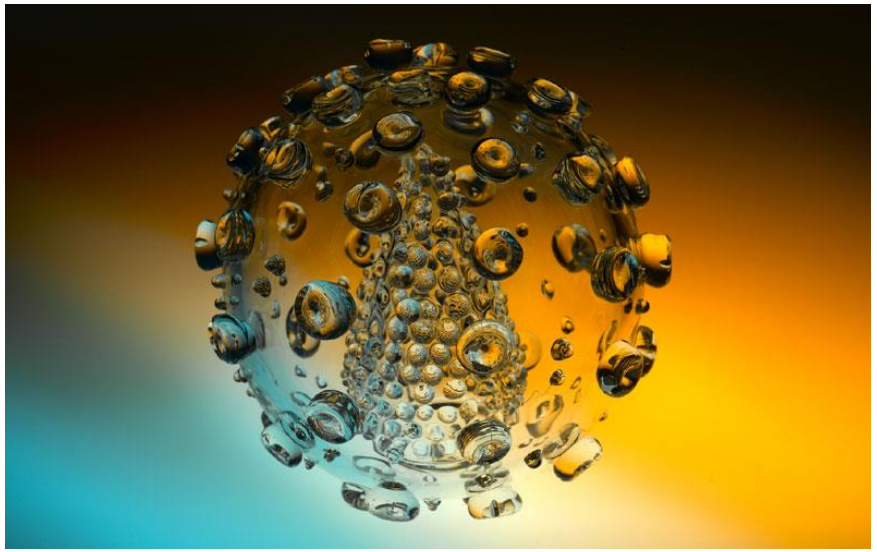
Hot Topics in HIV.

Research Directives in the HIV-1 Cure Field



Mario Stevenson, PhD.

Department of Medicine.

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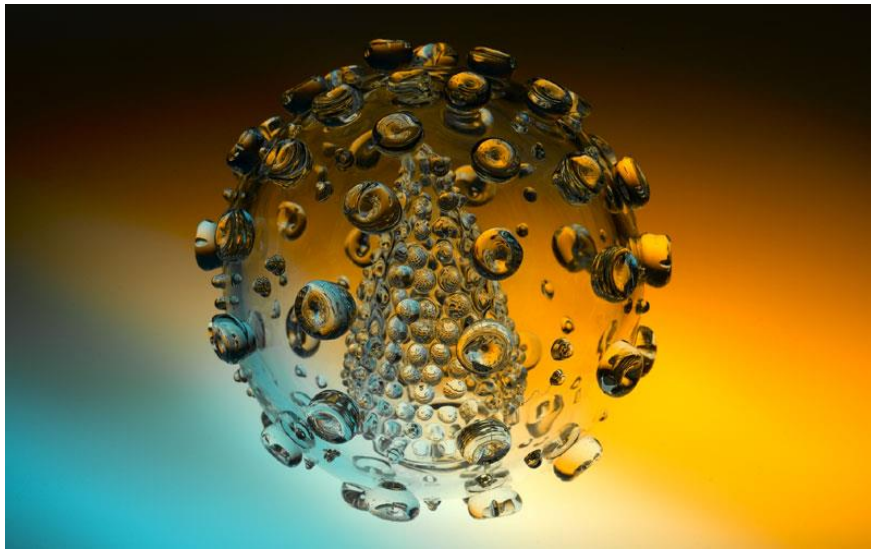

What are the obstacles to curing HIV?

How does the virus persist in the face of overwhelming antiviral therapy!

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Mechanisms of HIV persistence: the traditional view!



Latent reservoir

- **Major factor in lifelong HIV-1 persistence.**
- **No markers to distinguish the latently infected from the uninfected cell.**
- **Longevity matches that of the uninfected cell.**

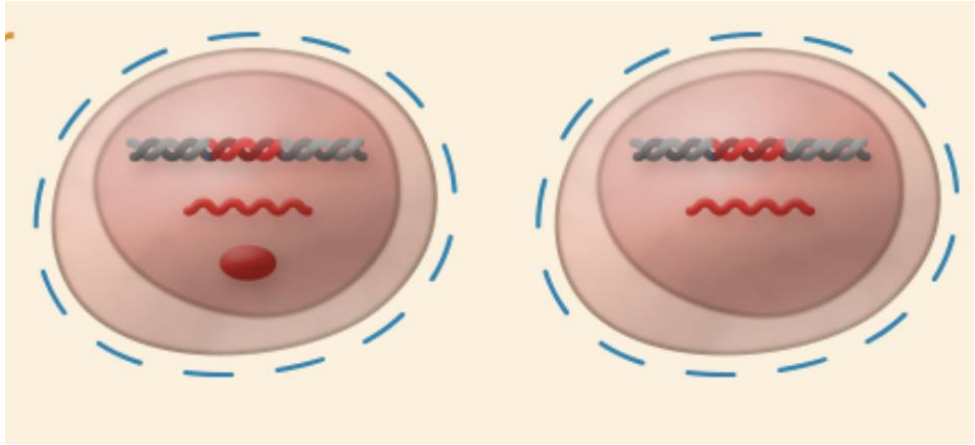
Courtesy N. Chomont

Finzi et al. Science 1997 ; Wong et al. Science 1997 ; Chun et al. PNAS 1997 ; Palmer et al. PNAS 2008 ; Chomont et al. Nat Med 2009

Current view: Provirus may be active in many reservoir CD4+ T cells

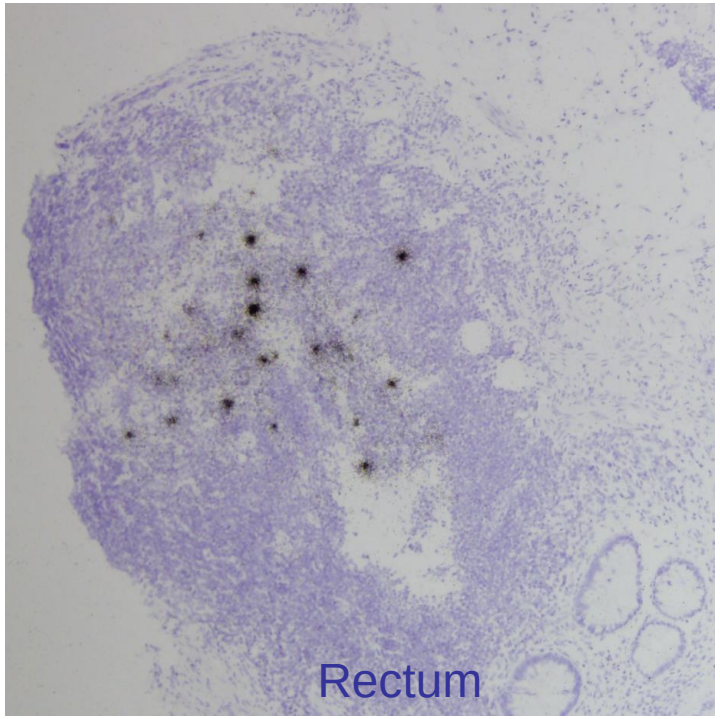
”Expressed Reservoir”

- Reservoir cells harbor viral transcripts *(Furtado et al.)*
- Transcripts originate from biologically competent proviruses *(Vignoles et al)*
- Transcript abundance predicts time to rebound post-ATI (*Li et al*)



“Primed reservoir”

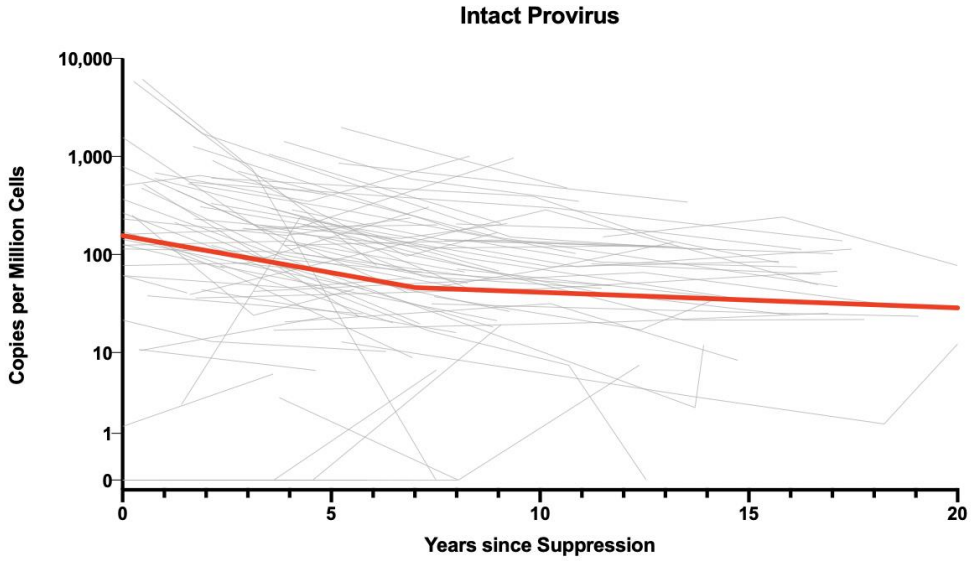
- Simultaneous, multifocal viral recrudescence post-ATI (*Rothenberger et al*)



Current view: Not all Proviruses have Equal Fates

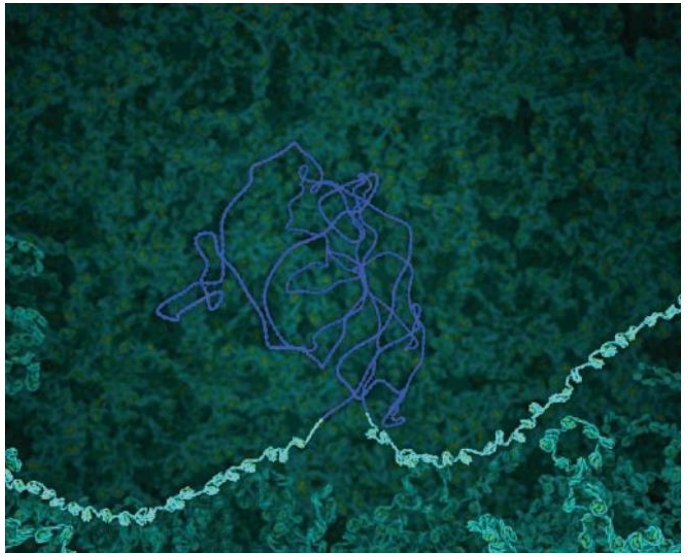
Differential Proviral Decay

- Intact proviruses have faster decay over first 7 years of ART ($t_{1/2}$ = 4.0 v $t_{1/2}$ = 19.0) *(Peluso et al)*
- Selection for "intractable" proviruses in individuals with spontaneous viral control *(Jiang et al)*

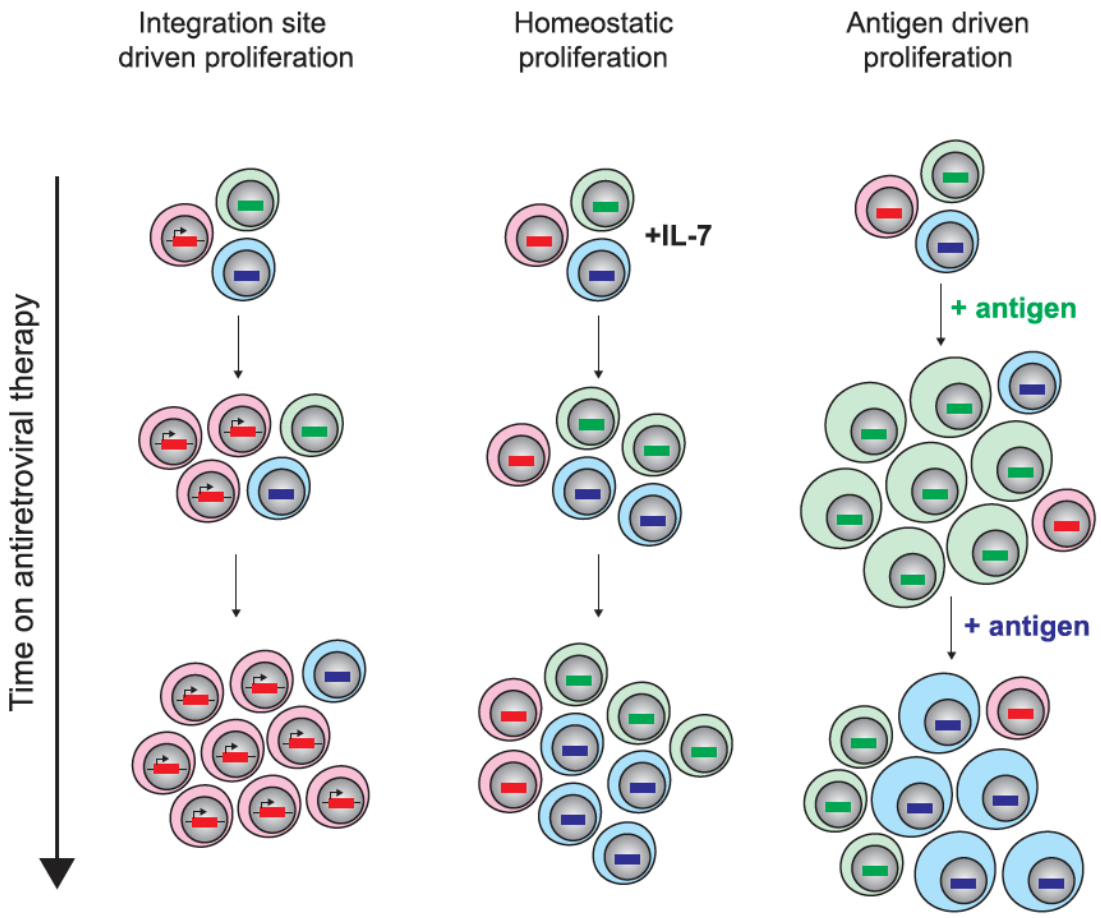


Effect of integration site

- Proviral enrichment in non-genic DNA during long-term ART (> 20 years) and loss of proviruses in genic DNA *(Einkauf et al. Huang et al)*



Current view: Provirus in CD4+ Cells are Expanded through Physiologic Processes



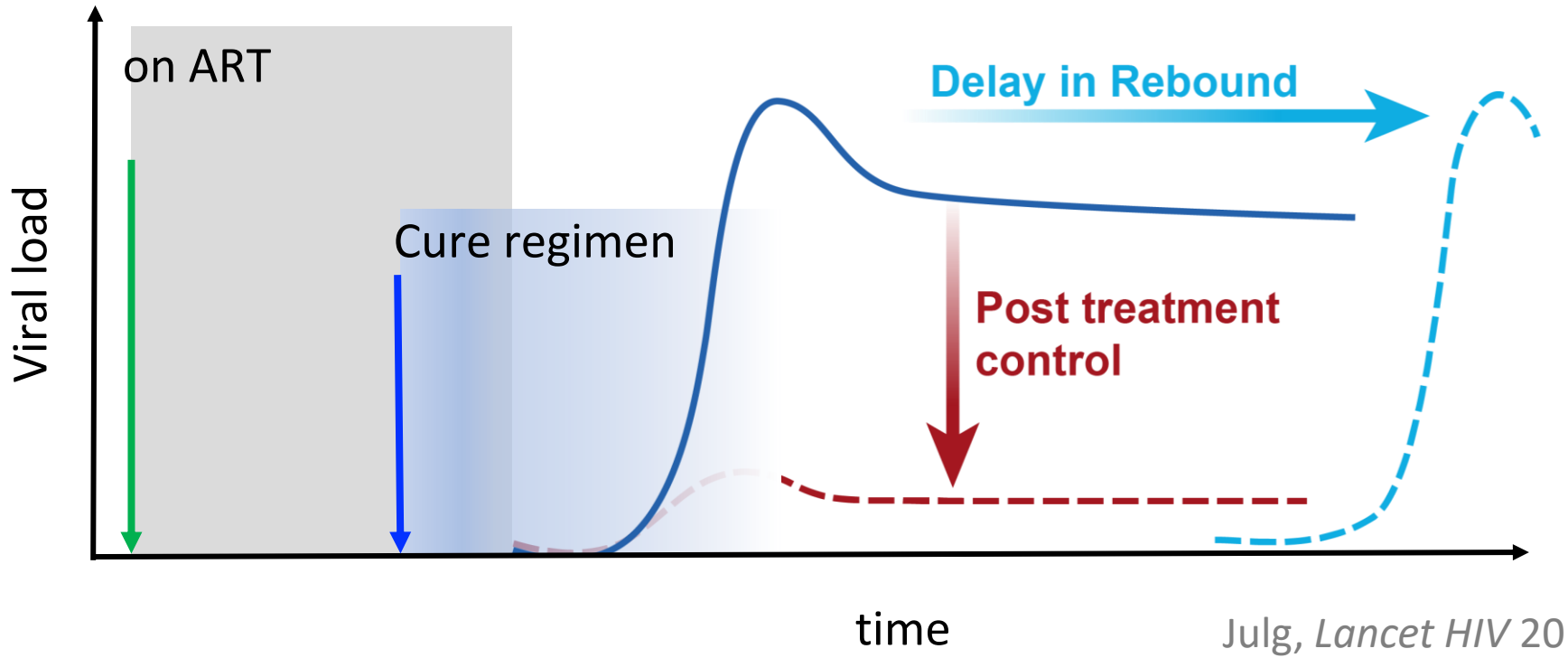
- **Reservoir size is driven by homeostatic T cell proliferation *(Chomont et al)***
- **Clonally expanded proviruses produce infectious virus i*n vivo (Simonetti et al)***
- **Post ATI rebound is fueled by genetically identical expansions form diverse reservoirs *(de Scheerder at al)***
- **Expression driven proviral decay is masked by clonal expansion *(Pinzone et al)***
- **Infected cell clones arise early after infection *(Coffin et al)***

HIV persists as an integrated provirus in CD4+ T cells (“reservoir”)

Macrophages and other cells may also be a reservoir

- Infected cells are rare: <1 in a 1000 CD4+ cells harbor an integrated provirus
- Most (> 90%) of these genomes are defective and unable to replicate (but may be able to produce proteins and hence contribute to inflammation)
- Maintained for life by normal memory T cell homeostasis
- The virus that matters (rebound-competent) is very difficult to measure – treatment Interruptions

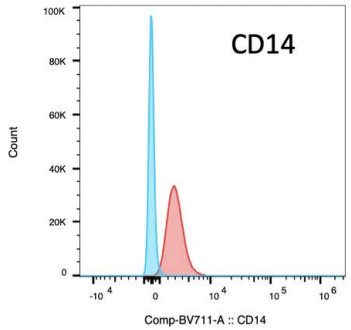
Clinical Trial Endpoint: Treatment Interruption

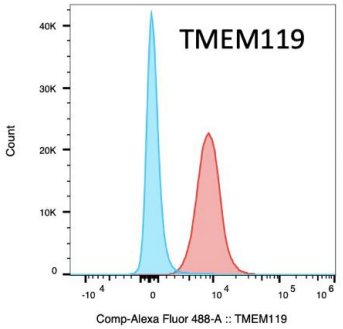


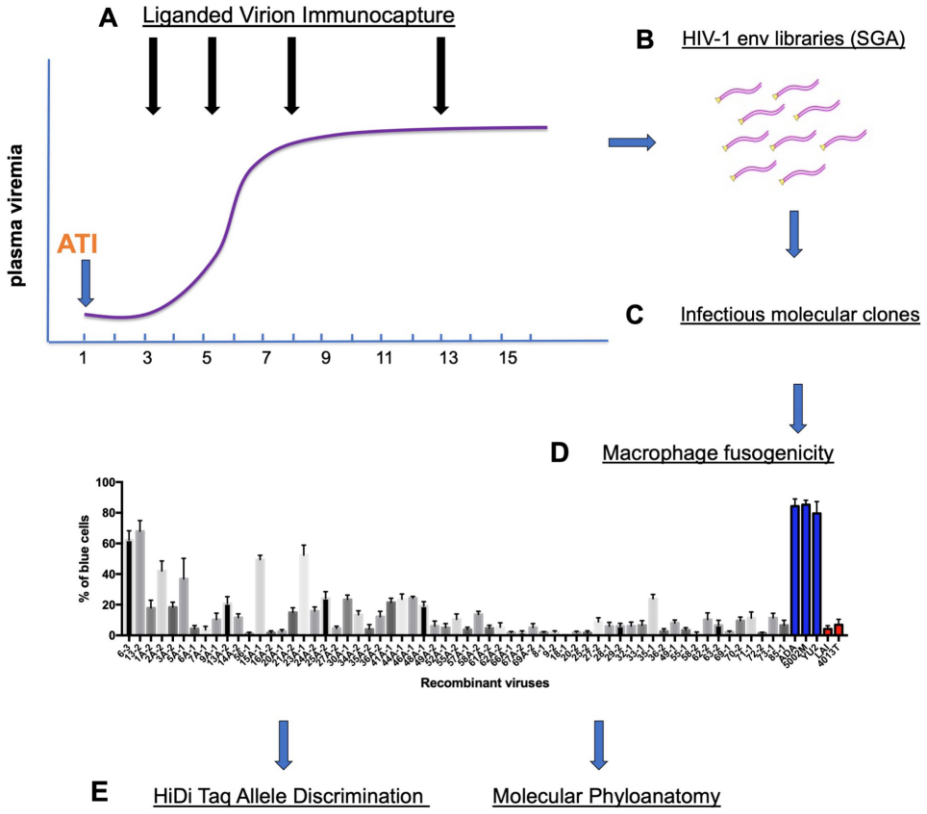
Julg, *Lancet HIV* 2019; Mitchell, *JCI* 2020

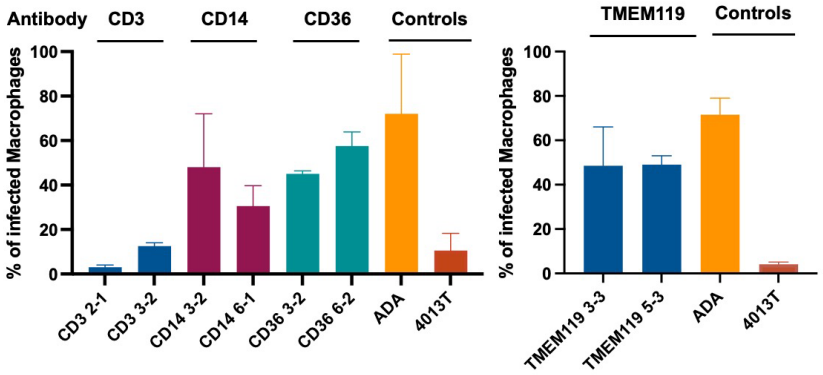
Treatment interruption may be only way to assess anatomic reservoirs

Some rebounding viruses post-ATI have myeloid origins









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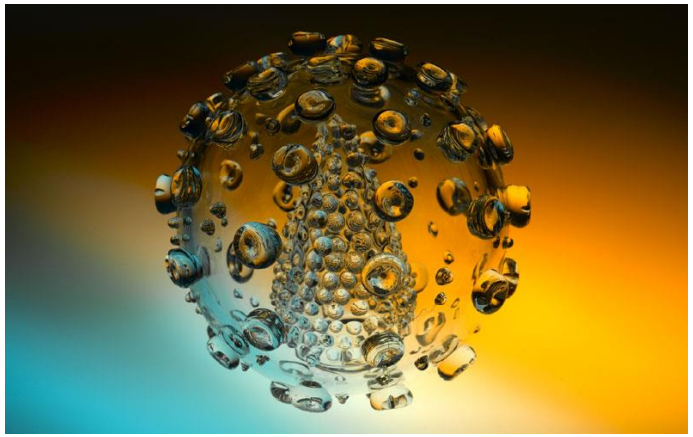

Setting the mandate for Cure Initiatives!

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IAS Global Scientific Strategy 2021

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

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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Biology of the reservoir

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

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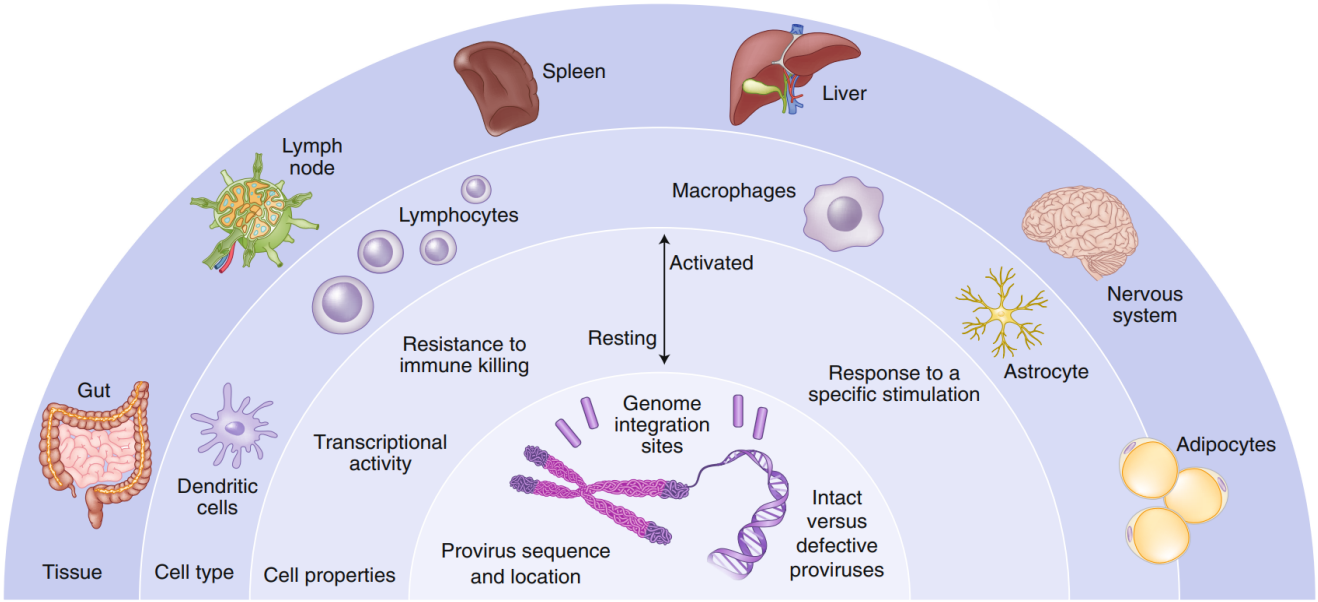


Landscape of the HIV reservoir

Within the US NIH, these directives are maintained by the Office of AIDS Research

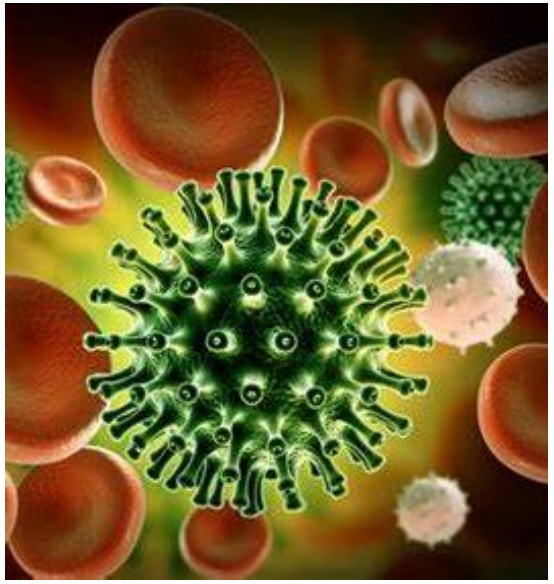
- Define and characterize the sources of the rebound-competent viruses
- Define the phenotype of infected cells
- Define the clinical significance of defective proviruses
- Define the mechanisms of clonal proliferation
- Determine if infected cells are resistant to cell death
- Define the impact of sex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

HIV “remission” strategies in the clinic

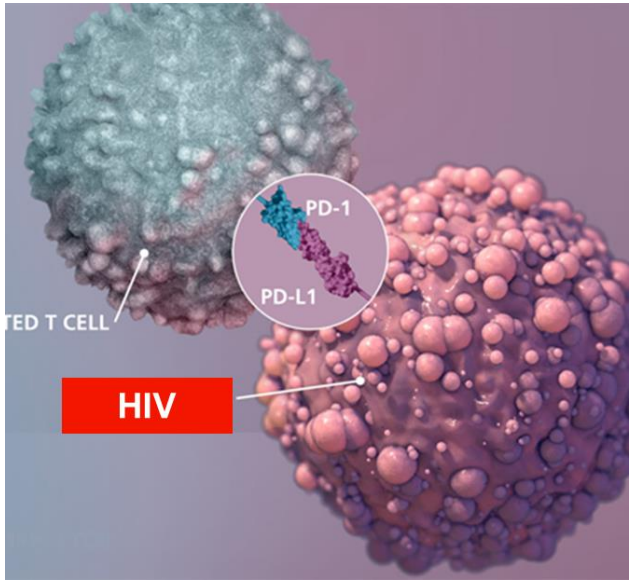
Most approaches involve combination of reservoir reduction and immune enhancement (“reduce and control”), with growing interest in gene therapy and eventually “one shot” cures

Early ART

Latency reversal
Latency silencing



Immunotherapy



Gene therapy

Limitations on Cures currently being tested in the clinic

- Early ART: not curative but can result in post-treatment control (remission)
- Shock and kill: Novel latency reversing agents identified in animal models; progress in people limited
- Block and lock: Compelling cases in natural infection, no viable treatments
- Immunotherapy
  - Enhanced CD8+ T cell response can induce remission in monkeys; combination approaches will be required (vaccine/adjuvants/bNAbS)
  - Innate immunity poorly studied but might key to eliminating virus during ART
- Gene therapy: Many promising approaches in development; safety and scalability are major limitations

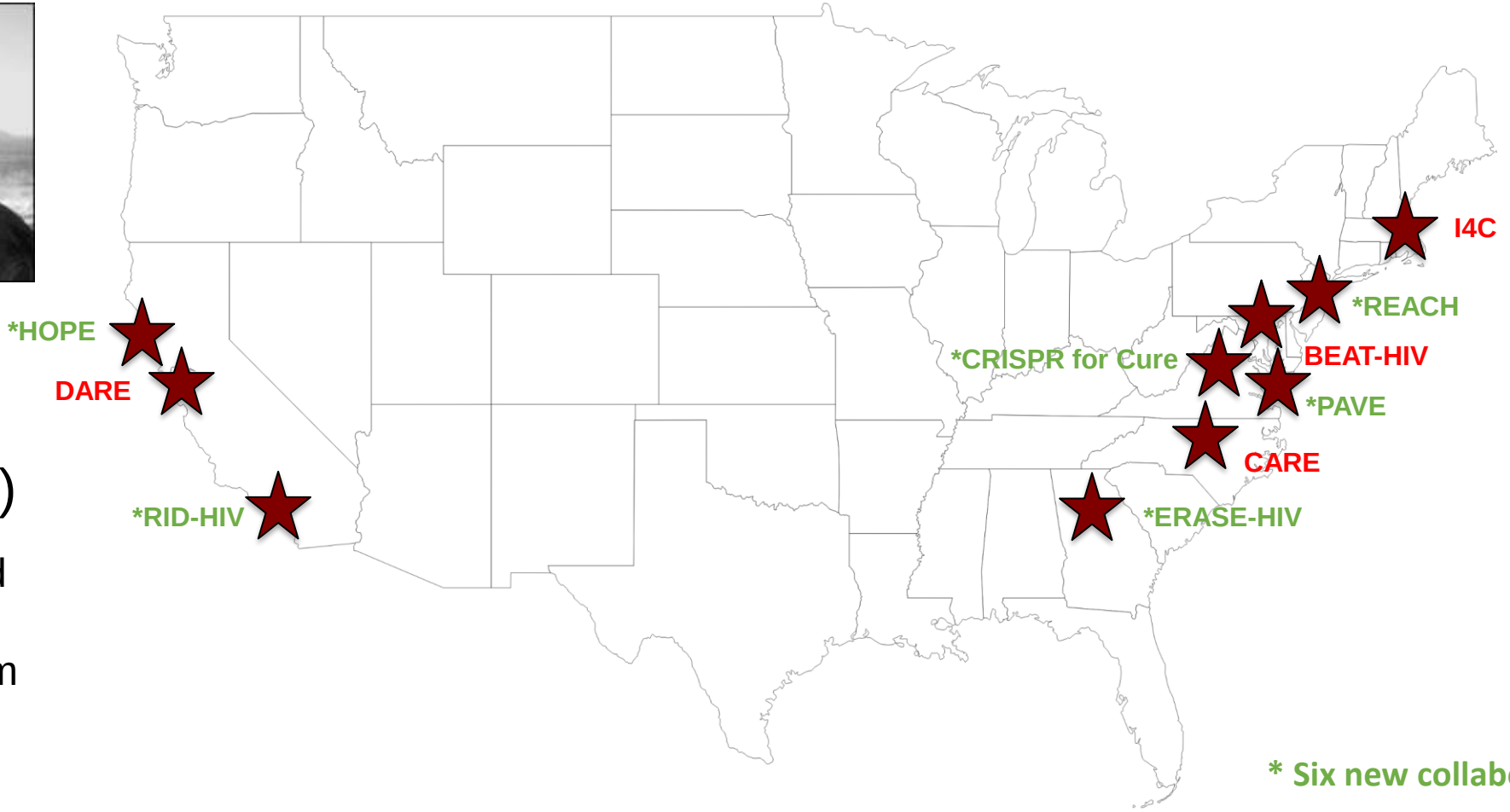
Many Cure initiatives in the US are being coordinated under the Martin Delaney Collaboratories

NIH-funded Martin Delaney Collaboratories

Third Funding Cycle: 2021

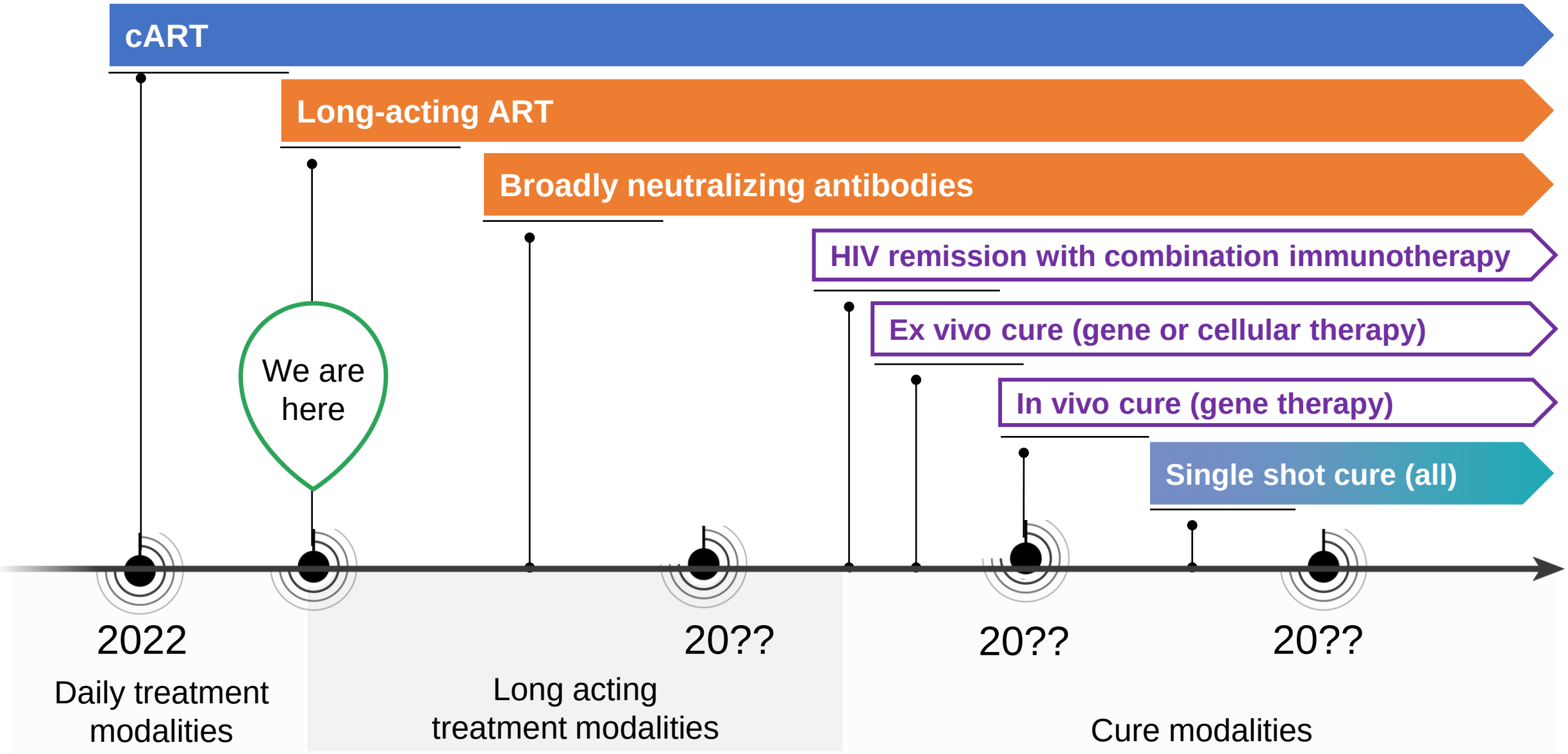
Martin Delaney (1945-2009)

Founder and Director of Project Inform



$35M/year for a period of 5 years

Current and future landscape for HIV treatment

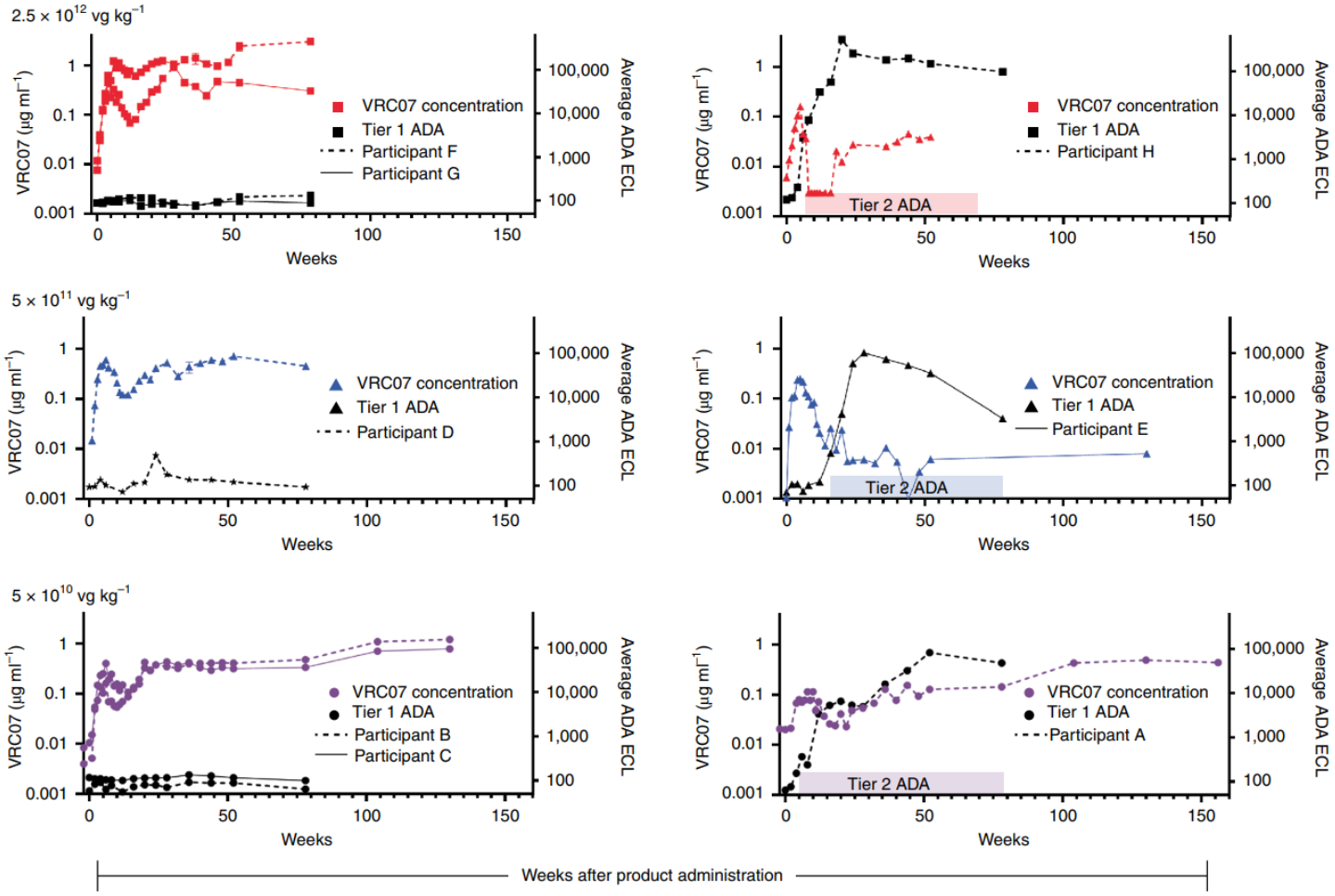


One-shot cure approaches

nature medicine

Safety and tolerability of AAV8 delivery of a broadly neutralizing antibody in adults living with HIV: a phase 1, dose-escalation trial

Joseph P. Casazza[1]✉, Evan M. Cale[1], Sandeep Narpala[1], Galina V. Yamshchikov[1], Emily E. Coates[1], Cynthia S. Hendel[1], Laura Novik[1], LaSonji A. Holman[1], Alicia T. Widge[1], Preeti Apte[1], Ingelise Gordon[1], Martin R. Gaudinski[1], Michelle Conan-Cibotti[1], Bob C. Lin[1], Martha C. Nason[2], Olga Trofymenko[1], Shinyi Telscher[1], Sarah H. Plummer[1], Diane Wycuff[1], William C. Adams[1], Janardan P. Pandey[3], Adrian McDermott[1], Mario Roederer[1], Avery N. Sukienik[1], Sijy O'Dell[1], Jason G. Gall[1], Britta Flach[1], Travis L. Terry[1], Misook Choe[1], Wei Shi[1], Xuejun Chen[1], Florence Kaltovich[1], Kevin O. Saunders[6], Judy A. Stein[1], Nicole A. Doria-Rose[1], Richard M. Schwartz[1,7], Alejandro B. Balazs[4], David Baltimore[5], Gary J. Nabel[8], Richard A. Koup[1], Barney S. Graham[1], Julie E. Ledgerwood[1], John R. Mascola[1] and the VRC 603 Study Team*

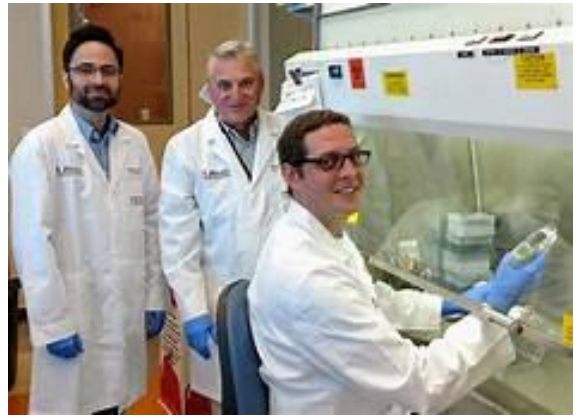


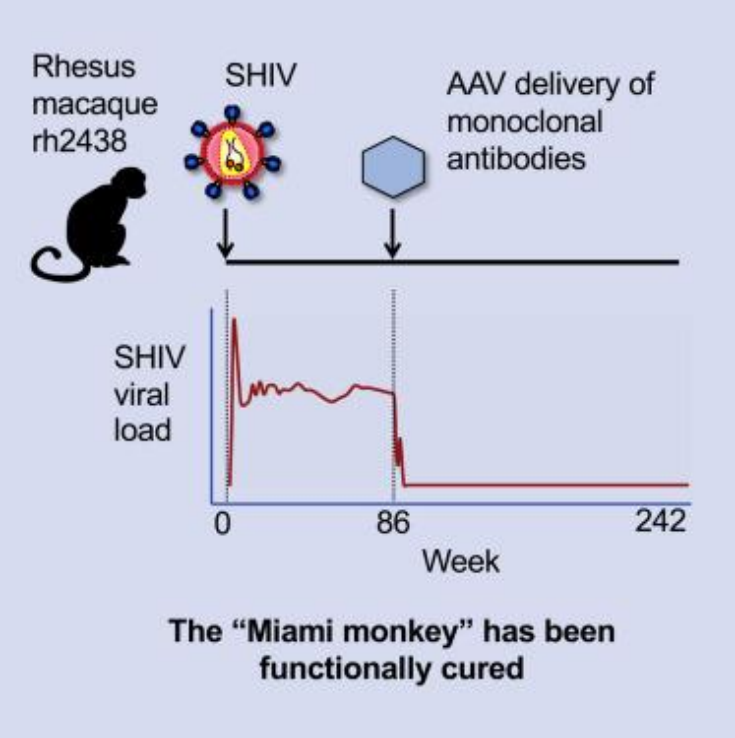
Gene delivery (AAV) of a gene for an HIV-specific antibody (VRC-07) was safe and resulted in sustained expression, albeit at low levels

Immunity. 2019 Mar 19;50(3):567-575.e5. doi: 10.1016/j.immuni.2019.02.005. Epub 2019 Mar 5.

Adeno-Associated Virus Delivery of Anti-HIV Monoclonal Antibodies Can Drive Long-Term Virologic Suppression.

Martinez-Navio JM[1], Fuchs SP[1], Pantry SN[1], Lauer WA[1], Duggan NN[1], Keele BF[2], Rakasz EG[3], Gao G[4], Lifson JD[2], Desrosiers RC[5].





The "Miami monkey" has been functionally cured

- Chronically SHIV-infected macaques were treated with AAV-delivered bnAbs
- Long-term virologic suppression is possible with AAV-delivered antibodies- in absence of ART
- A functional cure was achieved in one SHIV-infected macaque (now n=4)
- Unexpected given that bnAbs block infection but shouldn't clear reservoir cells
- **When it works, it works spectacularly well**!

Major Obstacle:

- Development of host-generated anti-antibodies limit treatment effectiveness.

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Vector based approaches in the cure for HIV

Developing an HIV cure is very tough and highly risky, likely to take years to achieve

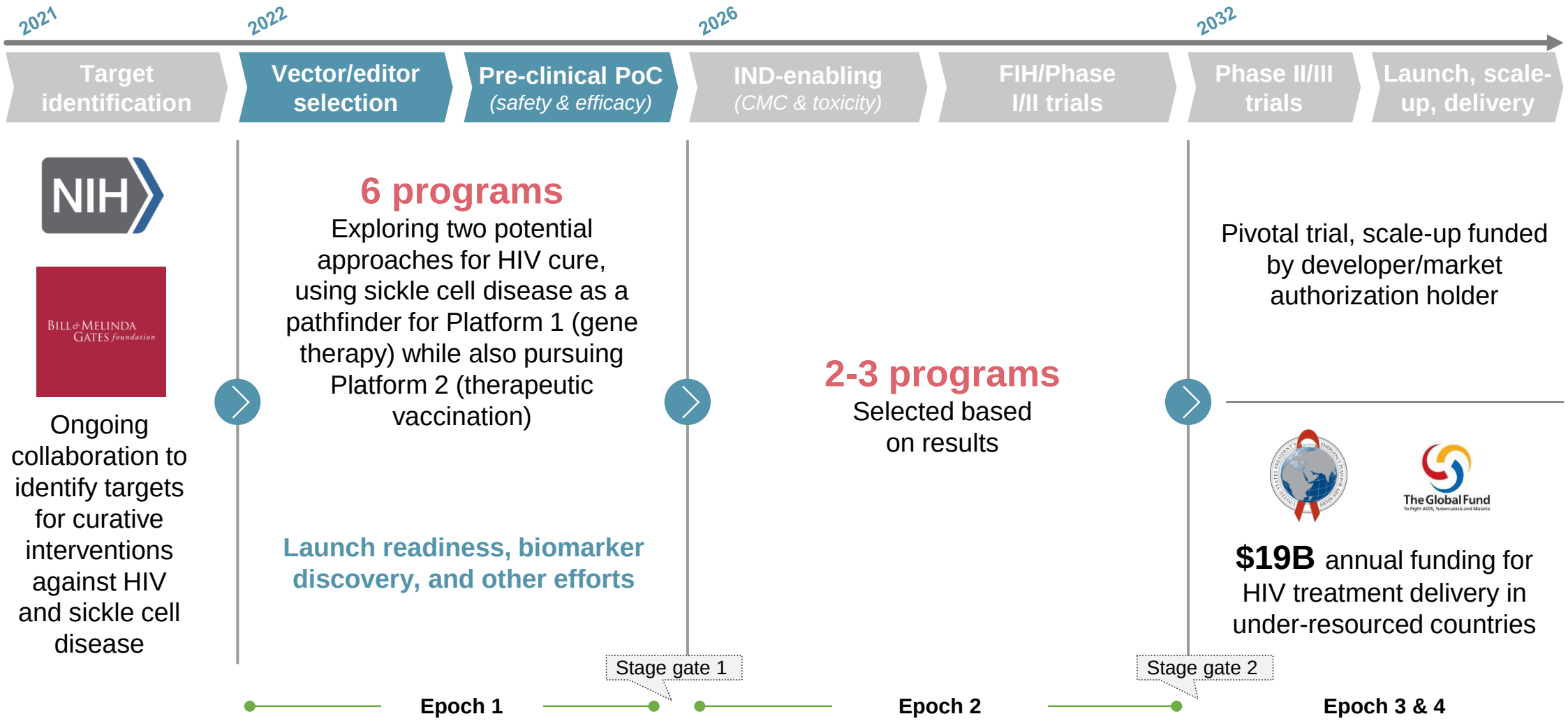
The incentive structure of academia does not encourage collaboration over a prolonged period of time

The resources required to bring an intervention to the stage of routine use are well beyond those that can be provided by the NIH

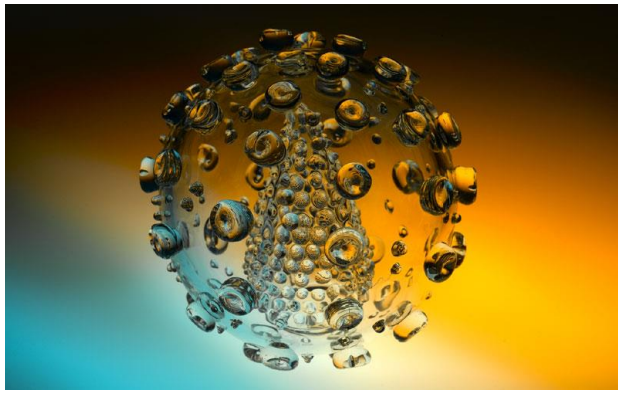
Biotech/pharma also has little commercial incentive to pursue risky science to develop therapies for those who cannot pay

Bill and Melinda Gates Foundation will focus on vector strategies for Cure and Sickle Cell Disease

B&MGF: Moving candidate interventions to the clinic



Grand ambitions but will it be accessible to all?



The Challenges to Curing HIV in LMIC and in Vulnerable Communities

Antiretroviral therapy can be maintained in the most under-resourced settings. Could the same be required of a cure?

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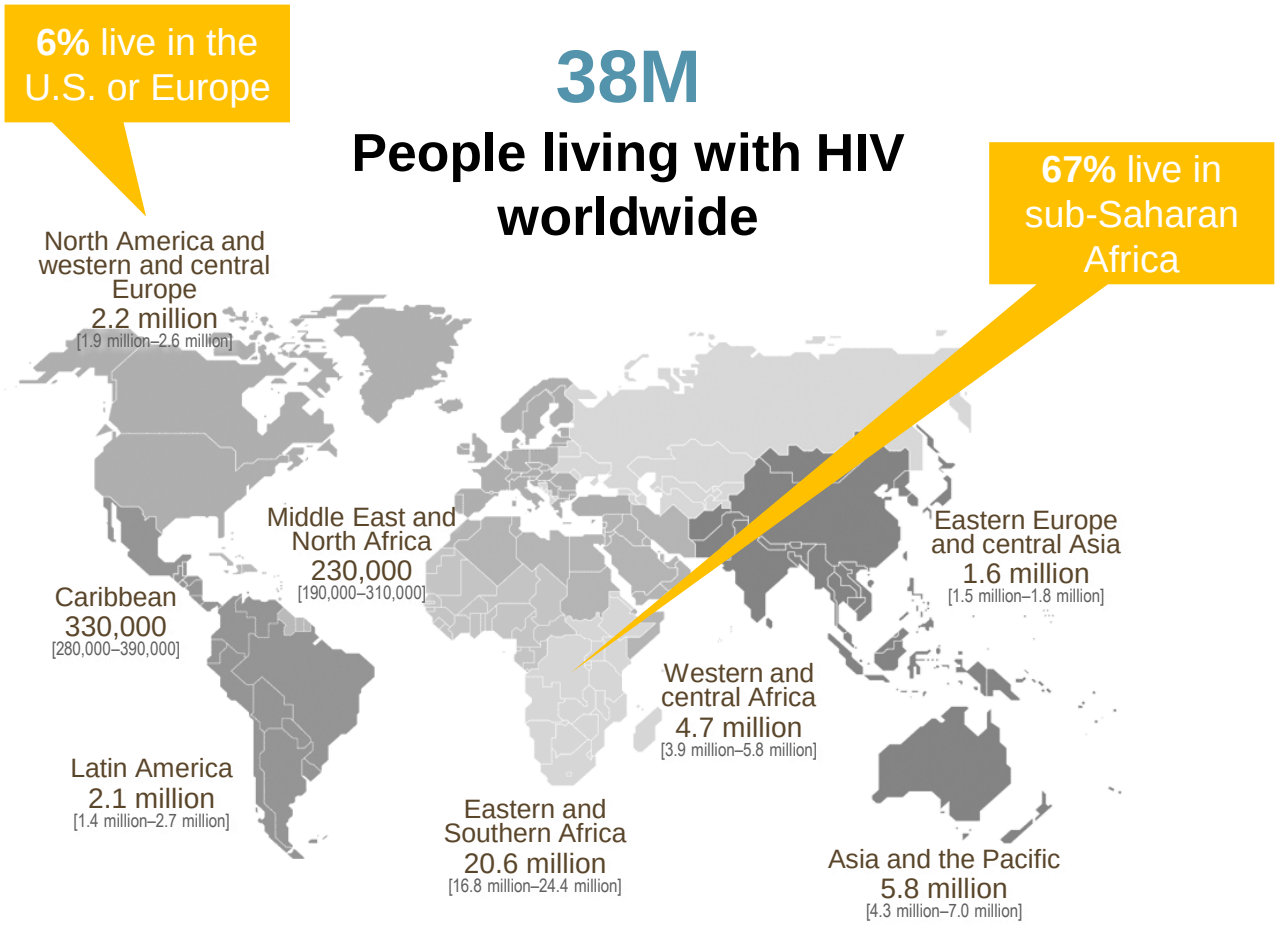
Even with simple ART regimens, HIV/AIDS remains a leading cause of death for those in resource-limited parts of the world.



Global rates are projected to remain steady through 2030[1]

Low uptake of ART in young people

In South Africa, the percentage of young people (aged 15-24) living with HIV who are on ART is only 14.3% compared to 31.2% in the 25-49 age group.

High incidence of HIV infection in young women

In South Africa, women aged 15-24 have an annual HIV incidence of 1.51%, three times higher than that found in men (0.49%) and more than 50% higher than in older women (0.93%).

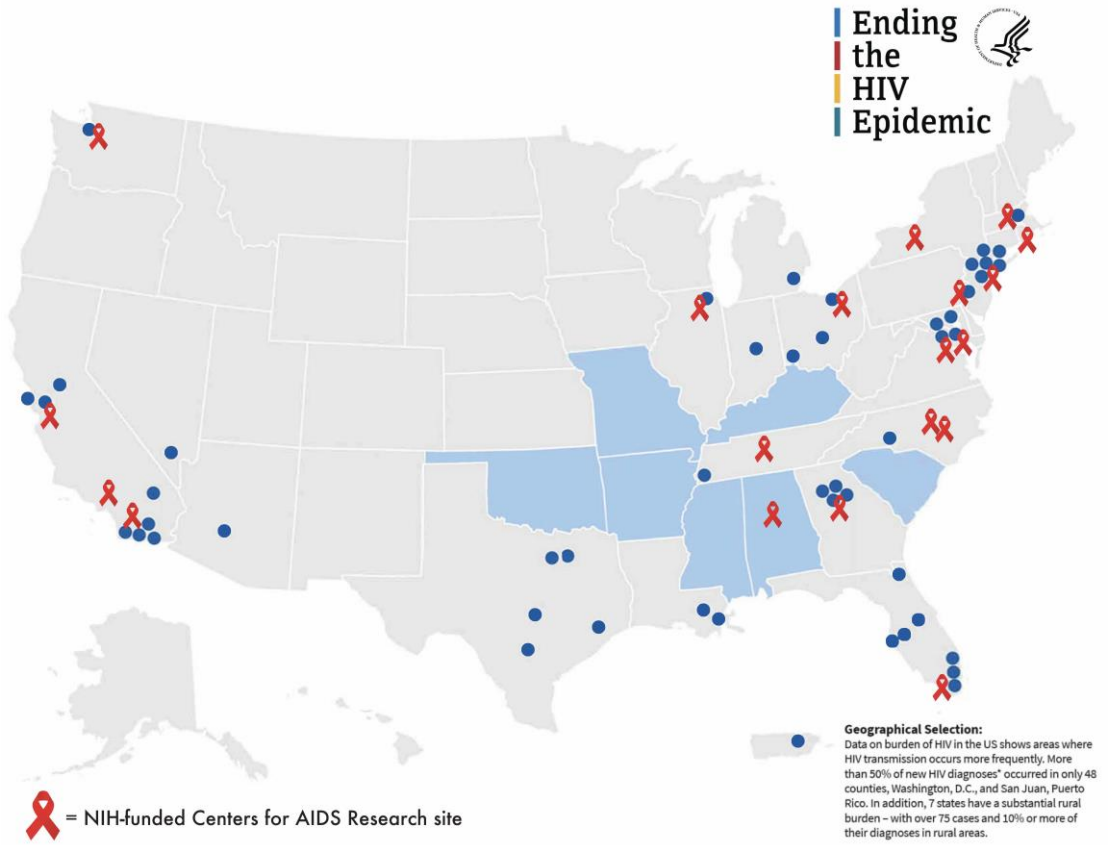
The "youth bulge"

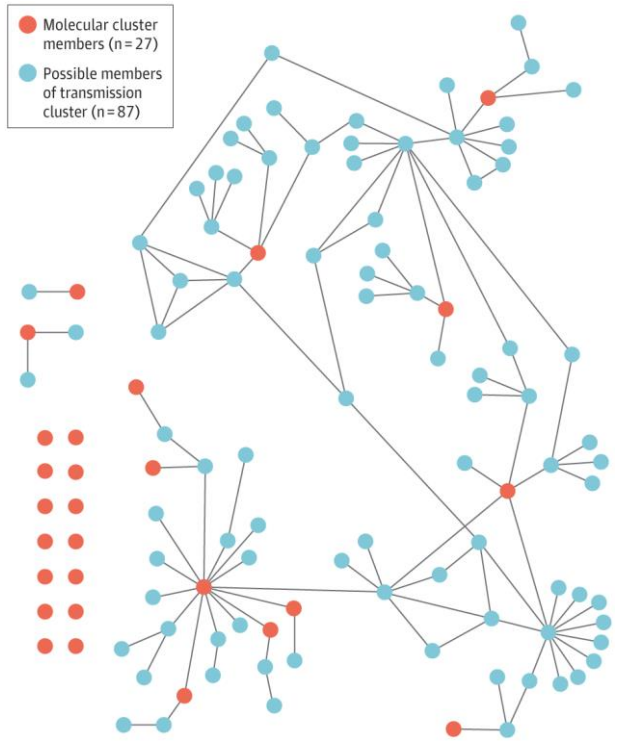
In sub-Saharan Africa, the number of young people under the age of 25 is projected to increase by over 80% between 2020 and 2060.

Sishana et al. *HSRC Press* 2014; HSRC Council, *HIV Impact Assessment Survey* 2018; *UN Projections* 2019

1. Goalkeepers Report, HIV. Map source: UNAIDS 2021 epidemiological estimates.

Less than 50 counties (7 in Florida) account for over 50% of the new HIV diagnoses in the US





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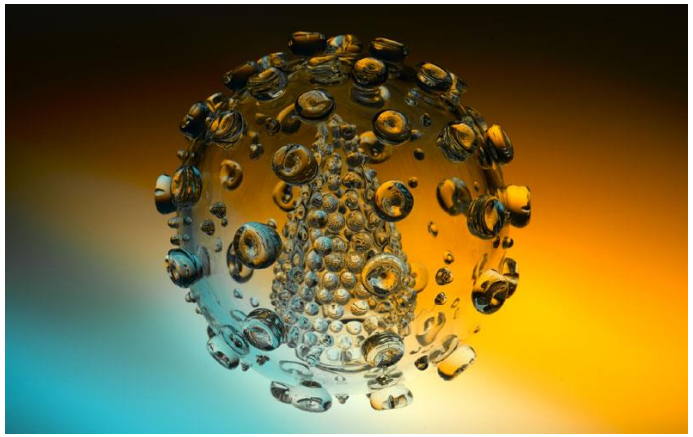

The Challenges to Curing HIV in vulnerable communities and in LMIC

If color film (LA ART) had been invented first, would we still have black and white movies?

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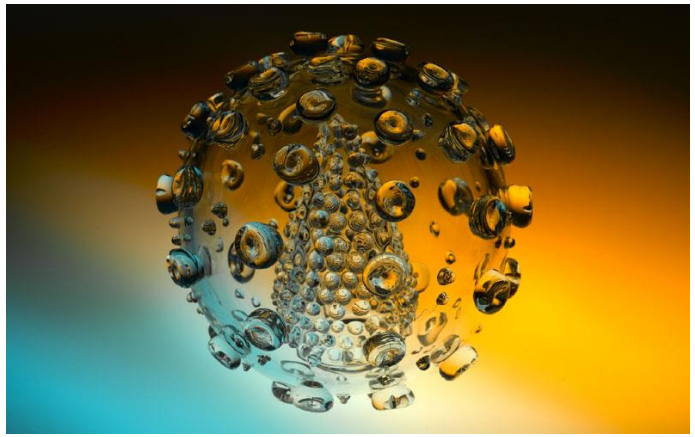
Game Changers or segues to an effective, “single shot” cure

DRUG	MOA	FORMULATION	PREP/TREATMENT	FREQUENCY
Cabotegravir	Integrase inhibitor	Injectable	Treatment	Every 4 weeks Every 8 weeks
Dapivirine	NNRTI	Vaginal Ring	PrEP	Every 3 months
Islatravir	NRTTI	Oral	Treatment Treatment PrEP	Once daily Once weekly Once monthly
Islatravir	NRTTI	Implant	PrEP	Once yearly
Lenacapavir	Capsid inhibitor	Oral	Treatment	Once weekly
Lenacapavir	Capsid inhibitor	Injectable	PrEP	Twice yearly
VRC01	bNAb	Intravenous	PrEP	Every 8 weeks

- **Islatravir implant uses existing (Nexplanon) technology developed for pregnancy control.**
- **Are such long-acting approaches the closest we might ever get to a single-shot cure?**



The Challenges to Curing HIV in LMIC and in Vulnerable Communities

The Cure enterprise may indeed deliver a remission/ cure for HIV but may not impact the populations that we haven't been able to impact with ART

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FLORIDA
MIAMI USA
www.hiv-persistence.com

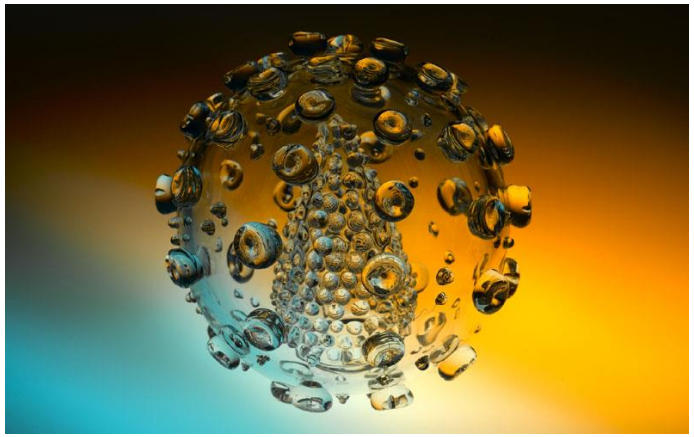
10TH EDITION

DECEMBER 13-16, 2022

HIV PERSISTENCE DURING THERAPY

Reservoirs & Eradication Strategies Workshop

Thanks to Steve Deeks, Mike McCune, Nicolas Chomont, Raj Ghandi, John Mellors and Ron Desrosiers for slide material.



Cure versus ART

CURE Cons

- Single shot cure is, at present, aspirational
- Safety profile of ART sets very high bar
- Different persistence mechanisms may need combination cure approaches
- Implementation will require new paradigms

CURE Pros

- “Moonshot” challenge
- Technological advances are driving the mission

ART Cons

- Some vulnerable populations have been difficult to reach
- ART doesn’t eliminate comorbidities & stigma
- Lifelong ART isn’t an end game (LA agents?)

ART Pros

- Very high safety profiles
- Works in LMIC
- Less vulnerable to country’s GDP
- Can stop and start it.

Obstacles confronting development of a cure for HIV

Developing an HIV cure is very tough and highly risky, likely to take years to achieve

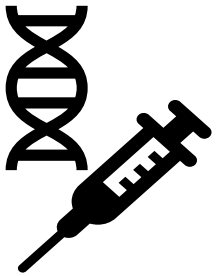
The incentive structure of academia does not encourage collaboration over a prolonged period of time

The resources required to bring an intervention to the stage of routine use are well beyond those that can be provided by the NIH

Biotech/pharma also has little commercial incentive to pursue risky science to develop therapies for those who cannot pay

Bill and Melinda Gates Foundation has moved to fill this gap

The goal of the BMGF HIV Frontiers Program



Development of an effective, durable, safe, accessible, and affordable

“curative” intervention for HIV disease -

one that could ultimately be scaled and implemented globally,

including in low- and middle-income countries

with high prevalence of these diseases, e.g., sub-Saharan Africa

Goal

A safe, effective, durable, and accessible cure for HIV disease

- "Single-shot" (administered simply and percutaneously in an outpatient setting)
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- The loss of remission (rebound viremia) can be predicted
- Safe
- Affordable: amortized cost including monitoring $50-100k in US and Europe, $1-2k in sub-Saharan Africa, $25-50k in the rest of the world[2]

1. Beacroft et al., Global Health Res Pol 2019;
2. Phillips et al., J Inf Dis 2016

Where we are today

- Identification of multiple candidate vectors for targeting and editing hematopoietic stem cells *in vivo*
- Progress in engagement of key stakeholders in sub-Saharan Africa
- Establishment of multiple partnerships to help drive the work forward
- Substantial progress in understanding the biology of the rebound-competent reservoir of HIV

Two platforms for a "single-shot" cure are emerging

1. Targeting and editing of long-lived cells *in vivo*

- Using viral or non-viral vectors to target and edit long-lived hematopoietic cells (e.g., hematopoietic stem cells, Tscm cells, and B cells) *in vivo*

2. Therapeutic vaccines for HIV cure

- Harnessing the "vaccinal effect" to generate T cell responses against HIV
- Using an mRNA vaccine to induce T cell responses against "highly-networked" epitopes

The need to form partnerships

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

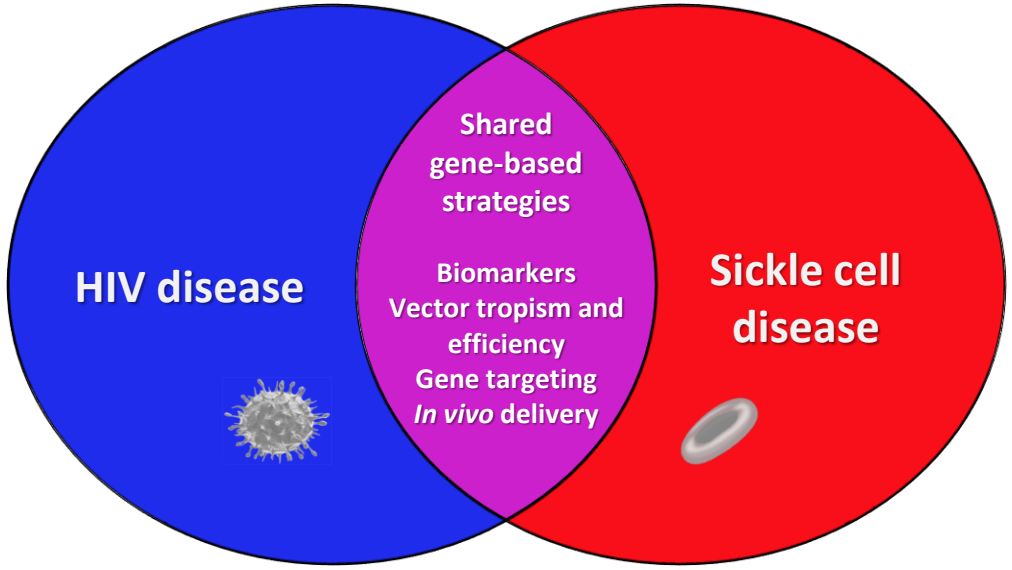
Design	Develop approaches for sustained viral suppression
Durability (Targeting & Editing)	Accelerate gene therapy for HIV
	Develop engineered B cells for HIV
Detection	Discover HIV reservoir biomarkers

NIH

$108M
HIV Frontiers
1/19

BILL & MELINDA GATES foundation

~$211M
6/19



NIH-BMGF collaboration on *in vivo* gene therapies for HIV and sickle cell disease

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

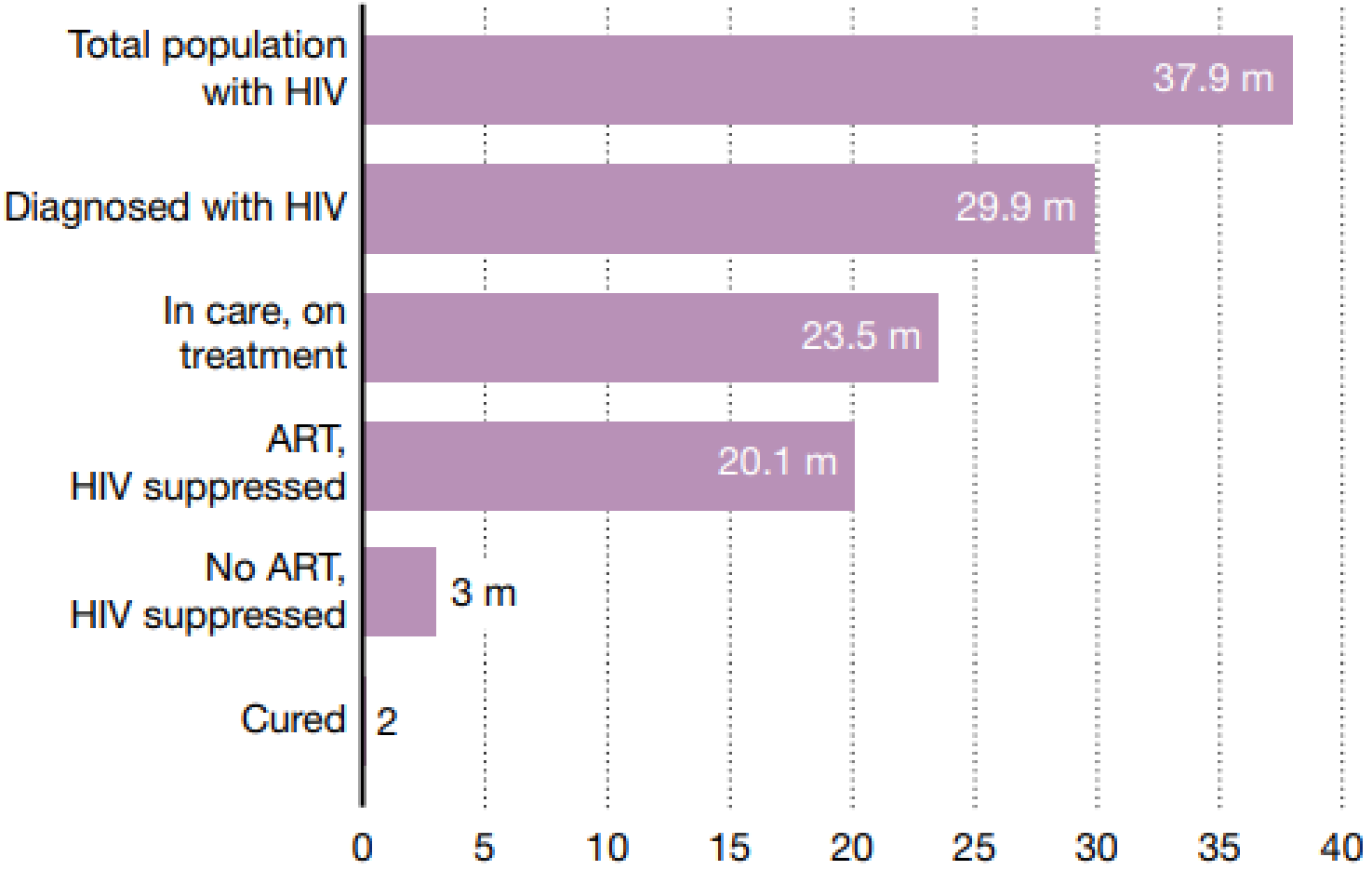
HIV cure cascade

Cure rare, control/remission uncommon

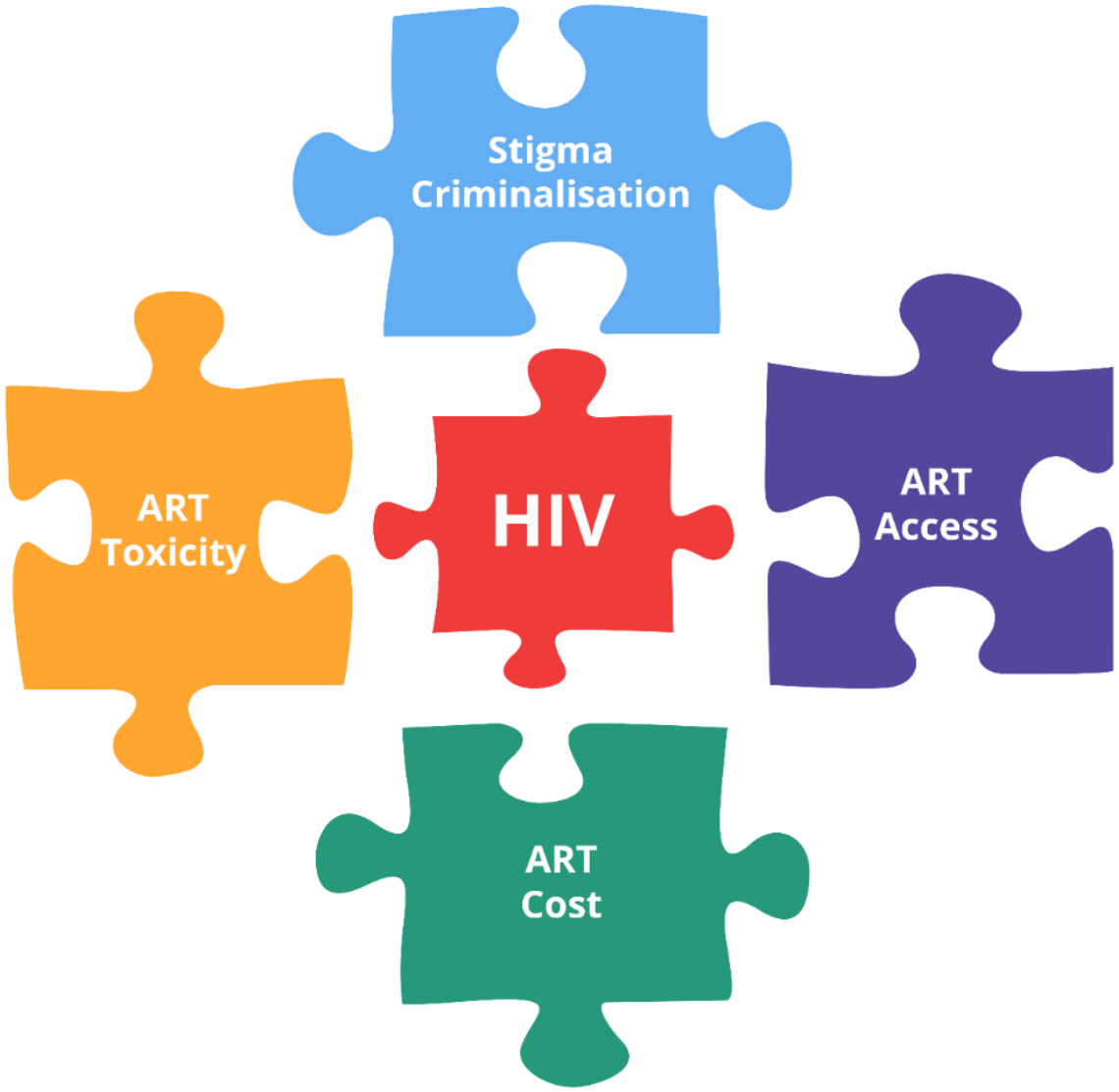
nature
Review

Why and where an HIV cure is needed and how it might be achieved

Thumbi Ndung'u[1,2,3], Joseph M. McCune[4] & Steven G. Deeks[5]*



Why we need a cure for HIV



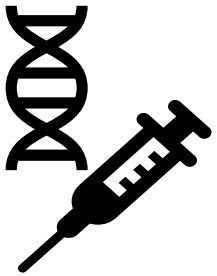
To achieve treatment uptake by 95% of people living with HIV by 2025 the projected costs are $29 billion/year

UNAIDS Report, June 2021

How do we get there?

	DEFINITION	EXAMPLE ACTIVITIES
Design	Understanding the mechanism(s) that might result in a cure for HIV	Discovery of biologic approaches that could lead to a "single-shot" cure of HIV
Durability	Understanding the approaches that could enable a “single-shot” cure to be long-lasting, **starting with targeting and editing of hematopoietic stem cells for the “cure” of sickle cell disease**	Discovery and prioritization of viral and non-viral vectors capable of targeting and editing hematopoietic stem cells *in vivo*
Detection	Identifying circulating biomarkers of the “rebound competent reservoir,” facilitating clinical trials while affording the ability to both monitor success and predict failure	Establishment of a five-team, 40-lab, four-continent effort to define the biology of the "rebound competent reservoir" of HIV
Delivery	Building the capability and capacity for regulators and health systems in resource-limited countries to introduce and scale the intervention	Establishment of the HIV Cure Africa Acceleration Partnership to engage stakeholders ahead of the product launches
Partnerships	Forming meaningful collaborations in which complementary areas of expertise can be merged, resources combined, and risk shared	Establishment of collaborations with the NIH and biotech/pharma focused on bringing *in vivo* gene therapies to all

The goal of the BMGF HIV Frontiers Program



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Distribution: Bringing *in vivo* gene therapy to sub-Saharan Africa

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

Dybul et al., *Lancet HIV*, 2021

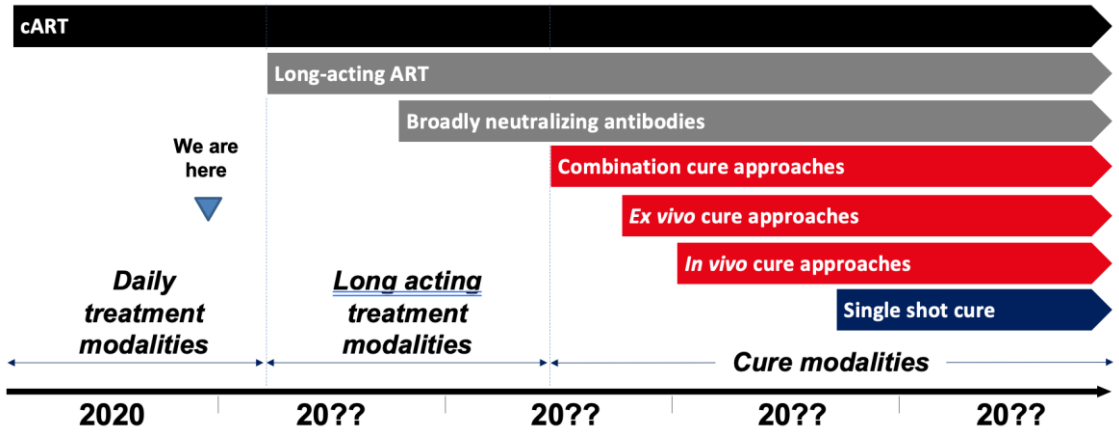
Global Gene Therapy Initiative

GGTI
GLOBAL GENE THERAPY INITIATIVE

Laying the groundwork
for the introduction
of *ex vivo* gene therapies for
HIV and sickle cell disease
in Uganda and India by 2024

Adair et al., *Gene Therapy*, 2021

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



Lewin et al., *Lancet HIV*, 2021

Sunnylands Summit III: The Path Towards Ending HIV April, 2022

Objective

To establish a pathway for the introduction of safe, effective, durable, and affordable "single-shot" gene therapy "cures" for HIV and sickle cell disease in Africa – moving HCAAP to the leadership by Africans in Africa for the healthcare of Africans

Rationale for an AIDS cure: The personal perspective!

If my HIV infection is cured, I lose my medical insurance benefits!

Courtesy: Steve Deeks

How can curative interventions for HIV be made available to all?

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A safe, effective, durable, and accessible cure for HIV disease

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Now is the right time to push forward

Advances in genome editing technology and gene delivery vectors

Development of an *ex vivo* gene therapy for sickle cell disease which can successfully edit hematopoietic stem cells (HSCs)

Development of vectors (AAV, lentiviral, and LNP) to target and edit hematopoietic cells

Ex vivo approaches are effective but expensive; *in vivo* technology could be a path to better access and affordability

Advances in understanding of HIV biology

Two successful "cures" of HIV upon bone marrow transplantation

Better definition of the rebound-competent HIV viral reservoir

Increasing understanding of immune responses to suppress this reservoir

The scientific groundwork has been laid for new innovations and practical applications

Evidence of the transformative power of new technologies

Rapid development of mRNA COVID-19 vaccines has increased awareness of the need to fund transformational technology platforms

HIV cure development can capitalize on momentum to support "big bets" on new technology

Increased awareness of disparities in access to healthcare

The COVID-19 pandemic has also heightened public awareness to disparities in healthcare access between different populations, especially those in high- vs. low-income countries

There is now a unique opportunity to advocate for global access to transformative technologies

The Inconvenient Truth

THE LANCET HIV

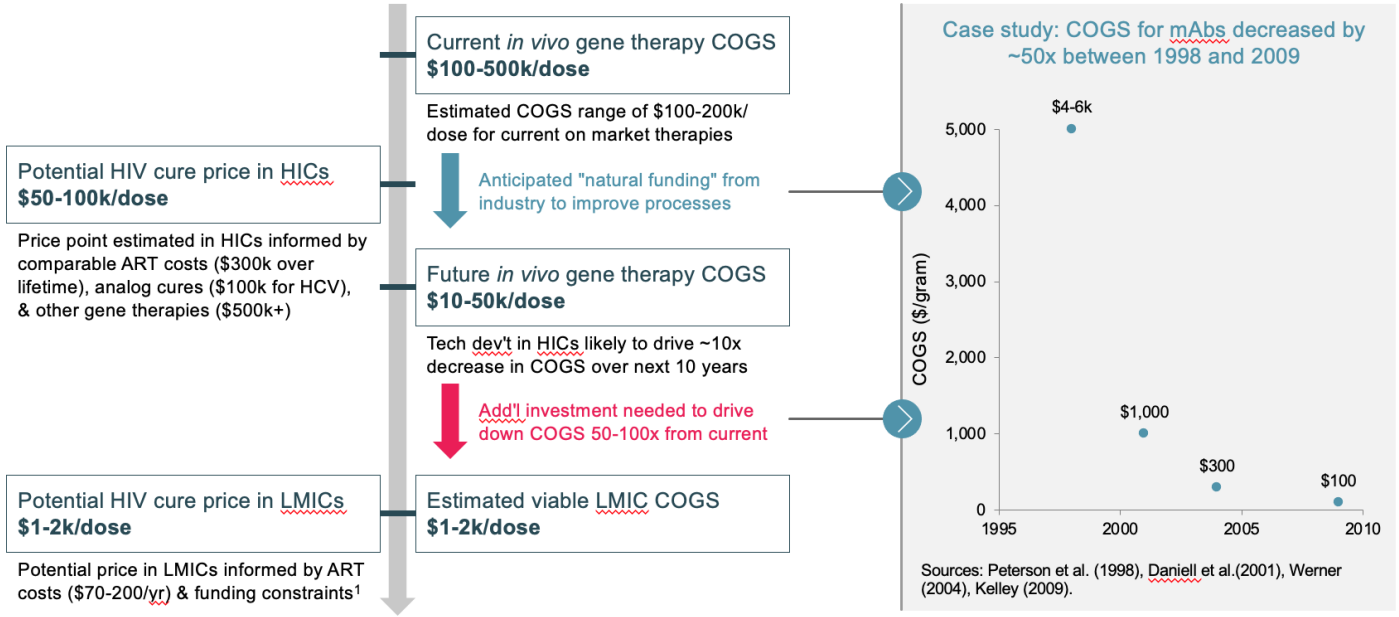
Recommendations for analytical antiretroviral treatment interruptions in HIV research trials—report of a consensus meeting

Boris Julg, Lynda Dee, Jintanat Ananworanich, Dan H Barouch, Katharine Bar, Marina Caskey, Donn J Colby, Liza Dawson, Krista L Dong, Karine Dubé, Joseph Eron, John Frater, Rajesh T Gandhi, Romas Geleziunas, Philip Goulder, George J Hanna, Richard Jefferys, Rowena Johnston, Daniel Kuritzkes, Jonathan Z Li, Udom Likhitwonnawut, Jan van Lunzen, Javier Martinez-Picado, Veronica Miller, Luis J Montaner, Douglas F Nixon, David Palm, Giuseppe Pantaleo, Holly Peay, Deborah Persaud, Jessica Salzwedel, Karl Salzwedel, Timothy Schacker, Virginia Sheikh, Ole S. Søgaard, Serena Spudich, Kathryn Stephenson, Jeremy Sugarman, Jeff Taylor, Pablo Tebas, Caroline T Tiemessen, Randall Tressler, Carol D Weiss, Lu Zheng, Merlin L Robb, Nelson L Michael, John W Mellors, Steven G Deeks, Bruce D Walker

- Carefully performed treatment interruptions are often the only interpretable way to determine if an intervention worked
  - No validated biomarker of the rebound-competent reservoir
  - No validated immunologic correlates of post-ART control
- Can it be done safely?
  - Exclude those with low nadir, history of cancer/CAD
  - Partner engagement (PrEP)
  - Conservative restart criteria
  - COVID risk mitigation

Obstacles to address

- **Focusing the gene therapy R&D pipeline** on HIV and sickle cell disease
- Assuring **global access rights** for the use of funded developments in low- and middle-income countries
- Better definition of the **“design”** for a ”single-shot” cure for HIV
- Assessment of **safety** of *in vivo* gene therapy for HIV and sickle cell disease
- Bringing down the **cost of goods** to hit target prices in LMICs



Source: BCG and external experts (n=8), Gerson Lehrman Group market report

1. Assumes 5-10 years of durable remission, lowest possible price of therapy must be comparable with ART costs excl. treatment costs (no discounting); see Phillips et al., J Inf Dis, 2016.

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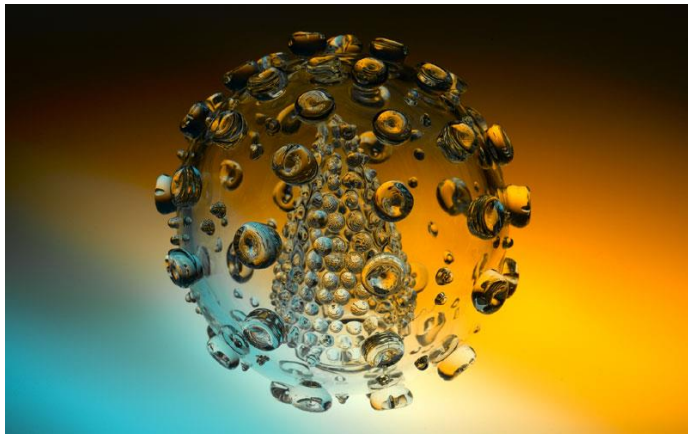
- Discovery of **biomarkers** of the rebound competent reservoir of HIV
- **Engagement of key stakeholders** in LMICs to make sure that cure interventions that are developed will ultimately be used



Long-acting ART formulations will set a high bar for approaches to managing HIV-1 infection in HIC and LMIC.

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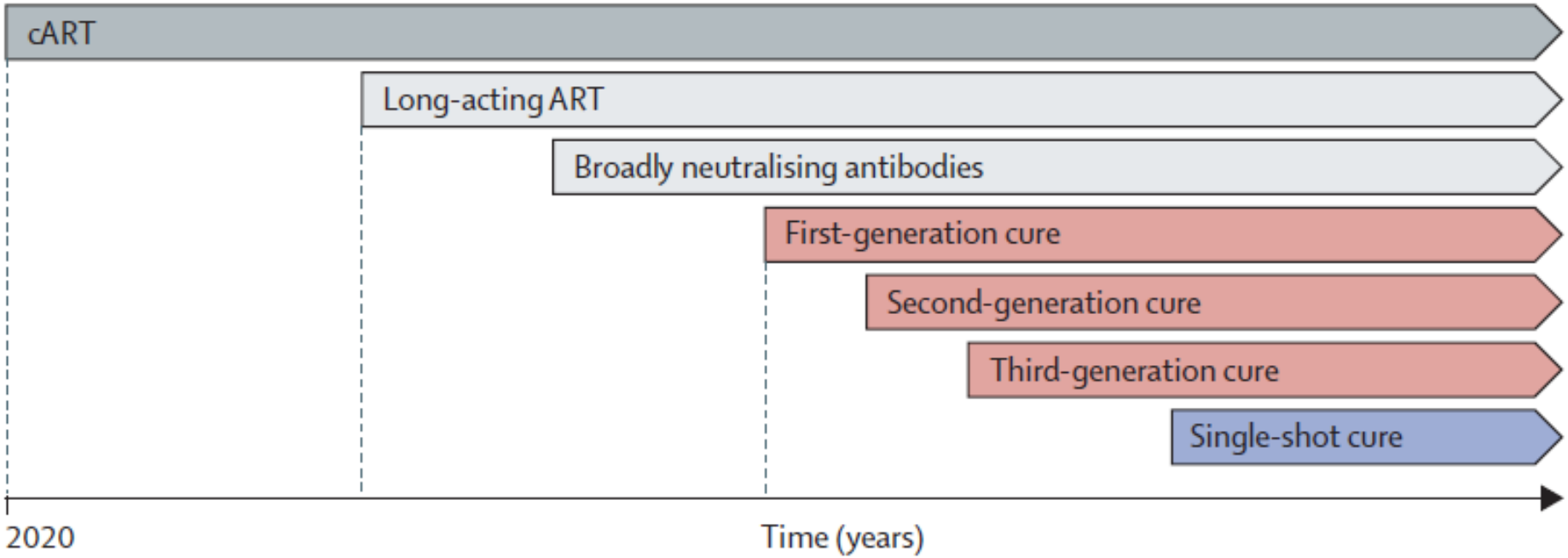
Treatment evolution and a cure/remission

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

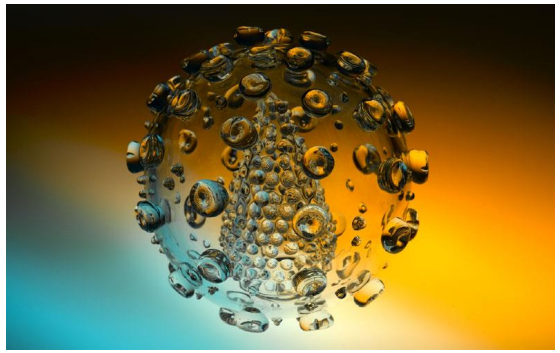


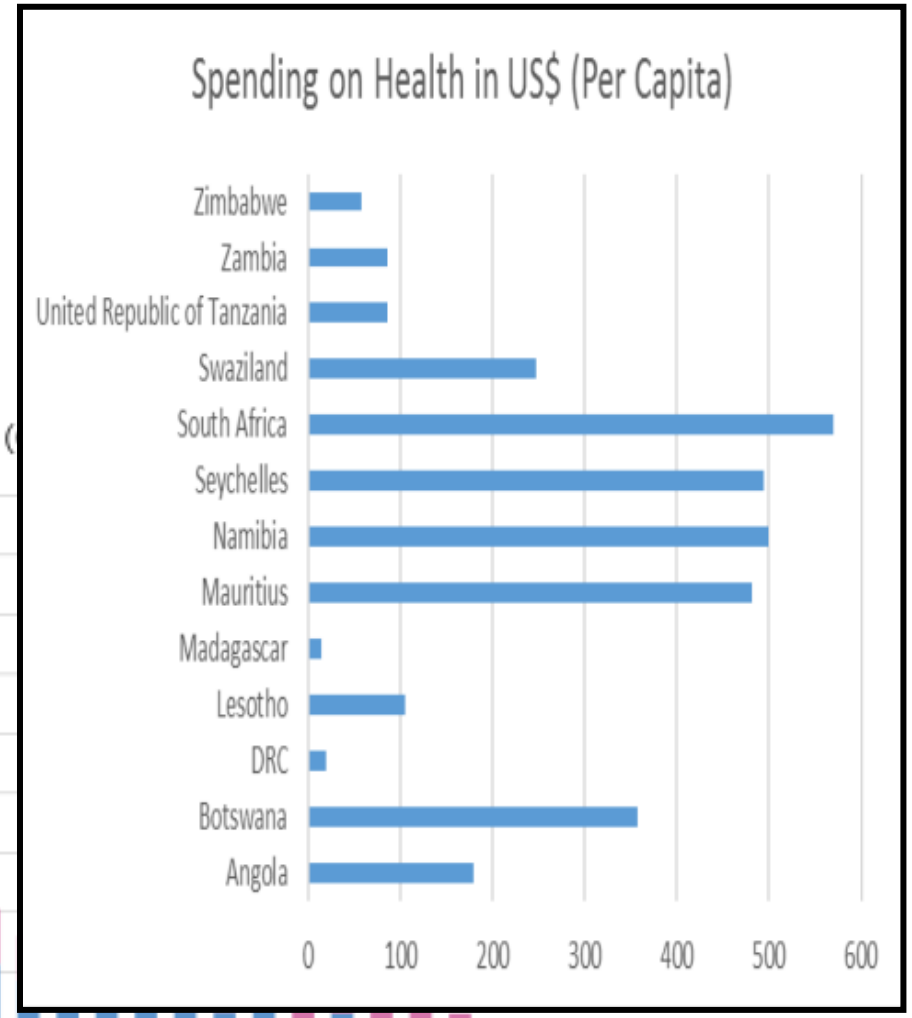
THE LANCET HIV

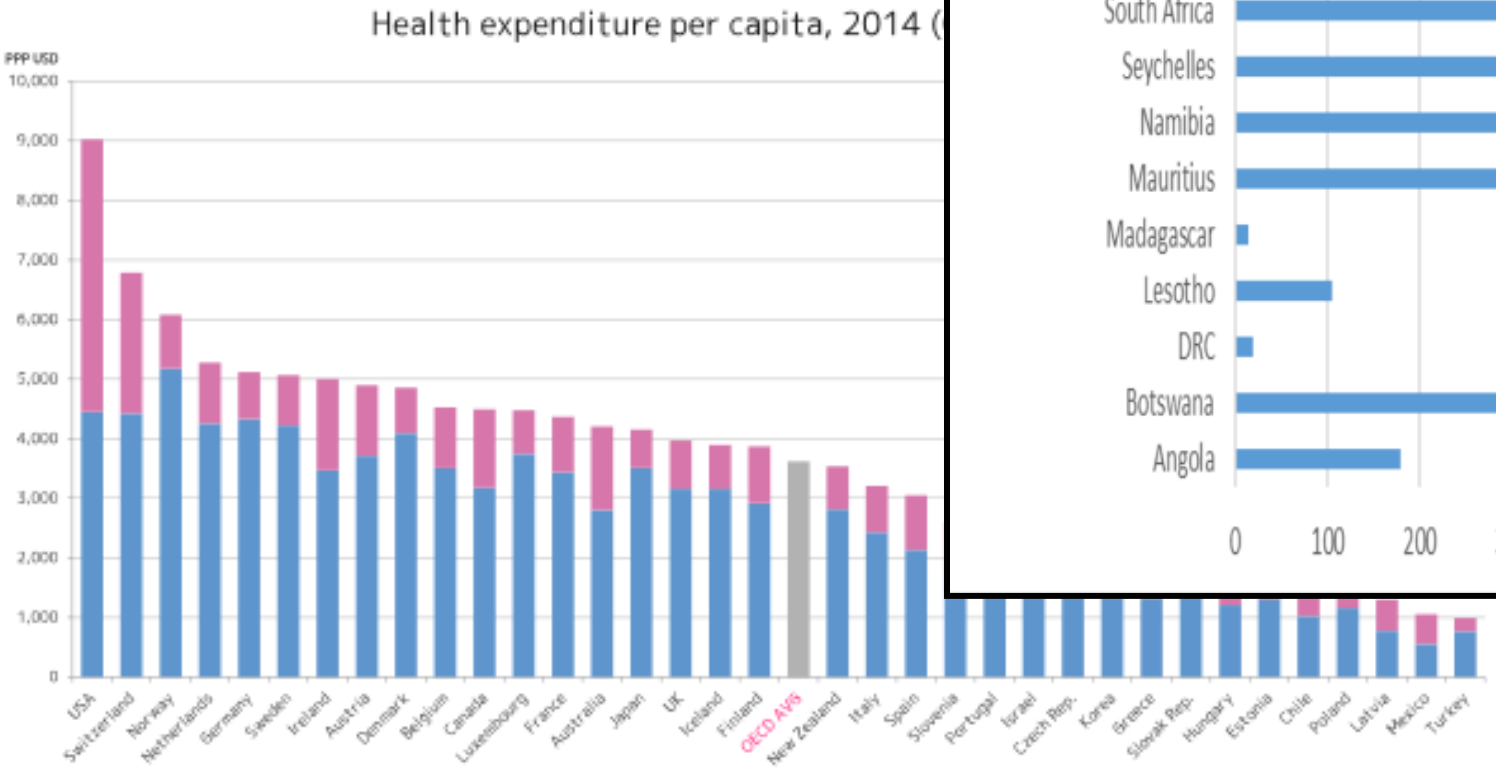
Multi-stakeholder consensus on a target product profile for an HIV cure

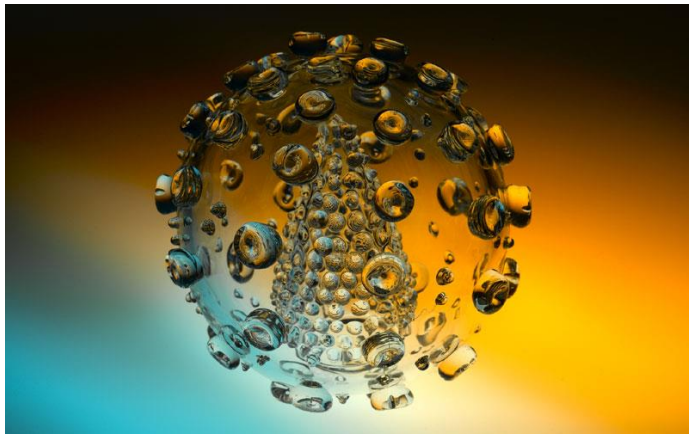
Sharon R Lewin, Timothy Attoye, Cathy Bansbach, Brian Doehle, Karine Dubé, Mark Dybul, Devi SenGupta, Adam Jiang, Rowena Johnston, Rosanne Lamplough, Joseph M McCune, Gary J Nabel, Thumbi Ndung'u, John Pottage, David Ripin, James F Rooney, Izukanji Sikazwe, Moses Nsubuga, Mitchell Warren, Steven G Deeks*, on behalf of the Sunnylands 2019 Working Group*

Health care expenditure in Africa is far below other nations









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- Works in LMIC
- Less vulnerable to country’s GDP
- Can stop and start it.

What fuels viral rebound following treatment interruption?

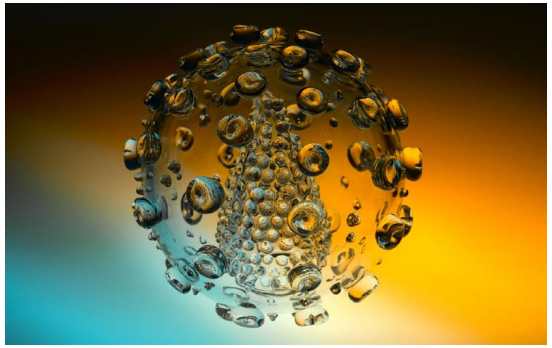
Latent reservoir

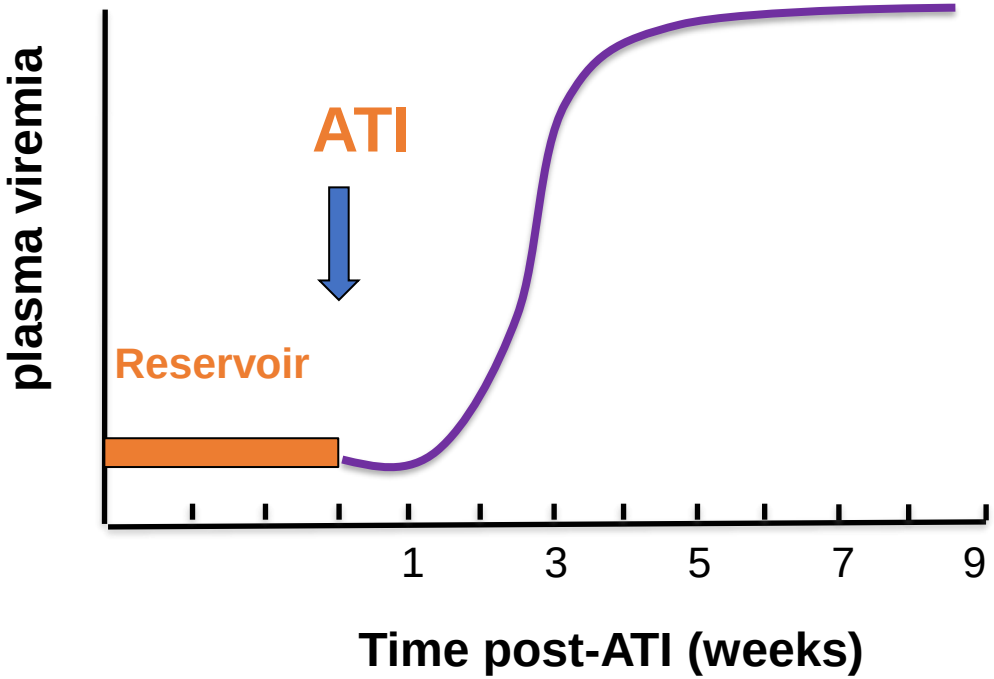
Expanded reservoir

unidentified reservoir

?

Viruses emerging post-ATI reflect the nature of the reservoirs from which they originated





I love you Ventura!