group of experts from academia, industry, and the community (Box 1) to evaluate recent progress and to outline cure-related research priorities for the next 5 years. The key recommendations for each component of the strategy are summarized in Box 2.

Understanding HIV reservoirs

A shared definition of the HIV reservoir is crucial for researchers, clinicians, and people living with HIV. Here, we use the term 'HIV reservoir' in the context of eradication or remission, as a representative term for all cells infected with replication-competent HIV in both the blood and different anatomical sites in individuals on ART—in other words, all potential sources of viral rebound in the context of a treatment interruption. Although the source of virus rebound is still not entirely understood, we now know that virus can persist in multiple forms, in multiple cells and in multiple sites.

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. These viral genomes are mainly defective. Only a small proportion (less than 5%) appear to be intact and potentially replication-competent[8]. But the HIV reservoir goes beyond circulating CD4$^+$ T cells; it also includes tissue-resident

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IAS Global Scientific Strategy 2021: focus

- Advances in the last 5 years
- Remaining knowledge gaps
- Research priority areas for next 5 years

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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

Deeks et al., Nature Med 2021; Lewin et al Lancet HIV 2020

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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

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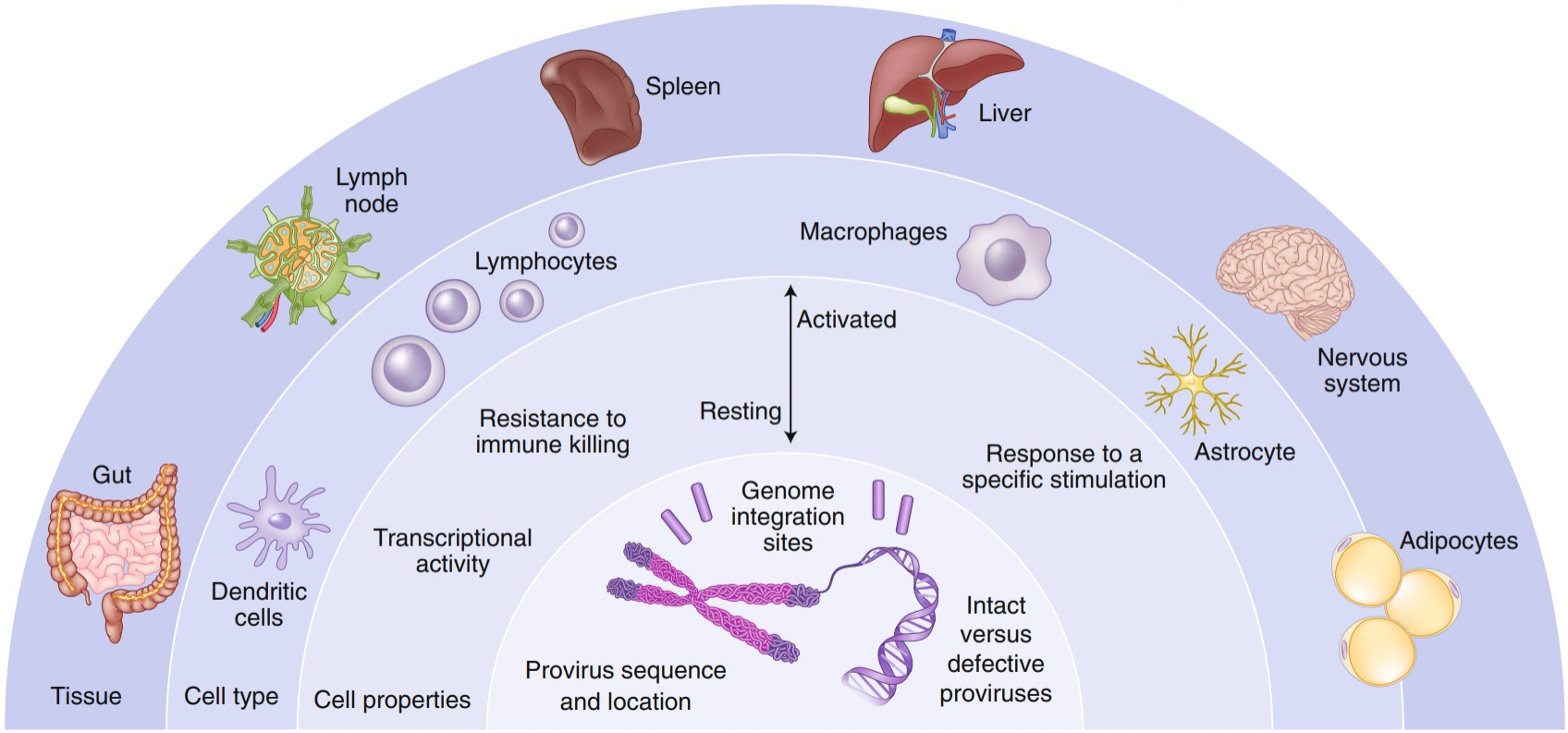
HIV reservoirs

Understanding HIV reservoirs: location



Landscape of the HIV reservoir

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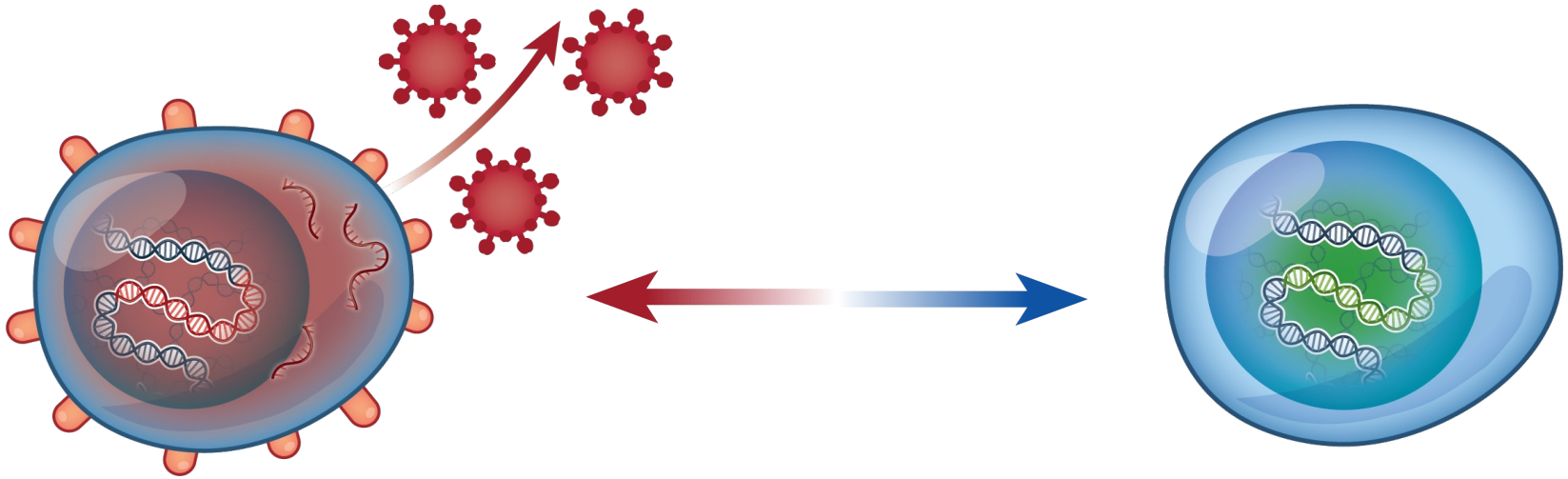
Understanding HIV reservoirs: biology

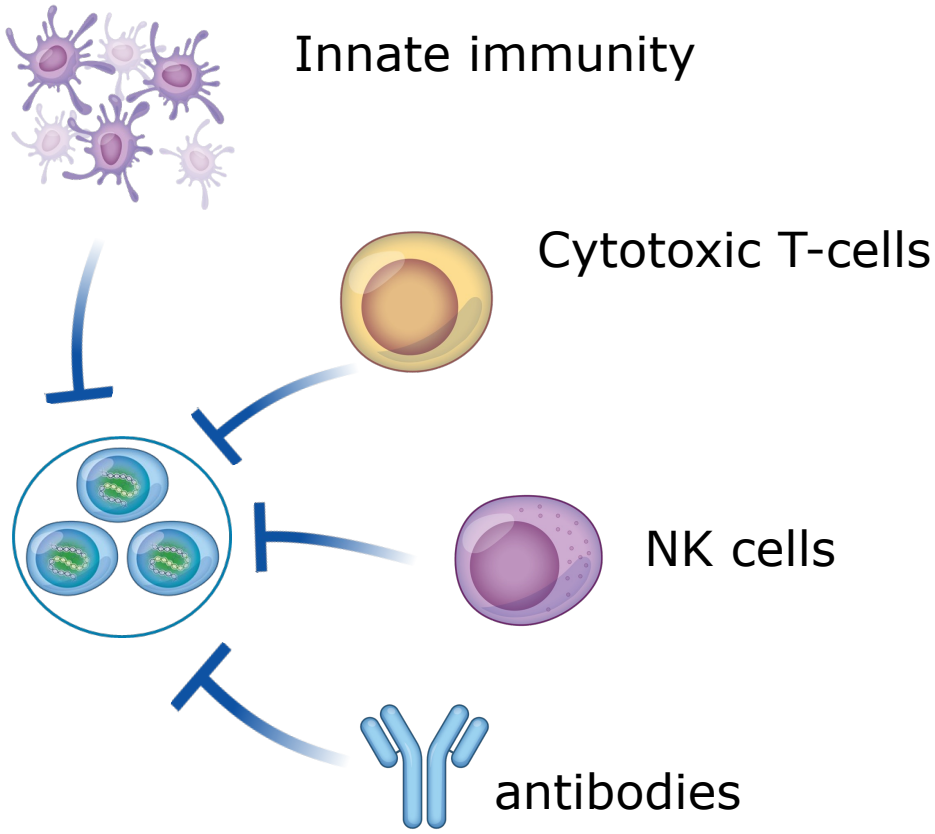
- Define and characterize the **sources of the rebound-competent** viruses
- Define the **phenotype** of infected cells
- Define the clinical significance of **defective** proviruses
- Define the mechanisms of **clonal proliferation**
- Determine if infected cells are **resistant to cell death**
- Define 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

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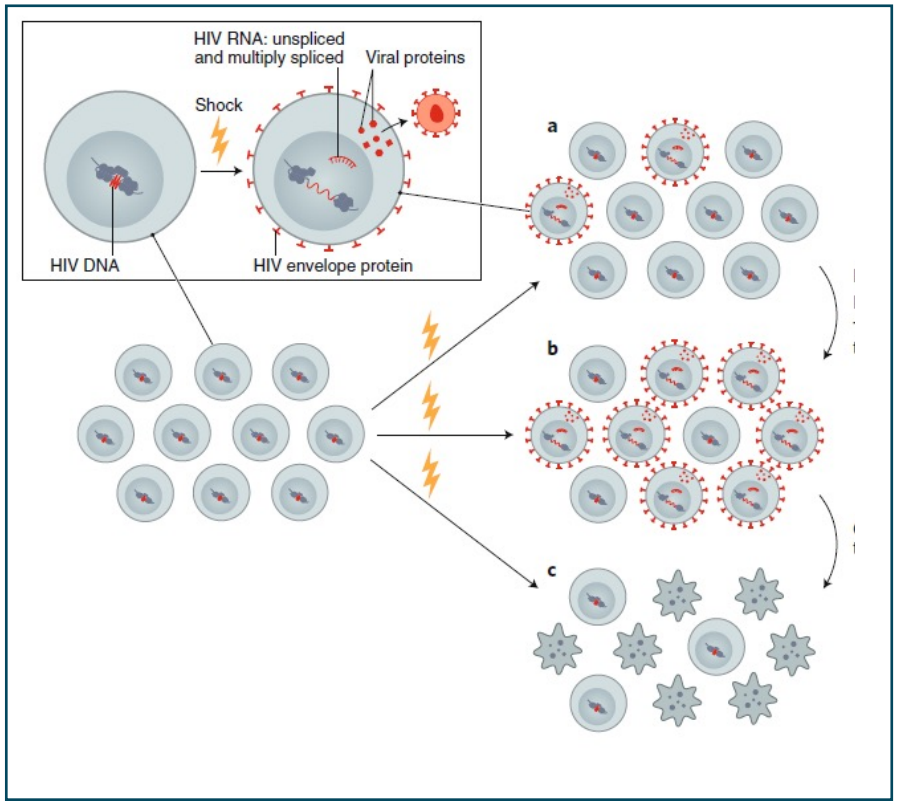
Cure interventions

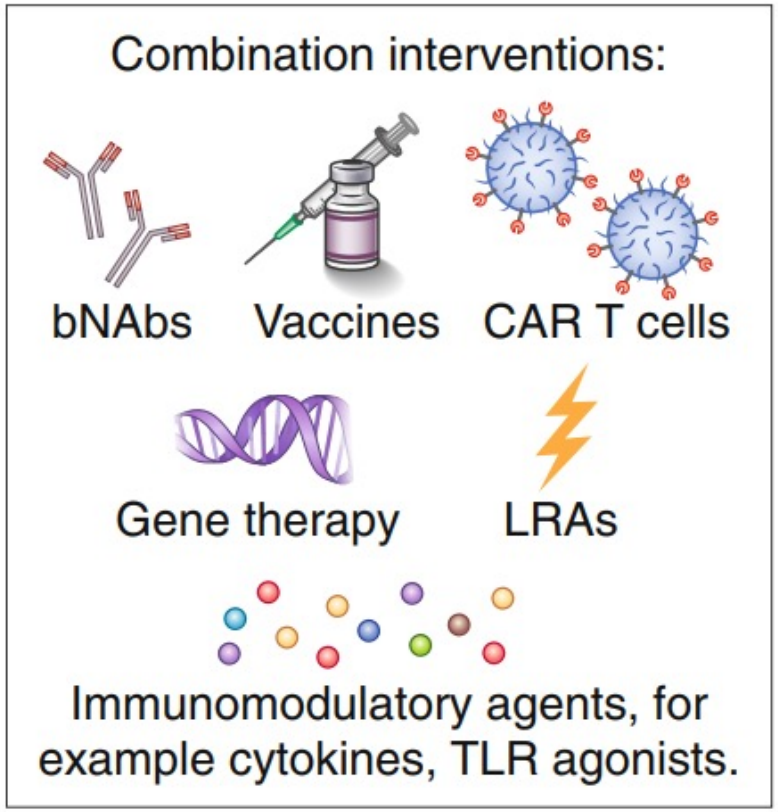
Targeting the provirus

- 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



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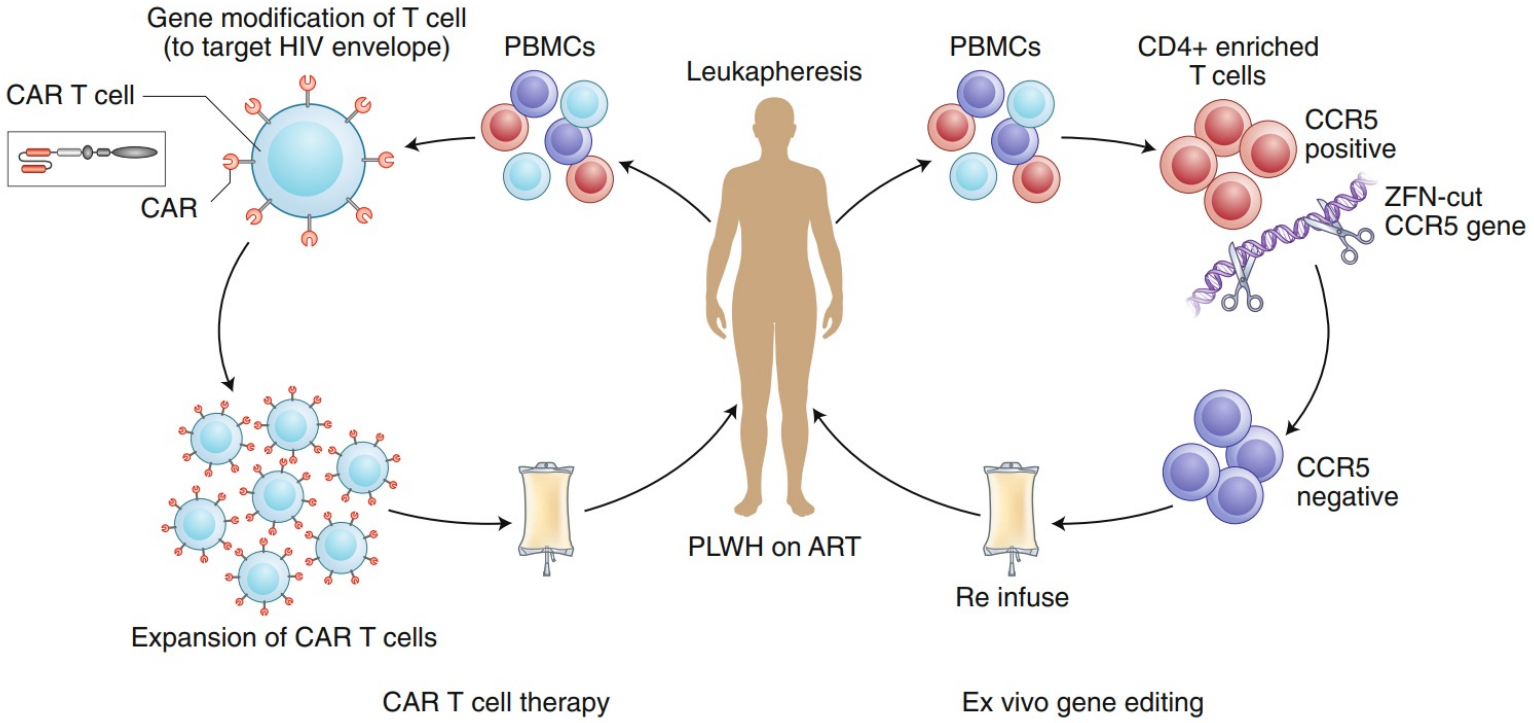
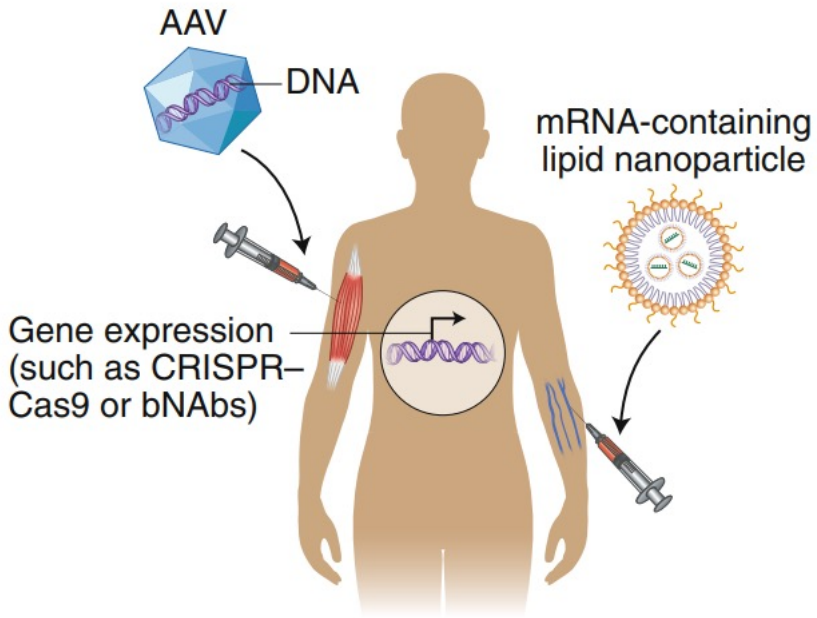
Cellular and gene therapy

Ex vivo gene therapy



In vivo gene therapy



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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

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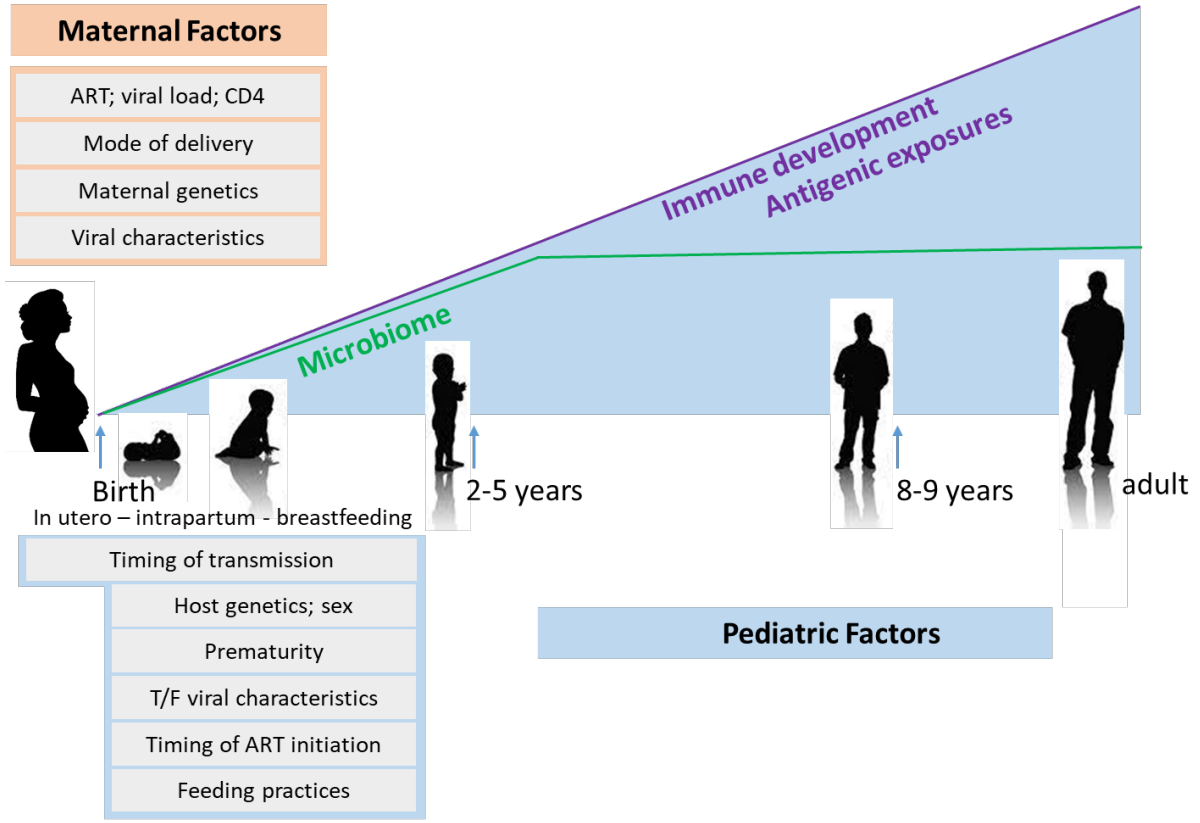
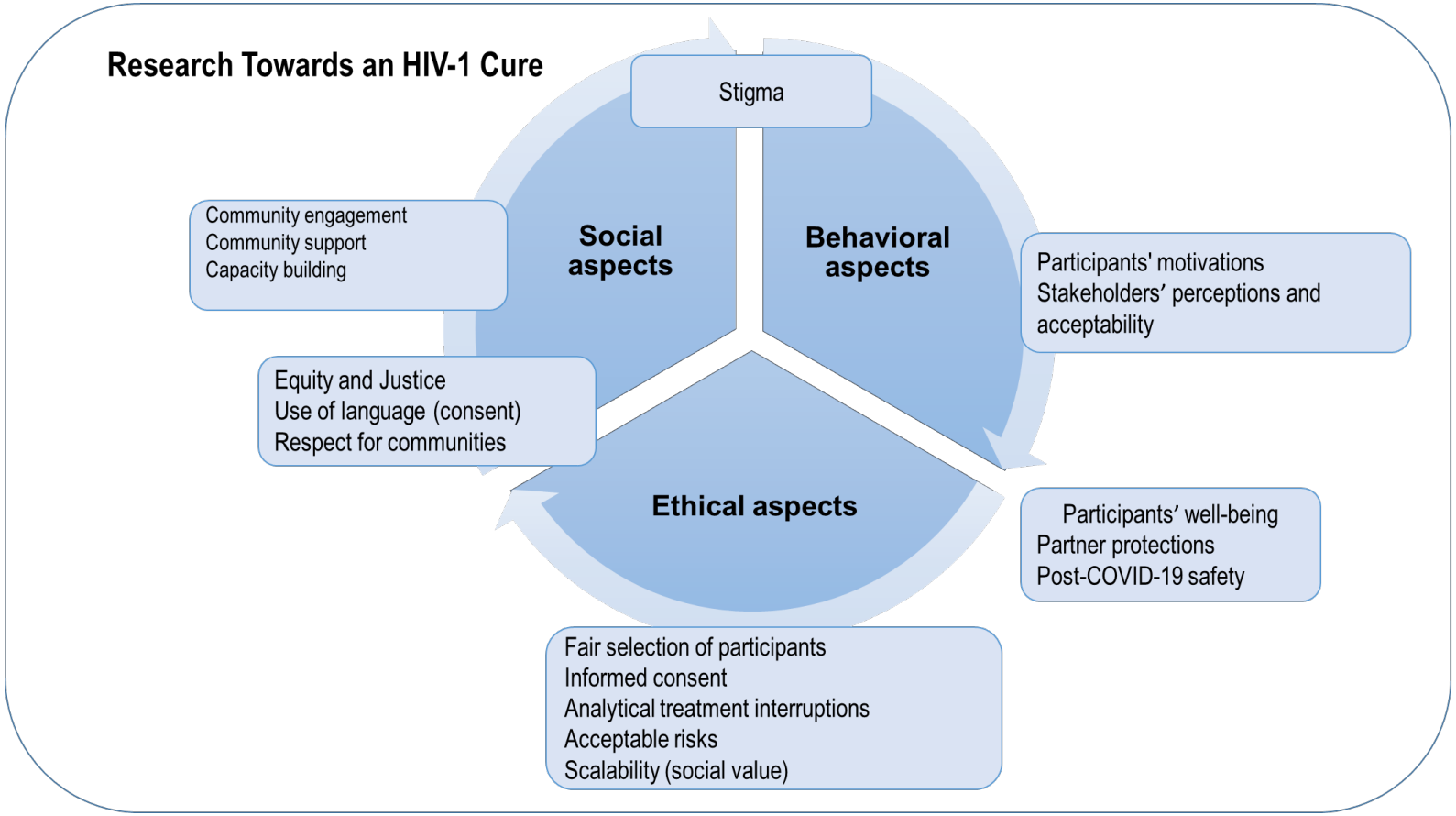
Cross cutting priorities

Pediatric cure

- 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



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HIV cure research in LMIC needs to be prioritised

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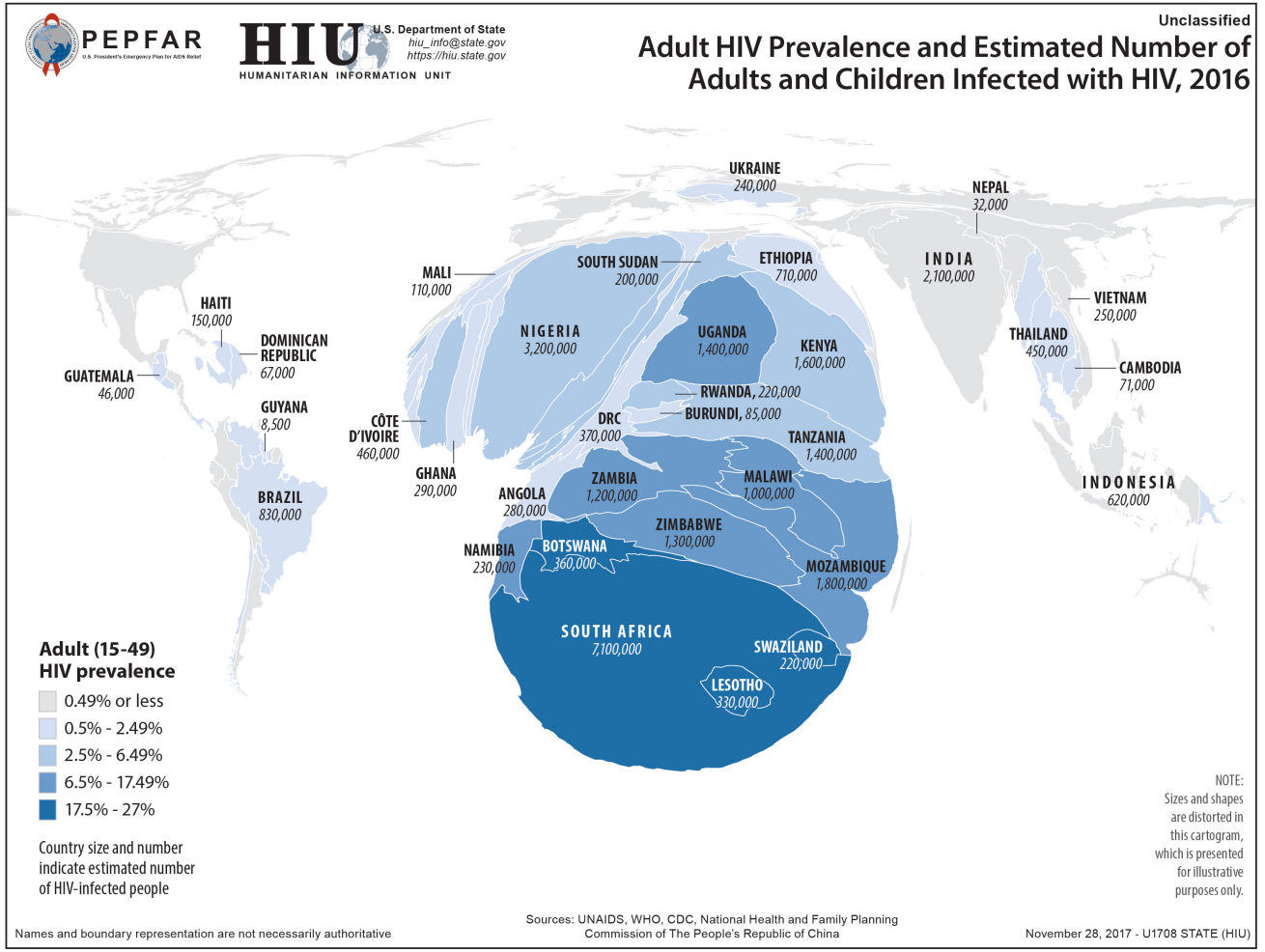
Burden of disease



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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

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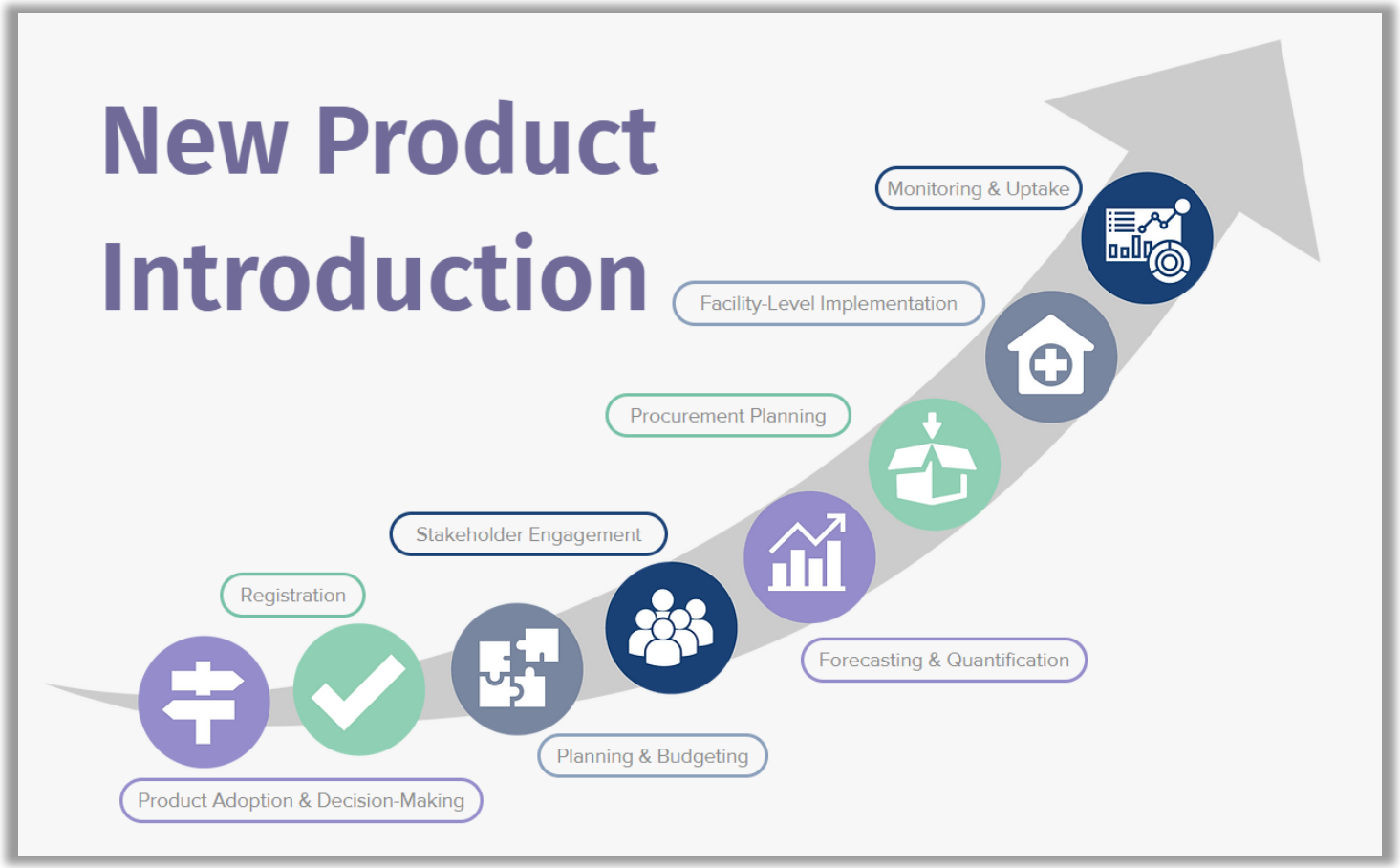
Time to implementation of a product is long



Clinton Health Access Initiative https://www.newhivdrugs.org/toolkit

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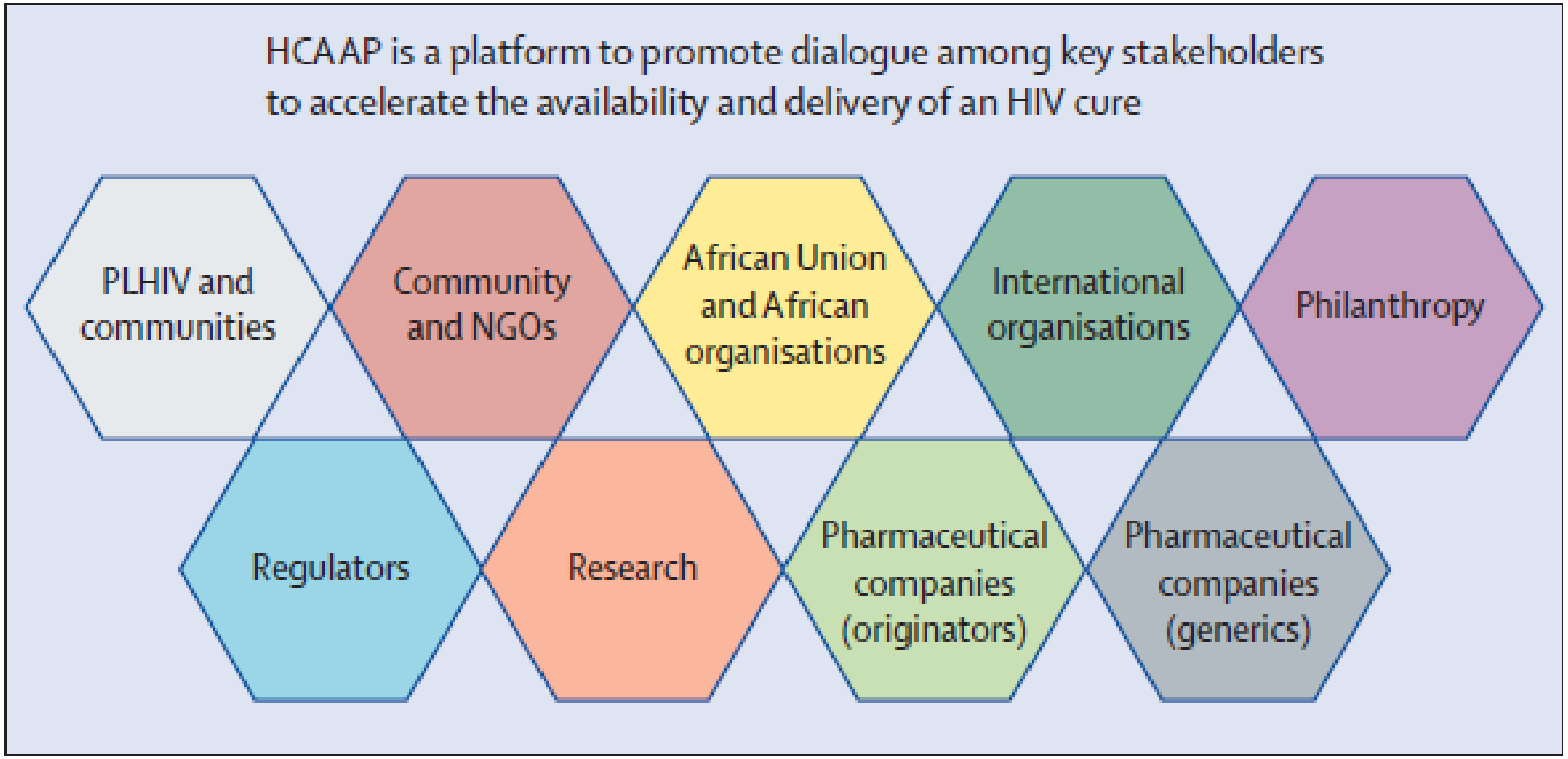
HIV Cure Africa Acceleration project



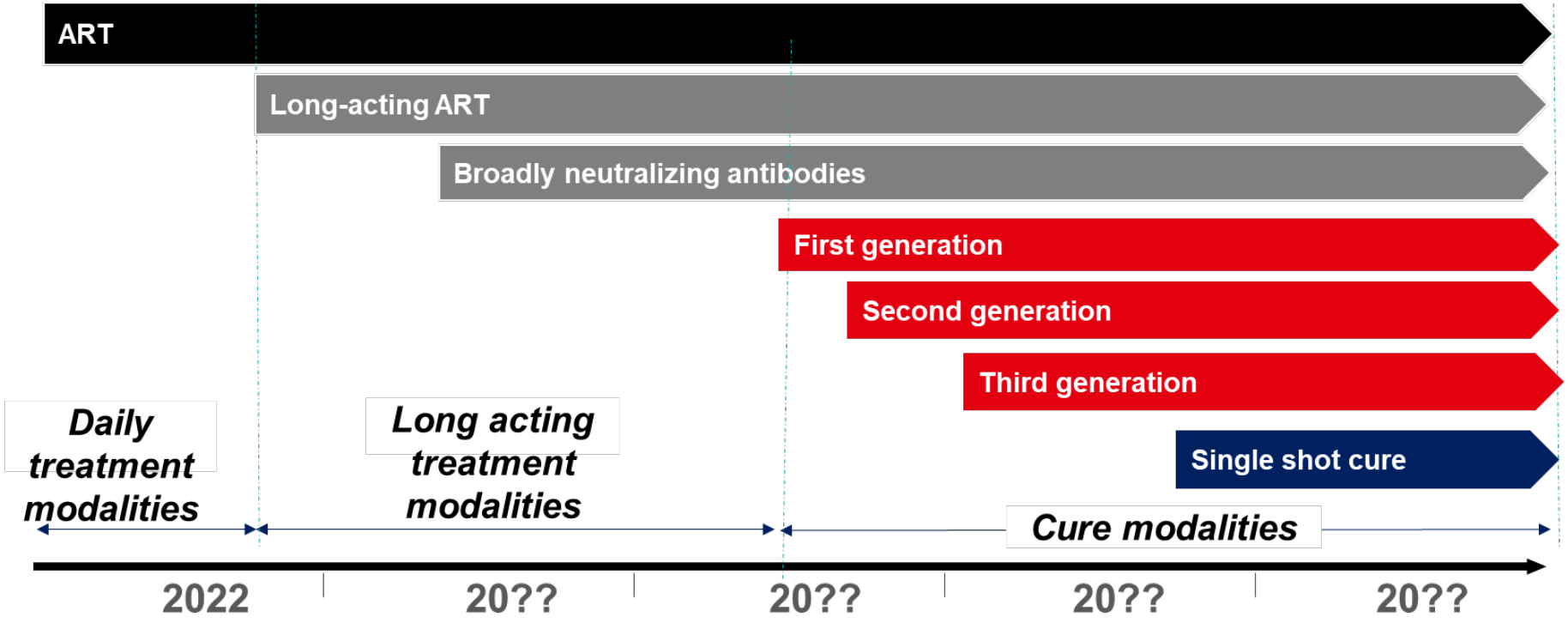
Dybul et al., Lancet HIV 2020

Izukanji Sikazwe

Mark Dybul

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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Jeremy Sugarman, Karine Dubé, Jennifer Power, Jessica Salzwedel, Udom Likhitwonnawut, Jeff Taylor, Oguzhan Latif Nuh, Krista Dong and Edward Nelson Kankaka

Acknowledgements