HIV cure: latest scientific updates

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IAS Educational Fund in partnership with Sociedad Chilena de Infectología (SOCHINF)
Santiago, Chile, October 27th., 2022

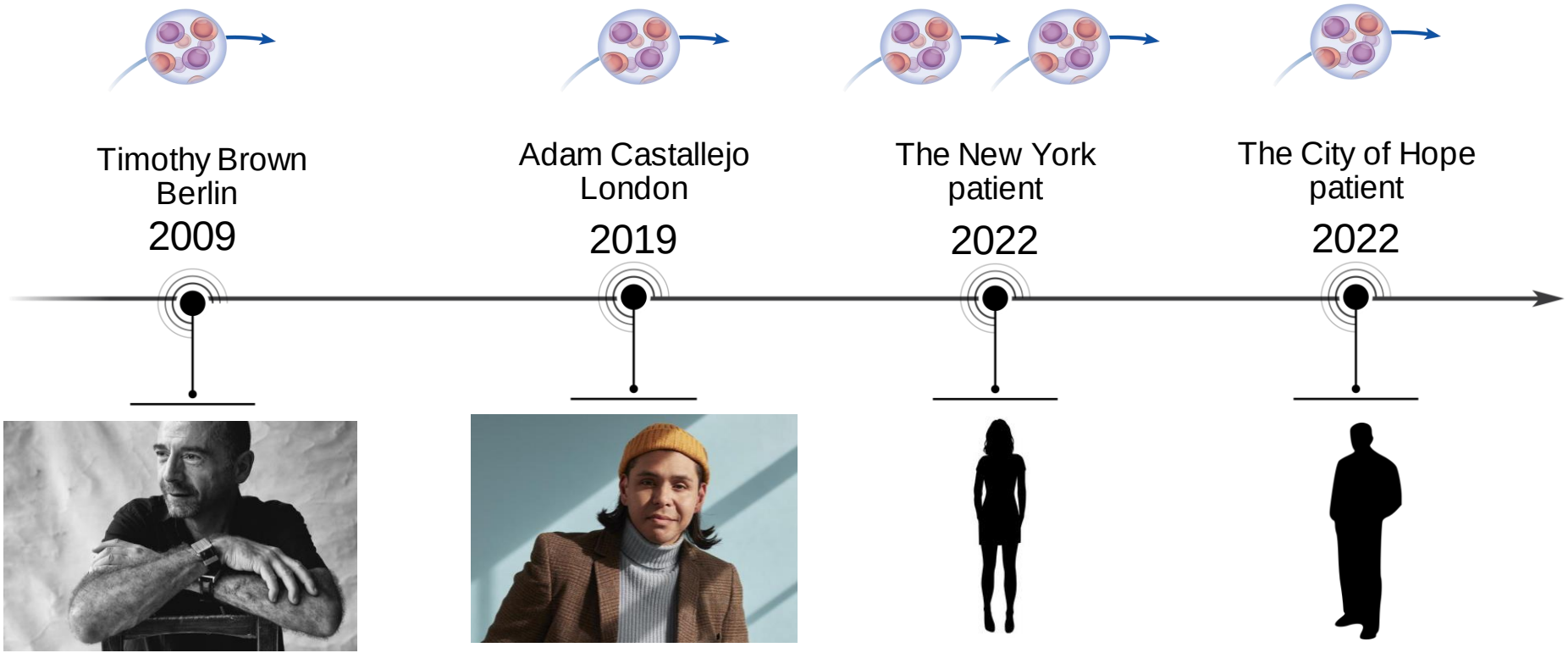
Doherty Institute

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

HIV cure is extremely rare but possible



Hutter, N Engl J Med 2010; Gupta, Nature 2019; Gupta, Lancet HIV 2019; Bryson, CROI 2022; Dickter IAS2022

HIV cure is extremely rare but possible

VISCONTI
SPARTAC
CHAMP

Post treatment control (remission)

Timothy Brown
Berlin
2009

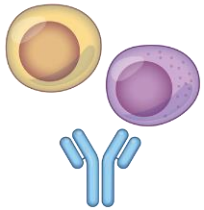
2010

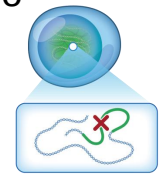
Adam Castallejo
London
2019

2020
Lorraine Willenberg
San Francisco

2021
The Esperanza patient

The New York patient
2022





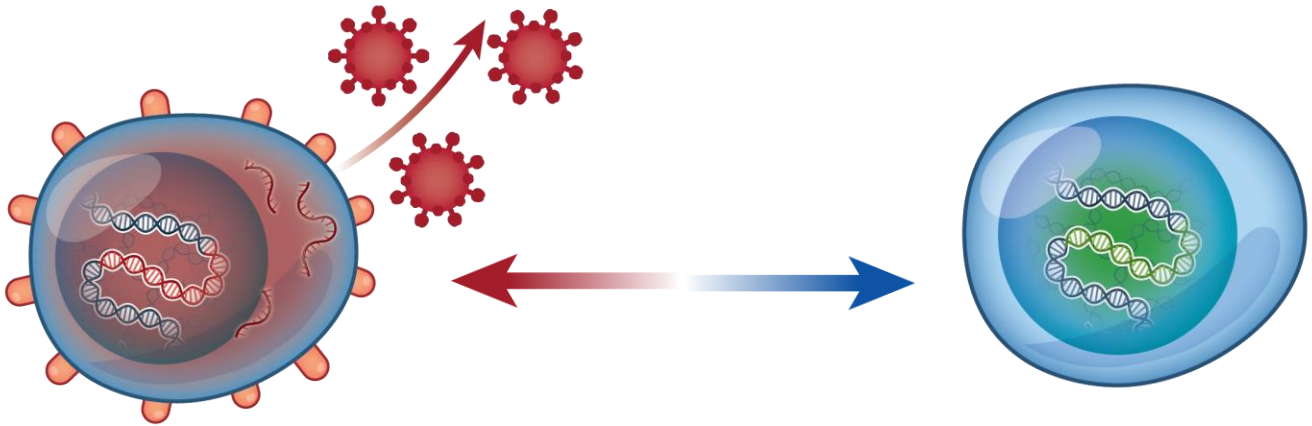
Hutter, N Engl J Med 2010; Gupta, Nature 2019; Gupta, Lancet HIV 2019; Bryson, CROI 2022; Jiang Nature 2020; Turk Annals Int Med 2021

Outline

- New concepts in understanding HIV latency
  - Clonal proliferation
  - Integration site

- Clinical strategies for an HIV cure and new studies
  - Latency reversal
  - Combination immunotherapy
  - Gene therapy

Two major forms of HIV infected cells



Productive infection

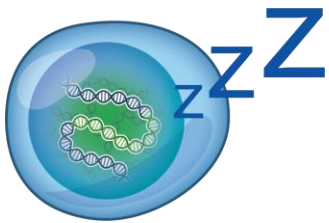
DNA positive
RNA positive
HIV protein positive
DEATH

Latent infection

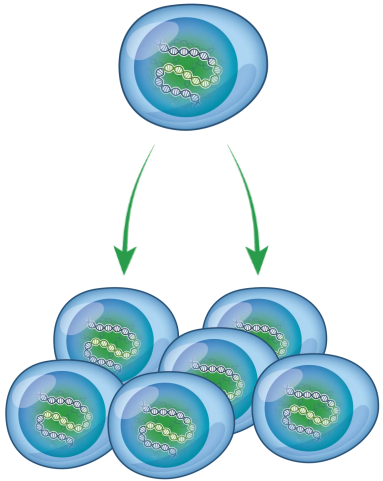
DNA positive
RNA negative
HIV protein negative
SURVIVAL

New concepts in HIV persistence and latency

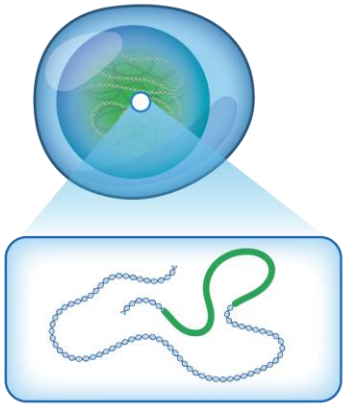
1.
Reservoir ‘activity’



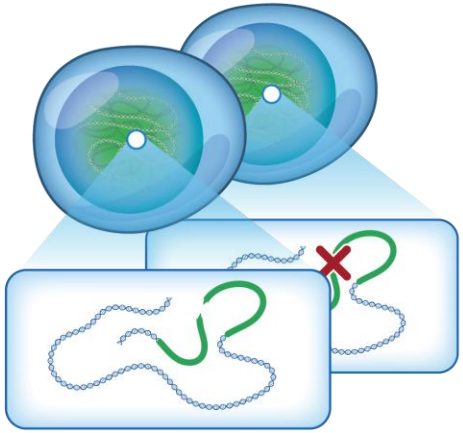
2.
Proliferation



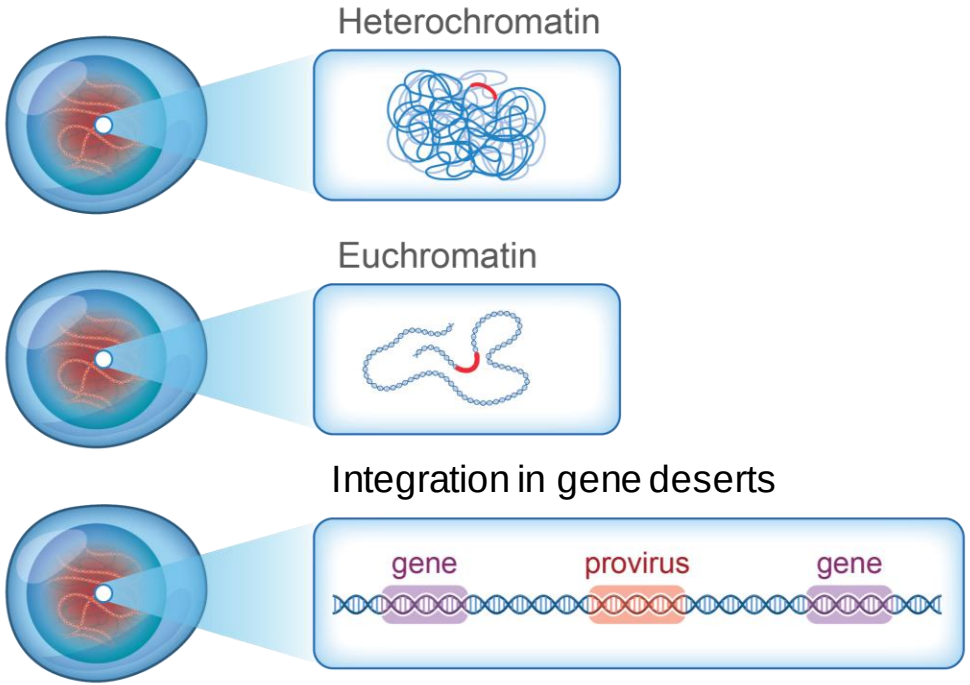
3.
Position matters



4.
Defective and intact virus



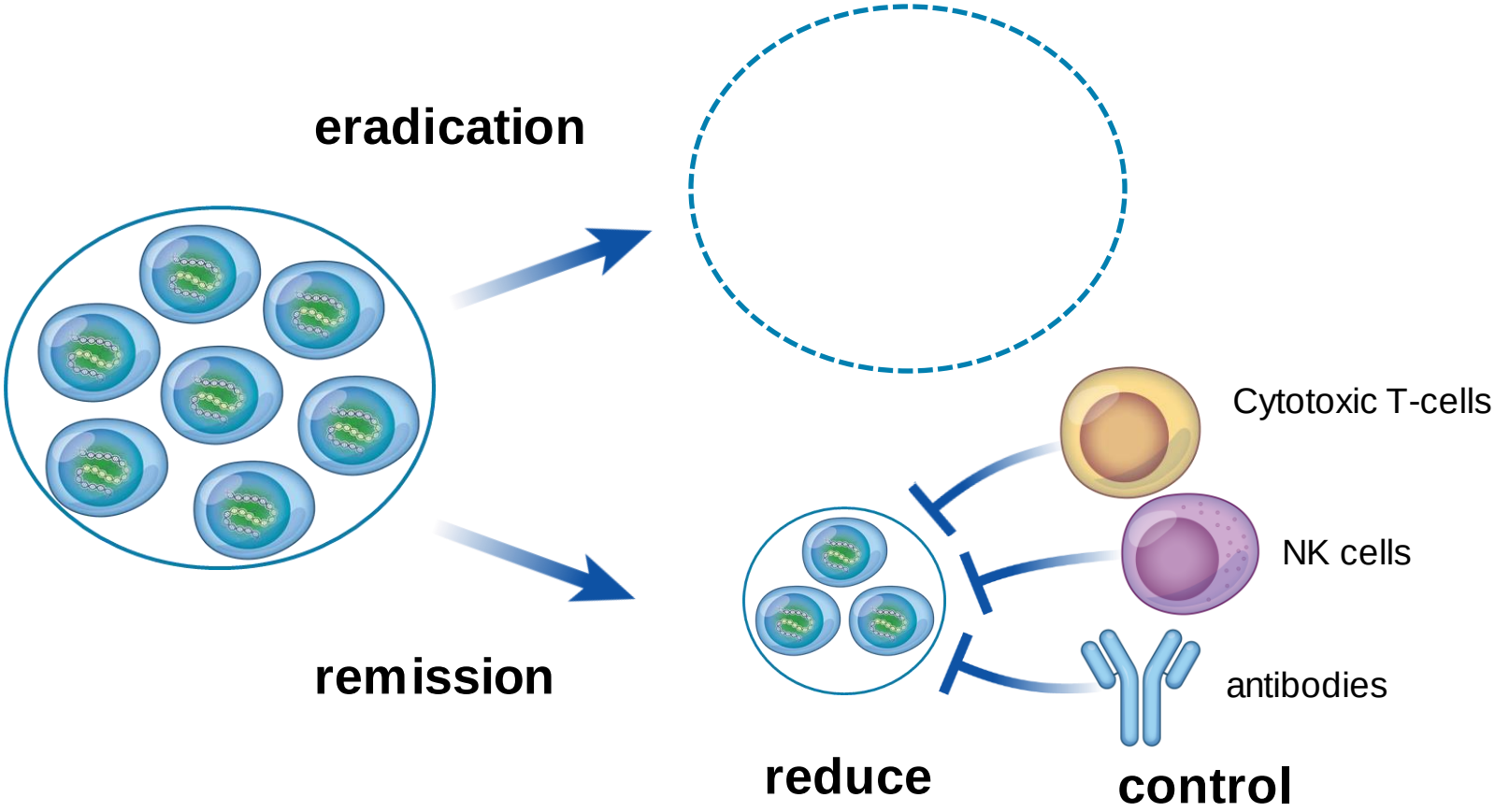
Position matters: HIV integration is important for virus transcription…..allowing it to stay silent or activate



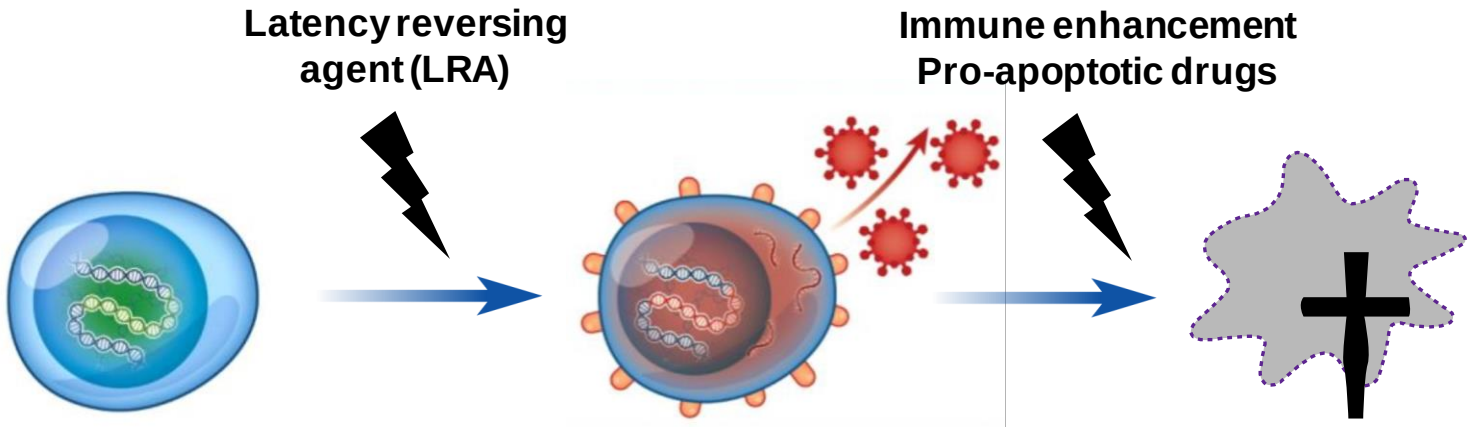
- Integration sites determine the likelihood of a virus being active or silent[1,2]
- In elite controllers, intact virus more commonly found in gene deserts ie limited or no transcription[3,4]
- Over prolonged ART, there is loss of transcriptionally active cells, leaving more deeply latent cells – some optimism![5]

1 Jordan et al., EMBO J 2010; 2 Chen et al., Nat Struct Mol Biol 2017; 3 Einkauf et al., J Clin Inv 2019; 4 Yu et al., Nature 2020; 5 Einkaupf et al., Cell 2022

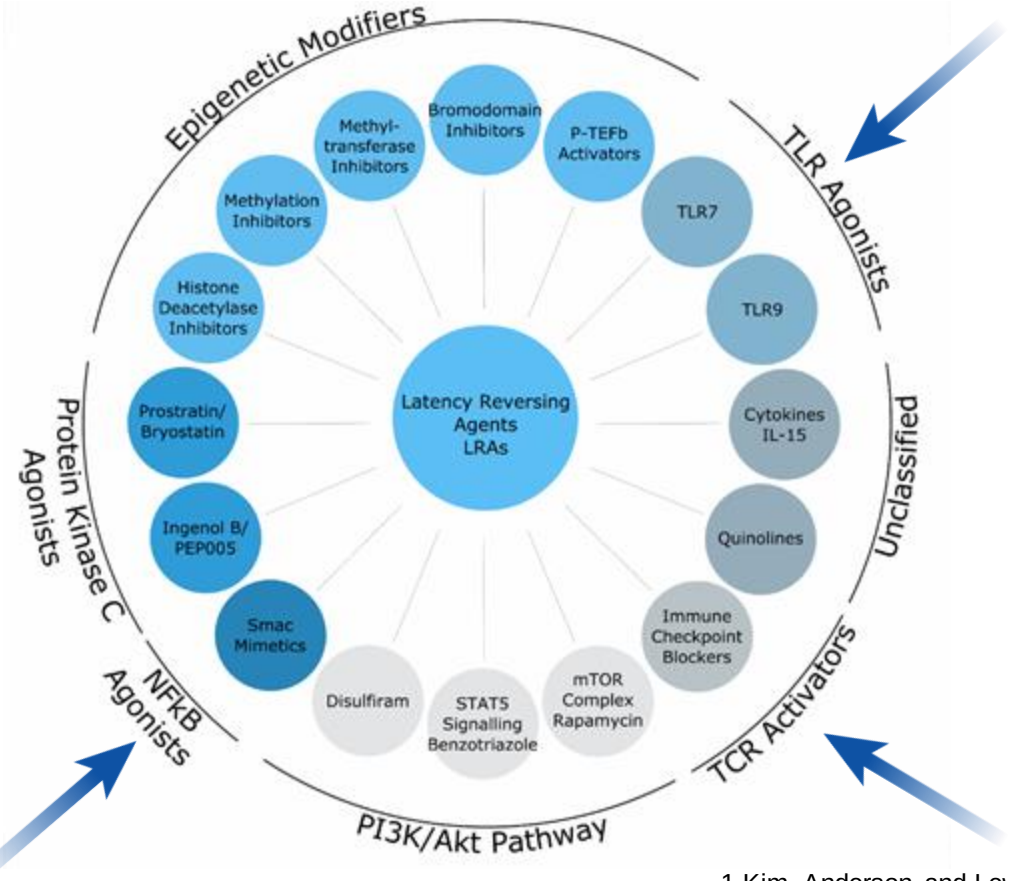
Overarching goals of cure strategies



HIV latency reversal: shock and kill



Latency reversing agents (LRA): can ‘shock’ but not ‘kill’



- In vivo, **LRAs increase transcription** but no decline in the number of infected cells
- Need to get the ‘kill’ into shock and kill: **pro-apoptotic drugs**[1]
- Immune modulating latency reversing agents such as **toll like receptor (TLR) agonists** or **anti-PD1** may have dual activity[2]

1 Kim, Anderson and Lewin, Cell Host Microbe 2018; 2 Zerbato et al., Curr Op Virol 2019

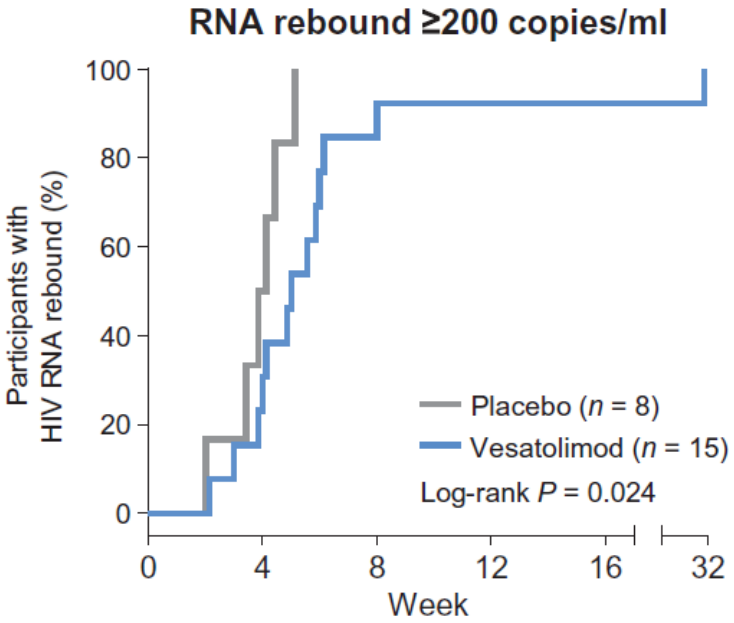
Immunomodulation: vesatolimod (TLR7 agonist)

Vesatolimod is a TLR7 agonist with important **immunomodulating activities** and can **reverse HIV latency** – in vitro and in (some) non human primates

In one monkey study, **TLR7 agonist plus antibodies** led to cure in 50% of animals

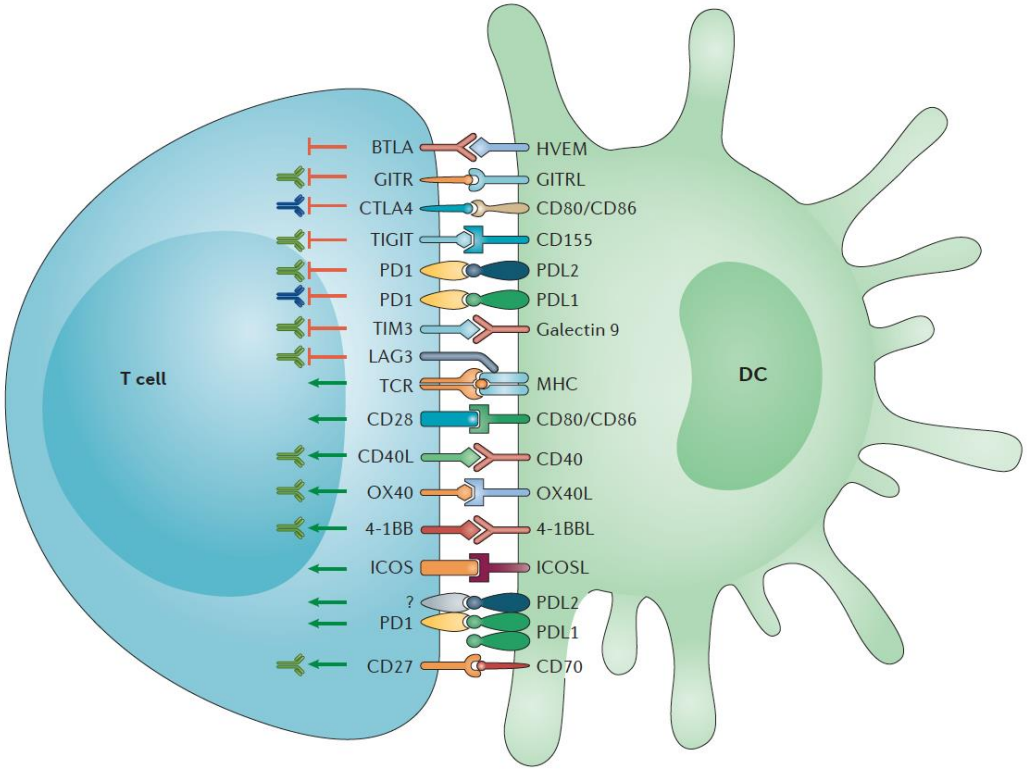
In PLWH on ART (n=48) **vesatolimod** (1-12mg) was safe with evidence of activation of innate immunity but no latency reversal

In viremic controllers (n=25) randomised to vesatolimod or placebo, vesatolimod induced a **delayed time to viral rebound** off ART



Borducchi et al., Nature 2018; Riddler et al., Clin Infect Dis 2020; Rasmussen and Lewin, Clin Infect Dis 2020; SenGupta, Science Trans Med 2021

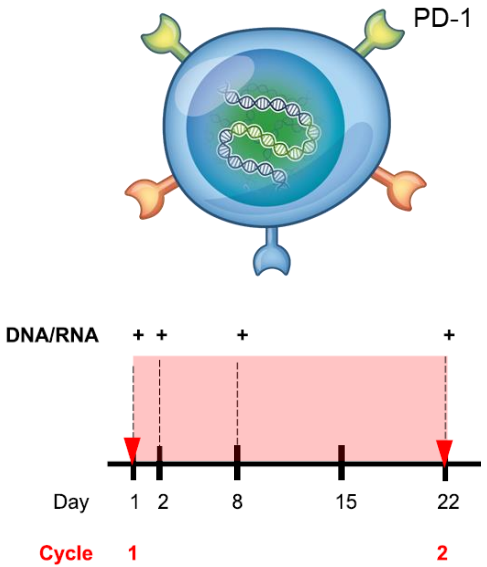
Immune checkpoints and HIV latency

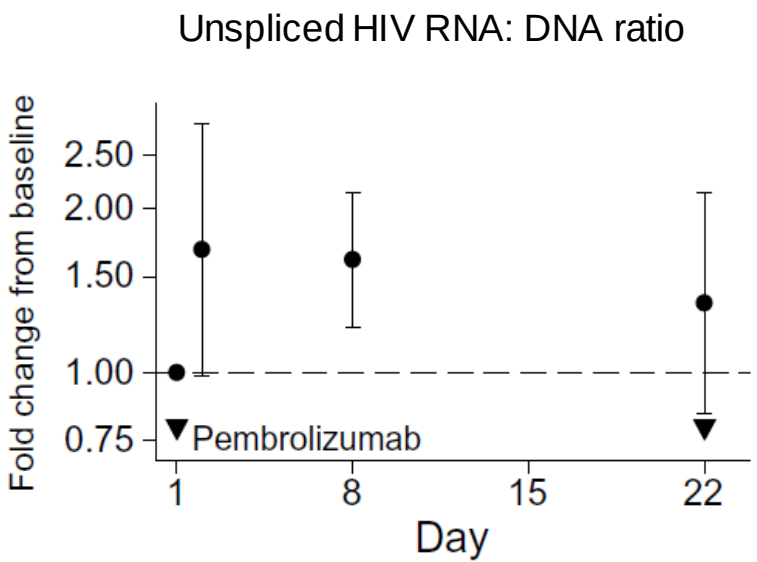


- PD-1 and CTLA-4, dampen the immune response and are expressed on exhausted T cells in treated and untreated HIV[1,2,3]
- Latent HIV is enriched in PD-1^{+} cells in blood and lymph nodes from people on ART and in both PD-1+ and CTLA4+ cells in non human primates on ART [4-7]
- Case reports of anti-PD1 in HIV-infected individuals on ART with cancer show a decline in infected cells [7,8,9]

1 Ahmed J Immunol 2010; 2 Day Nature 2006; 3 Chiu J Immunol 2022; 4 Chomont Nat Med 2010; 5 Fromentin PLoS Pathogens 2015; 6 Banga Nat Med 2016; 7 McGarry Immunity 2017; 8 Evans AIDS 2018; Chomont Nat Comms 2018; 9 Lau AIDS 2021

Anti-PD1 reverses HIV latency in vivo in PLWH on ART



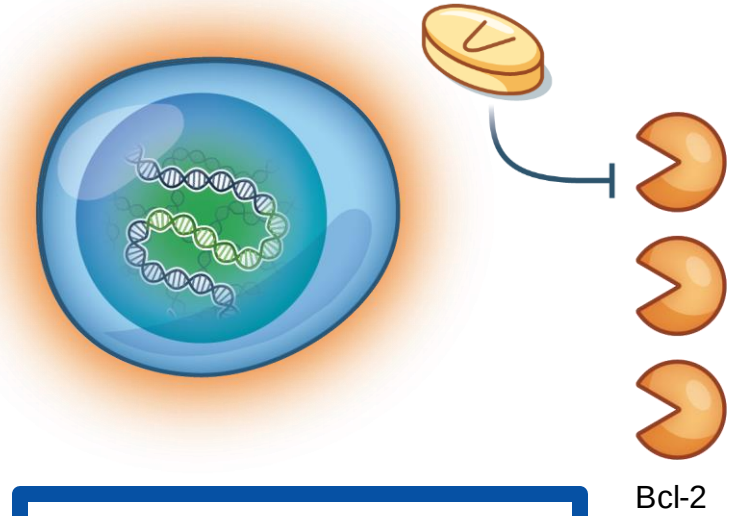


Dashed line indicates no change from baseline; and exclusion of dashed line from confidence interval indicates $P < 0.05$ by Wald test of regression coefficient

CITN12: n=35 PLWH with malignancy received pembrolizumab 200mg IV; 3 cohorts with low, intermediate and high CD4 counts. Toxicity profile similar to observations in HIV negative cohorts

Uldrick et al., JAMA Oncology 2018; Uldrick et al., Science Translational Medicine 2022

Pro-apoptotic drugs: BCL-2 antagonists



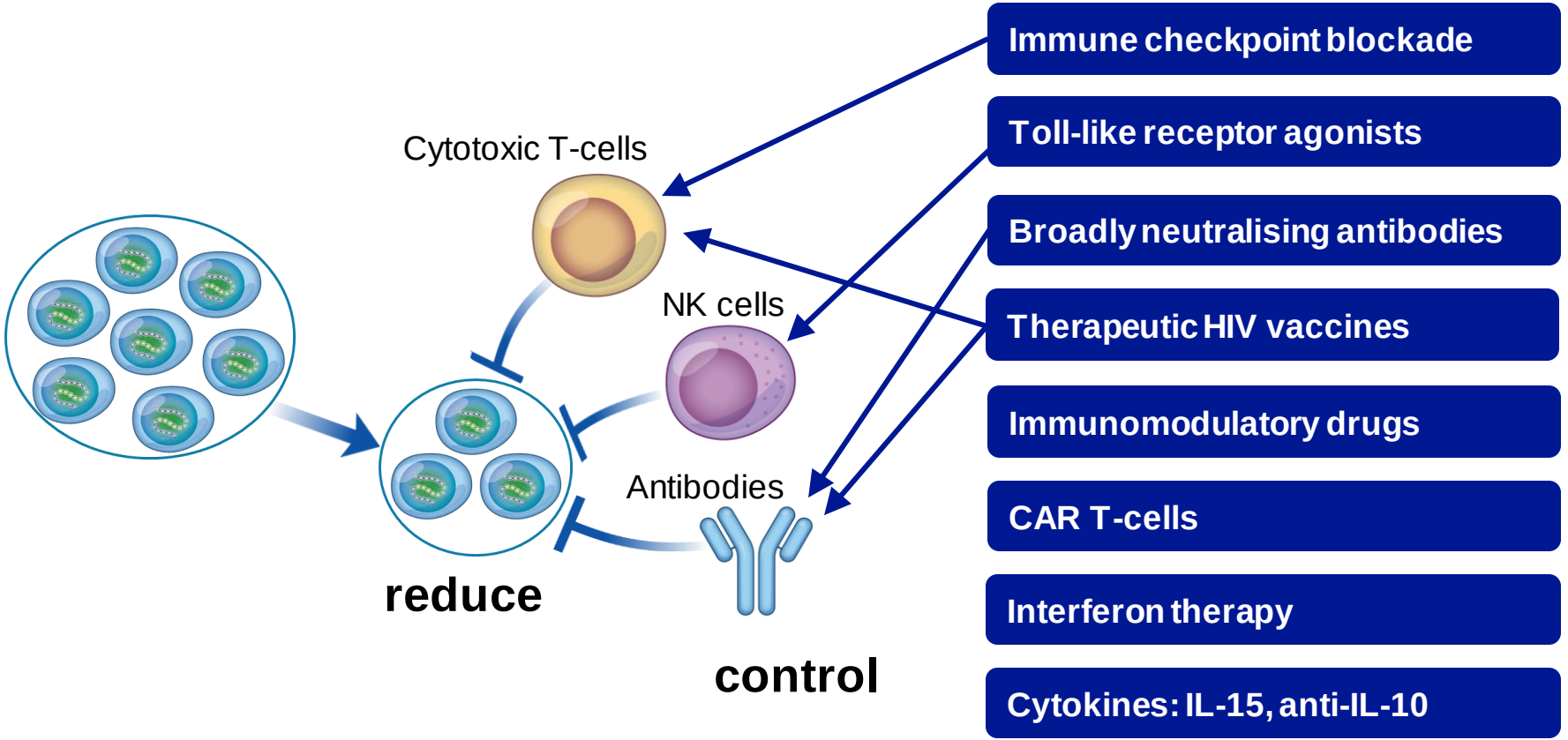
Latent infection

DNA positive
RNA negative
HIV protein negative
SURVIVAL

- Venetoclax is a **BCL-2 antagonist** and a licensed treatment for chronic lymphocytic leukemia[1]
- Ex vivo, venetoclax leads to the **enhanced selective death** of latently infected cells[2]
- Effect **enhanced** in the presence of
  - CD8+ T-cells[3]
  - Latency reversing agents[4]

1 Roberts et al., N Engl J Med 2016; 2 Cummins et al., J Virol 2017; 3 Ren at al., J Clin Inv 2020; 4 Kim et al., CROI2020, **abs 354**

Immunotherapies under investigation for HIV cure

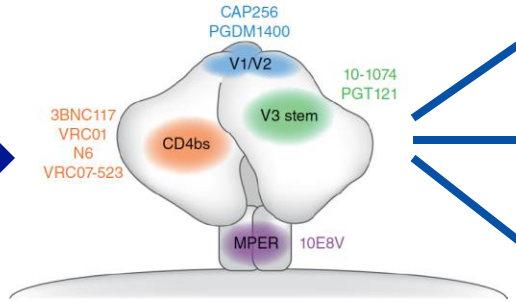


Rasmussen T, AIDS2022

Broadly neutralising antibodies (bNAbs) against HIV

Isolation of bNAbs in a minority of HIV-infected individuals

Technological advances in B-cell cloning → bNAb production



Caskey, Nature Medicine 2019

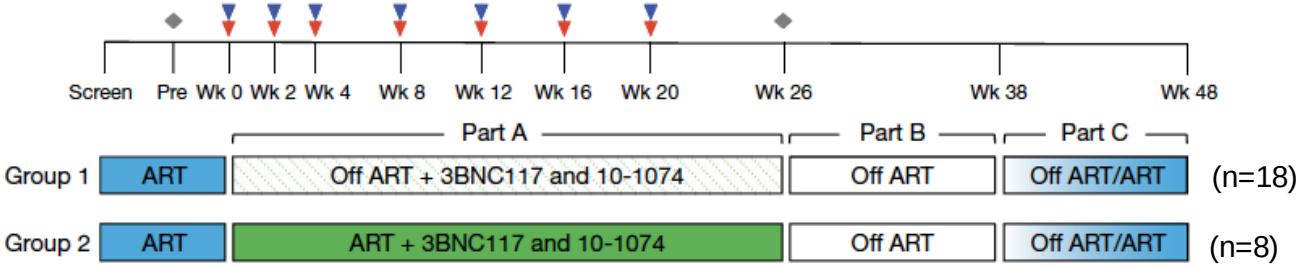
Many bNAbs identified and produced for clinical applications

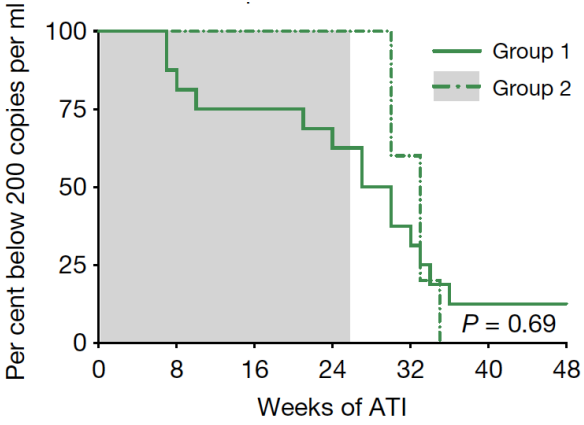
HIV prevention

HIV treatment

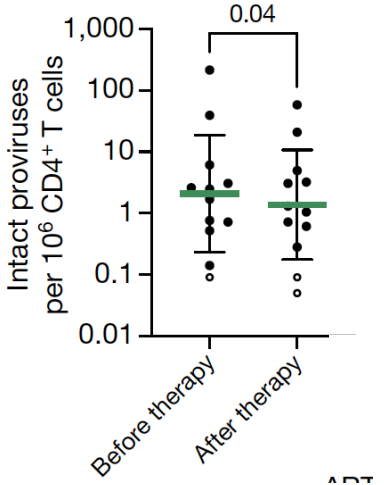
HIV cure

bNAbs provide long term viral suppression and can modestly reduce the reservoir





- Group 1: Median time to rebound 28.5 weeks
- No difference between group 1 and 2
- 2 participants remained aviremic at end of study



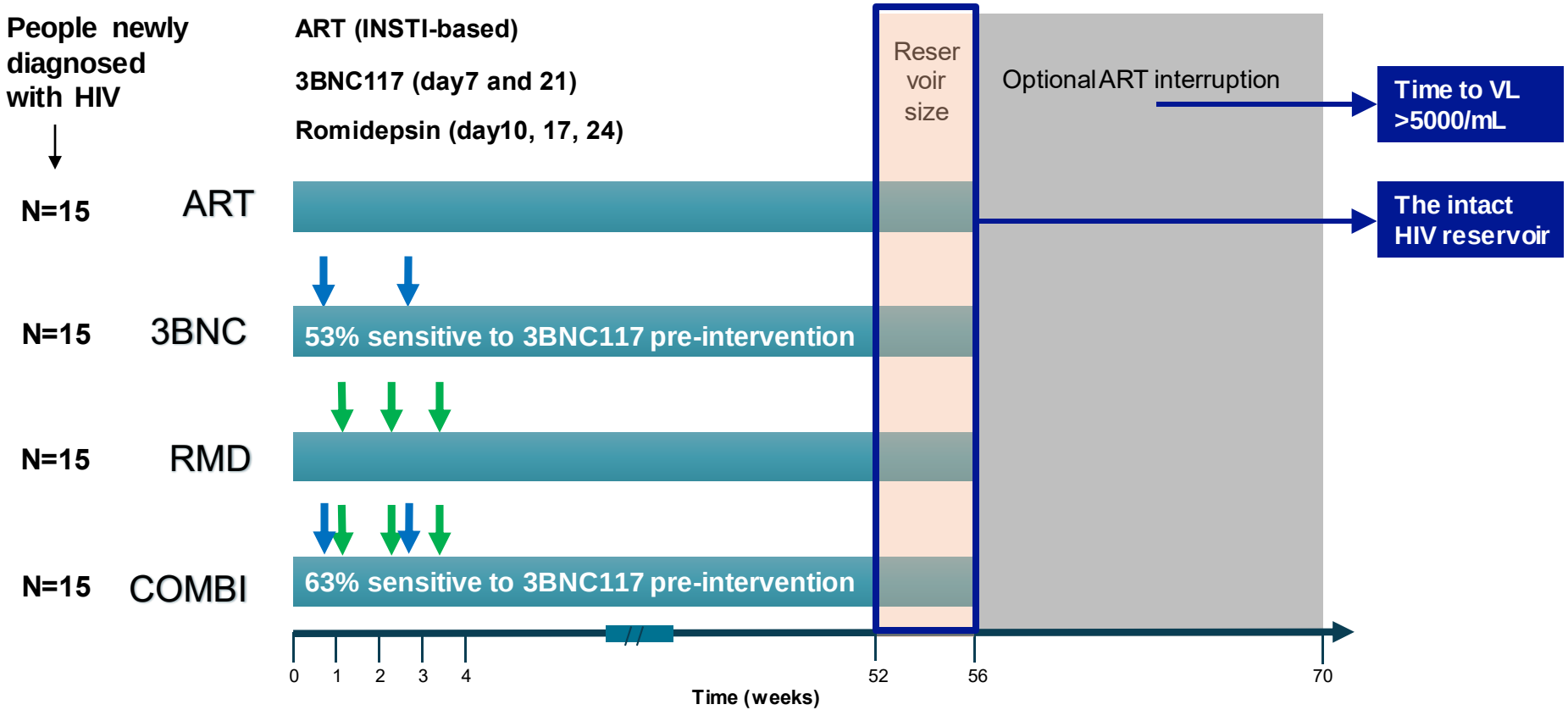
Gaebler Nature 2022

Combination immunotherapy: larger and/or randomised clinical trials currently underway

name	Reduce and control		Reservoir	ATI
RIVER[1]	vorinostat	Vaccine (ChAd)	No change	no
ROADMAP[2]	romidepsin	bNAb (3BNC)	No change	No change
TITAN	TLR9 agonist	bNAb (3BNC+10-1074)	Fully enrolled	yes

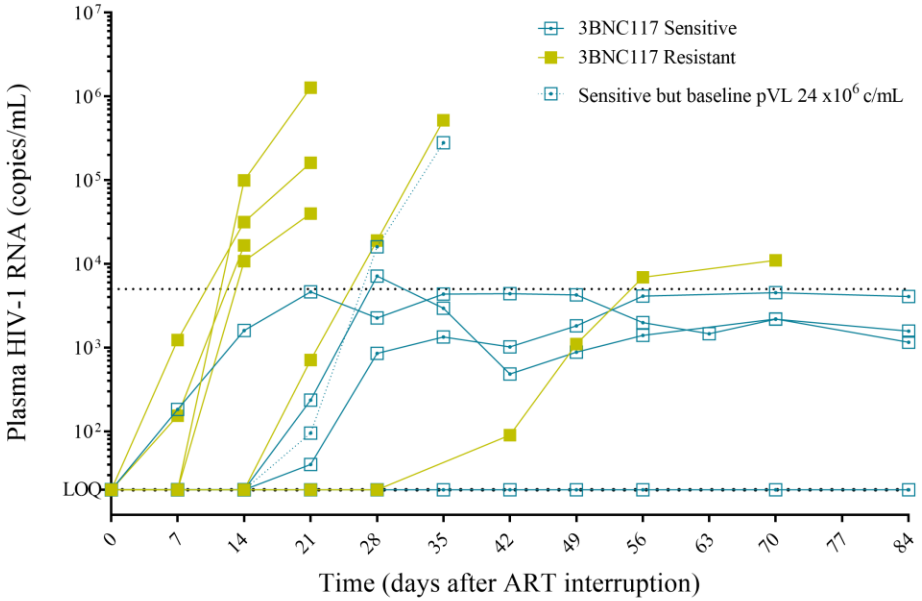
ATI = antiretroviral treatment interruption 1 Fidler et al., Lancet 2020; 2 Gruell Lancet Microbe 2022; 3 Sogaard CROI 2022

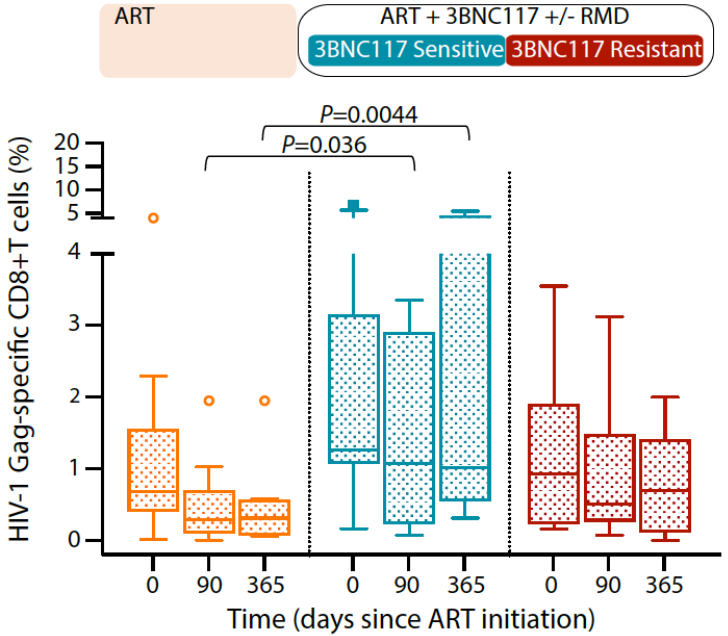
eCLEAR: 3BNC117 (bNAb) + romidepsin (LRA) at ART initiation



Sogaard CROI 2022

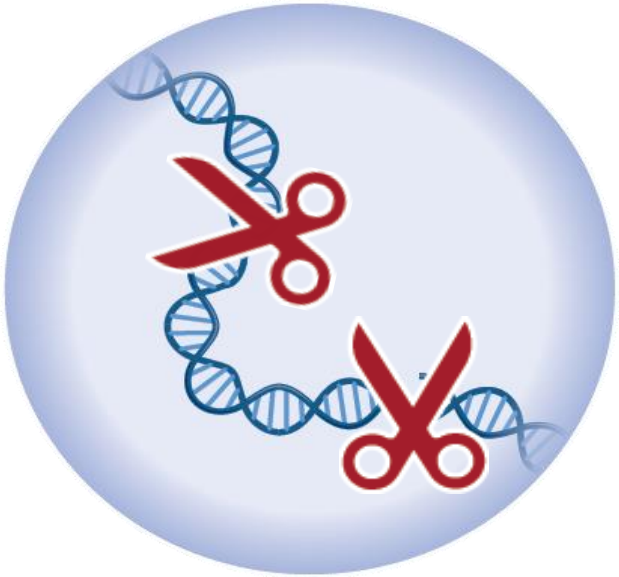
3BNC117 (bNab) enhances viral suppression off ART and boosts HIV-specific immunity





Sogaard CROI 2022

Gene therapy: targets and strategies



Attack: enhance anti-HIV immune responses

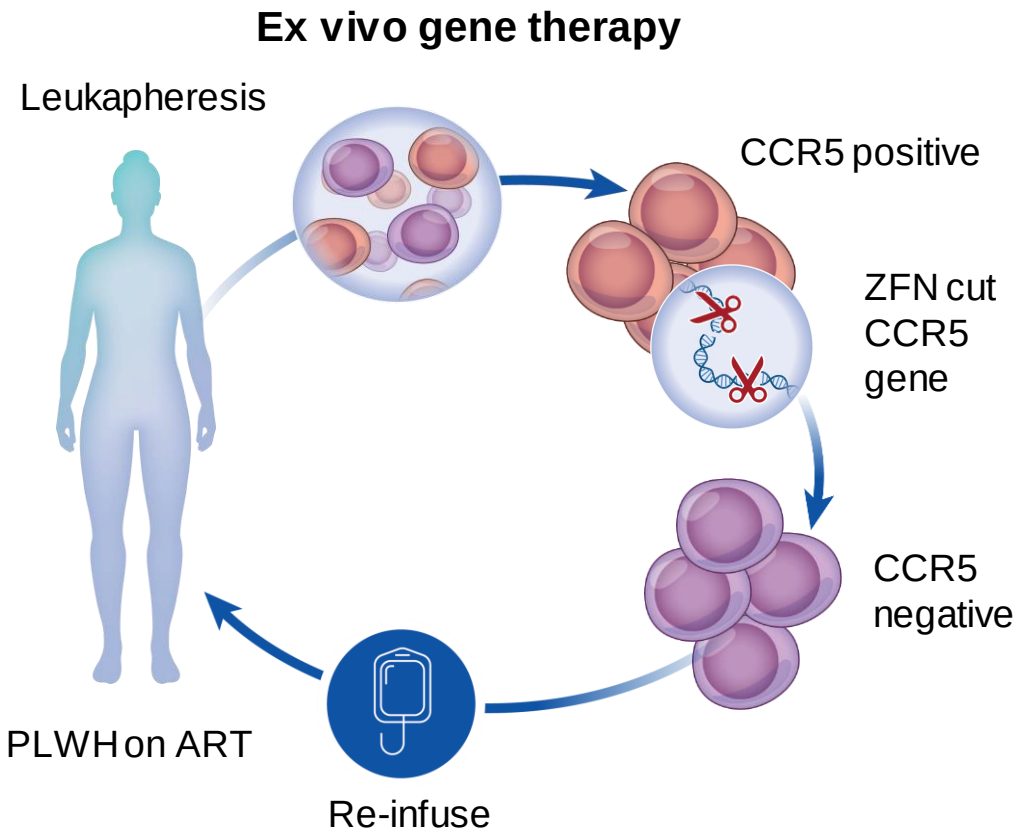
Protect: engineer uninfected cells to be resistant to HIV

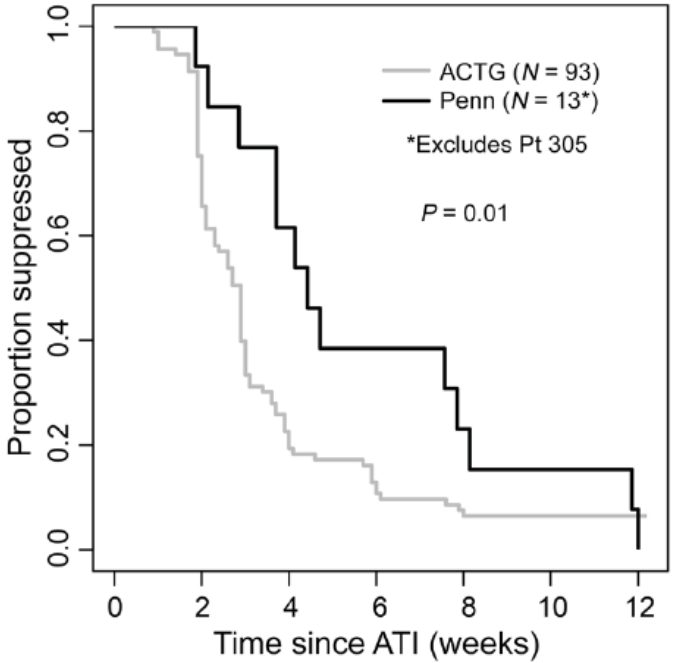
Purge: directly eliminate the virus itself

Delivery of gene therapy a major challenge :
ex vivo (gene editing of cells outside the body) or **in vivo** (gene editing in the body)

Slide courtesy of Paula Cannon

Gene therapy: ex vivo gene modification

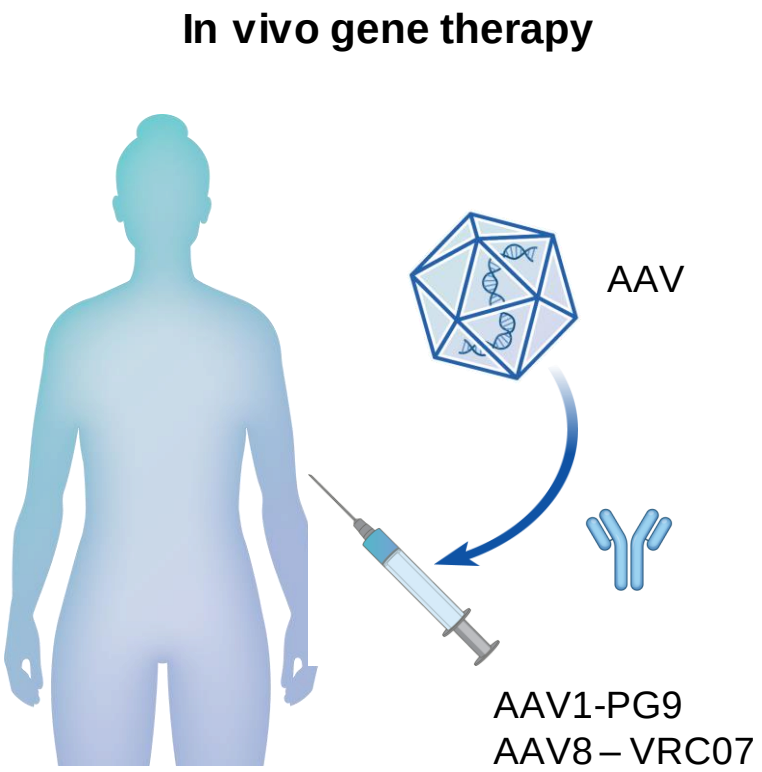


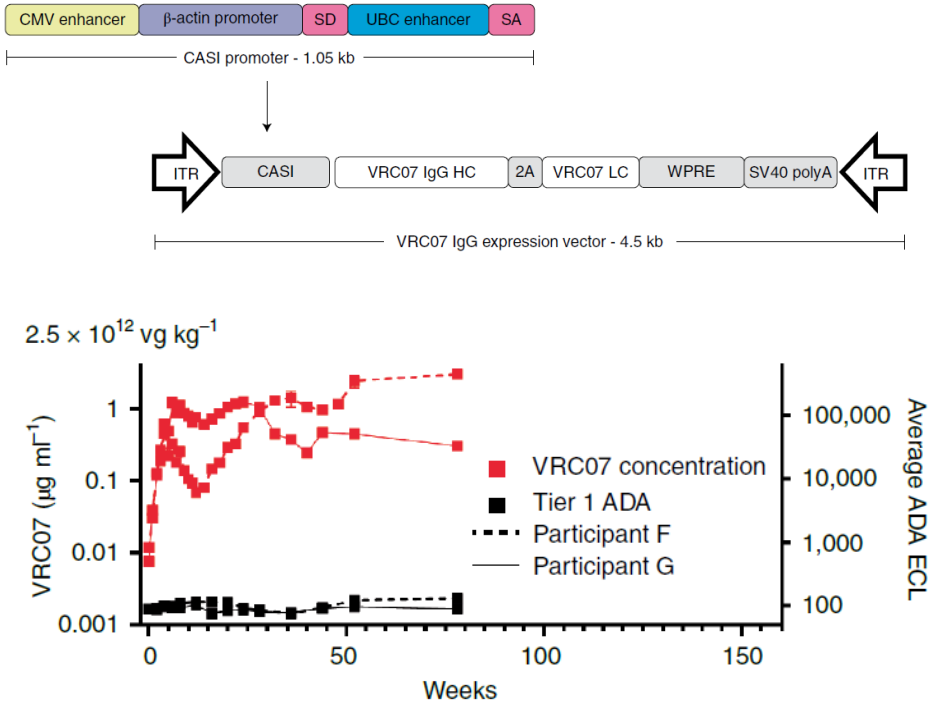


Participants were PLWH on ART who received ex vivo CCR5-modified cells (SB-728mRT) ± cyclophosphamide had delayed time to viral load rebound after interruption of ART

Tebas et al., N Engl J Med 2014; Xu et al., N Engl J Med 2019; Tebas et al., J Clin Inv 2021

Gene therapy: in vivo modification





Priddy et al., Lancet HIV 2019; Casazza Nat Med 2022

In vivo gene therapy for SIV/HIV with CRISPR-Cas9

nature COMMUNICATIONS

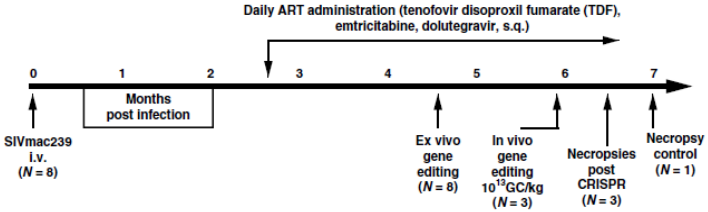
ARTICLE

https://doi.org/10.1038/s41467-020-19821-7 OPEN

Check for updates

CRISPR based editing of SIV proviral DNA in ART treated non-human primates

Pietro Mancuso[1], Chen Chen[1], Rafal Kaminski[1], Jennifer Gordon[1], Shuren Liao[1], Mandy D. Smith[1], Hong Liu[1], Ilker K. Sariyer[1], Rahsan Sariyer[1], Tiffany A. Peterson[2], Jaclyn B. Williams[2], Summer Siddiqui[2], Bruce A. Bunnell[2,3,4,5], Binhua Ling[2,6,7✉], Andrew G. MacLean[2,3,6✉], Tricia H. Burdo[1✉] & Kamel Khalili[1✉]

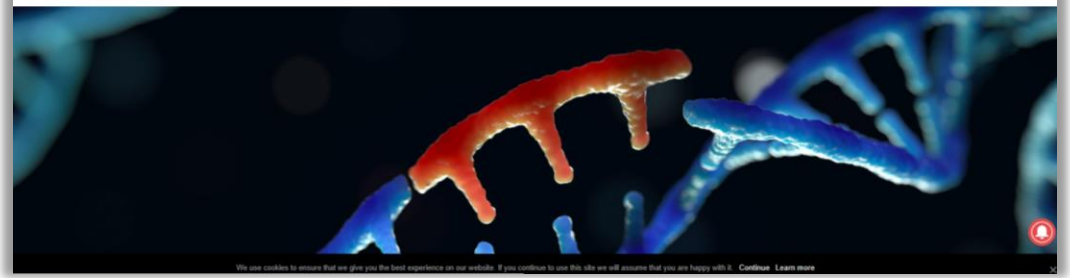


NEWS

FDA approves first trial investigating CRISPR gene editing as HIV cure

By Kezia Parkins | 16 Sep 2021

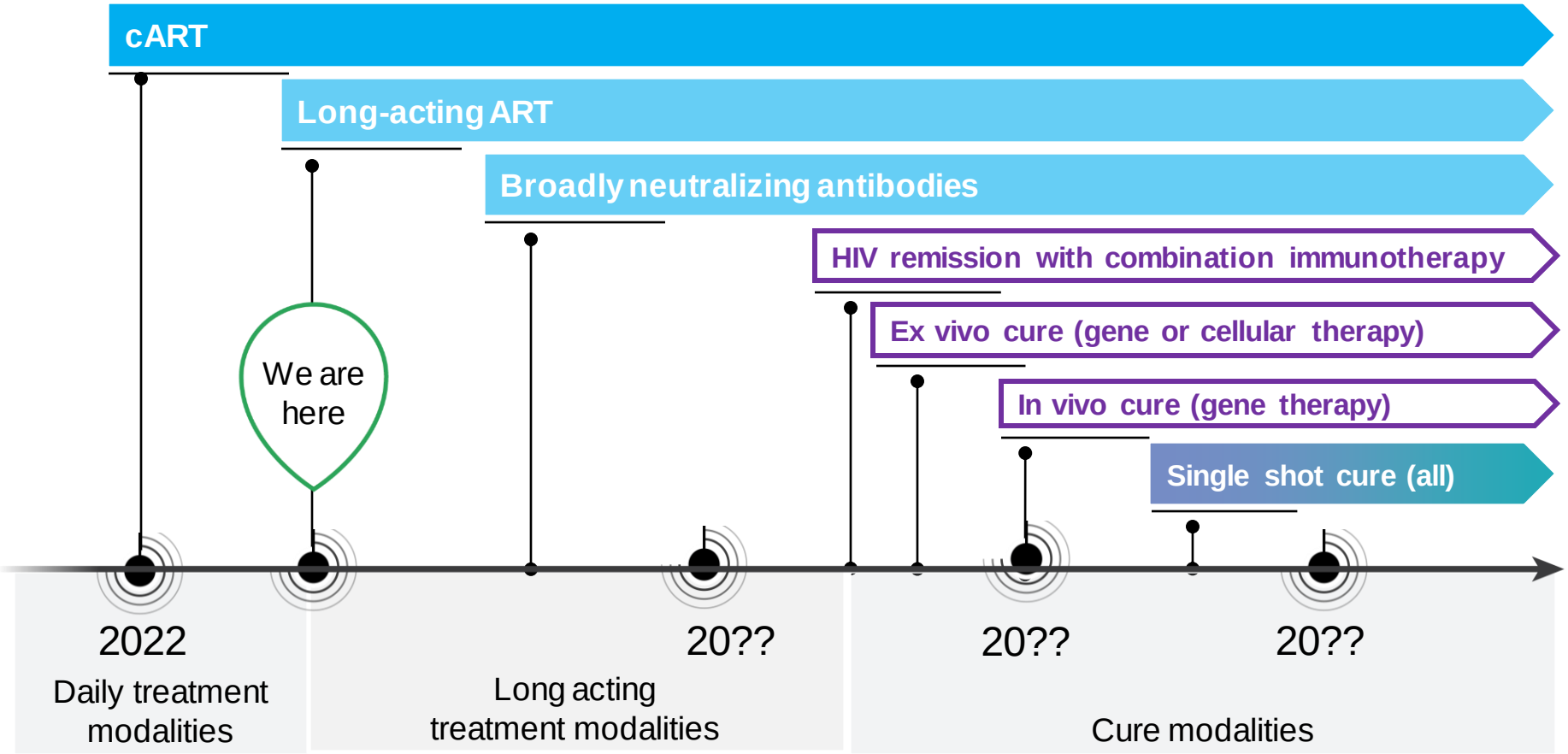
A new paradigm for HIV treatment is on the horizon as FDA gives nod for startup to begin trials of CRISPR-based gene therapy.



Excision Biotherapeutics: first-in-human Phase I/II trial to evaluate the safety, tolerability and efficacy of EBT-101 in healthy individuals living with HIV. EBT-101 uses Adeno Associated virus (AAV), CRISPR-Cas9 plus 2 x gRNAs

First patient enrolled in September 2022

Current and future landscape for HIV treatment



Summary and implications for future directions

- The **HIV reservoir is dynamic** and is made up of truly latent and transcriptionally active cells which can also undergo clonal expansion.

- **Latency reversal agents alone** don't reduce the reservoir and therefore need to be combined with other agents that directly kill the infected cell. Some of the newer latency reversing agents also have immunomodulatory activities such as TLR agonists and immune checkpoint blockers

- New strategies for delivery of **gene therapy** in vivo using Adeno Associated Virus or Lipid Nanoparticles (LNP) are a major advance for implementation and are of high interest

- We remain far from a cure for HIV but ongoing discussions about a **target product profile** for a cure is needed now to ensure that any advance will be delivered quickly to those at highest need and acceptable to the community

nature medicine

REVIEW ARTICLE

https://doi.org/10.1038/s41591-021-01590-5

Check for updates

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*

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Cancer Immunotherapy Network
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Becky Ho
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Rachel Rutishauser
Peter Baccheti
Rick Hecht

Oregon Health Sciences University
Afam Okoye
Louis Picker
Jake Estes
Lydie Trauttman

Australian Government
National Health and Medical Research Council

D&RE

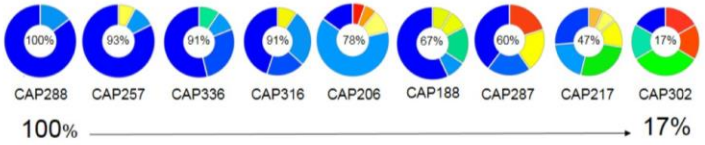
NHMRC

NIH National Institute of Allergy and Infectious Diseases

amfAR
MAKING AIDS HISTORY

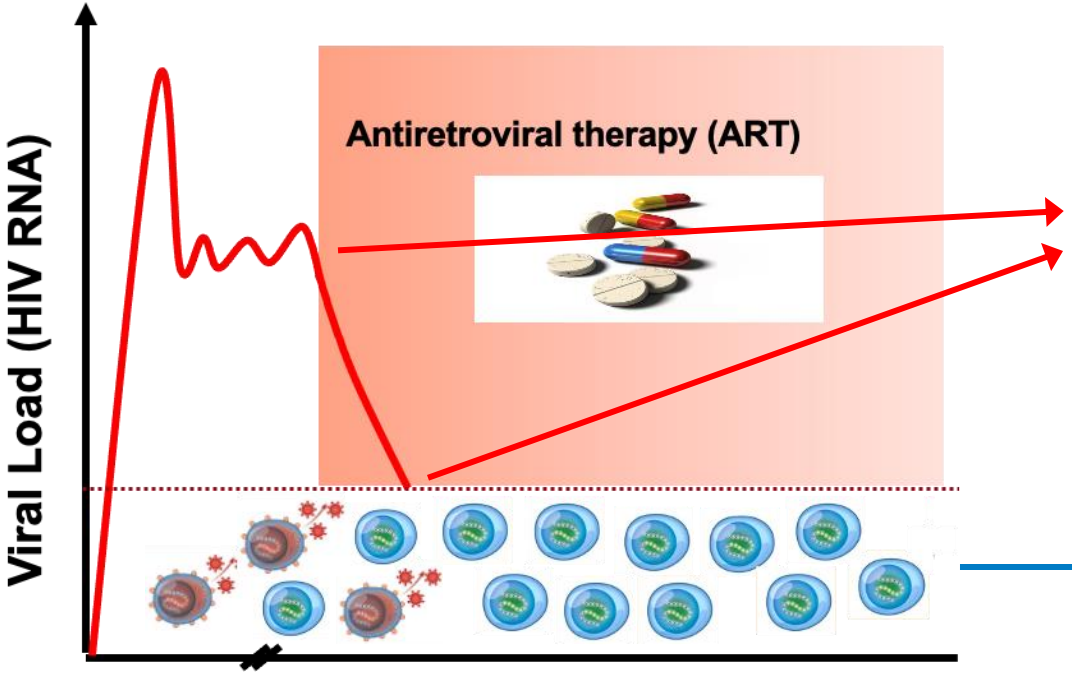
ACH2 Australian Centre for HIV and Hepatitis Virology Research

Are we targeting the reservoir at the right time?



- The size and composition of the latent HIV reservoir is seeded at the time of ART initiation

Abrahams, Science Transl Med 2019



Immunotherapies relying on antigen expression may have greater efficacy if delivered during viremia?

Most cure studies to date have tested interventions in the setting of long-term viral suppression by ART