Towards an HIV Cure:

Understanding HIV Persistence and Therapeutic Approaches

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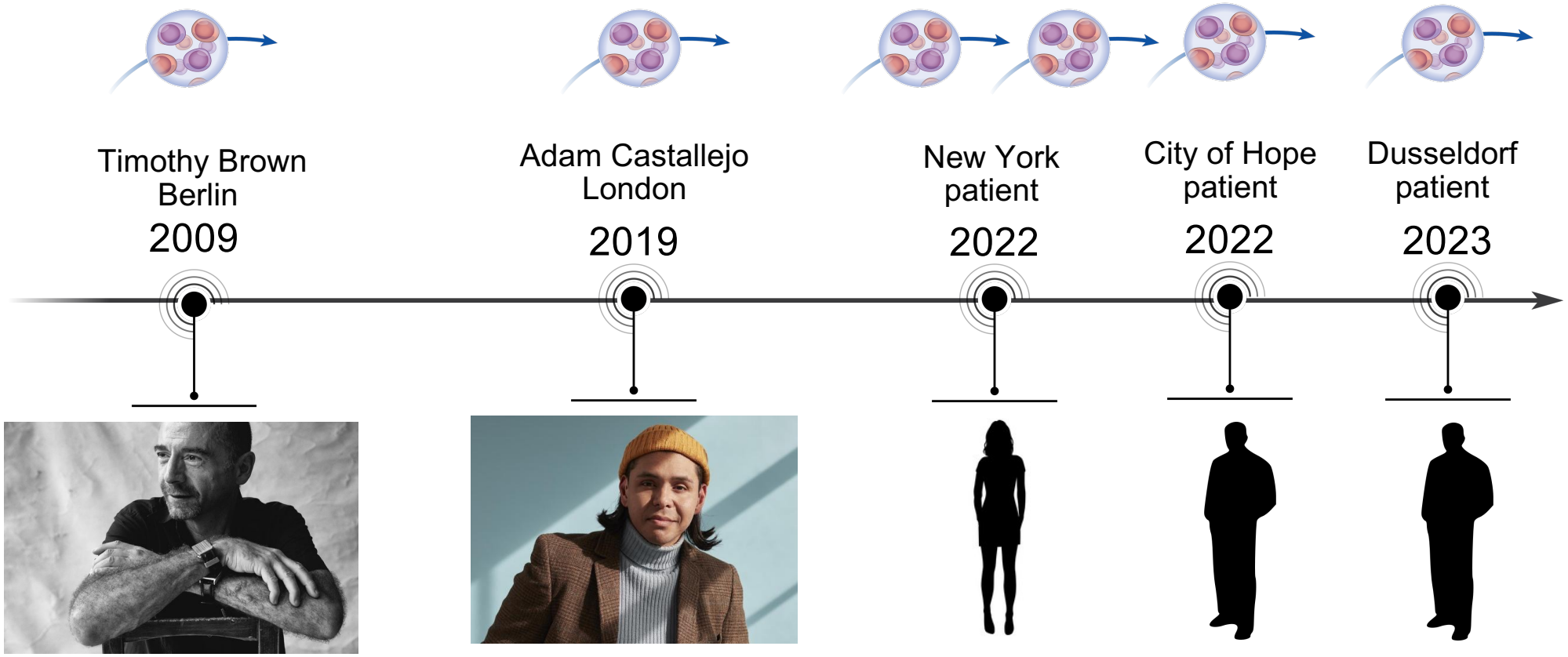
International Co-Chair IAS2023 (Brisbane, AUS) & AIDS2024 (Munich, DEU)

This activity is jointly provided by Physicians' Research Network and the Medical Society of the State of New York.

Outline

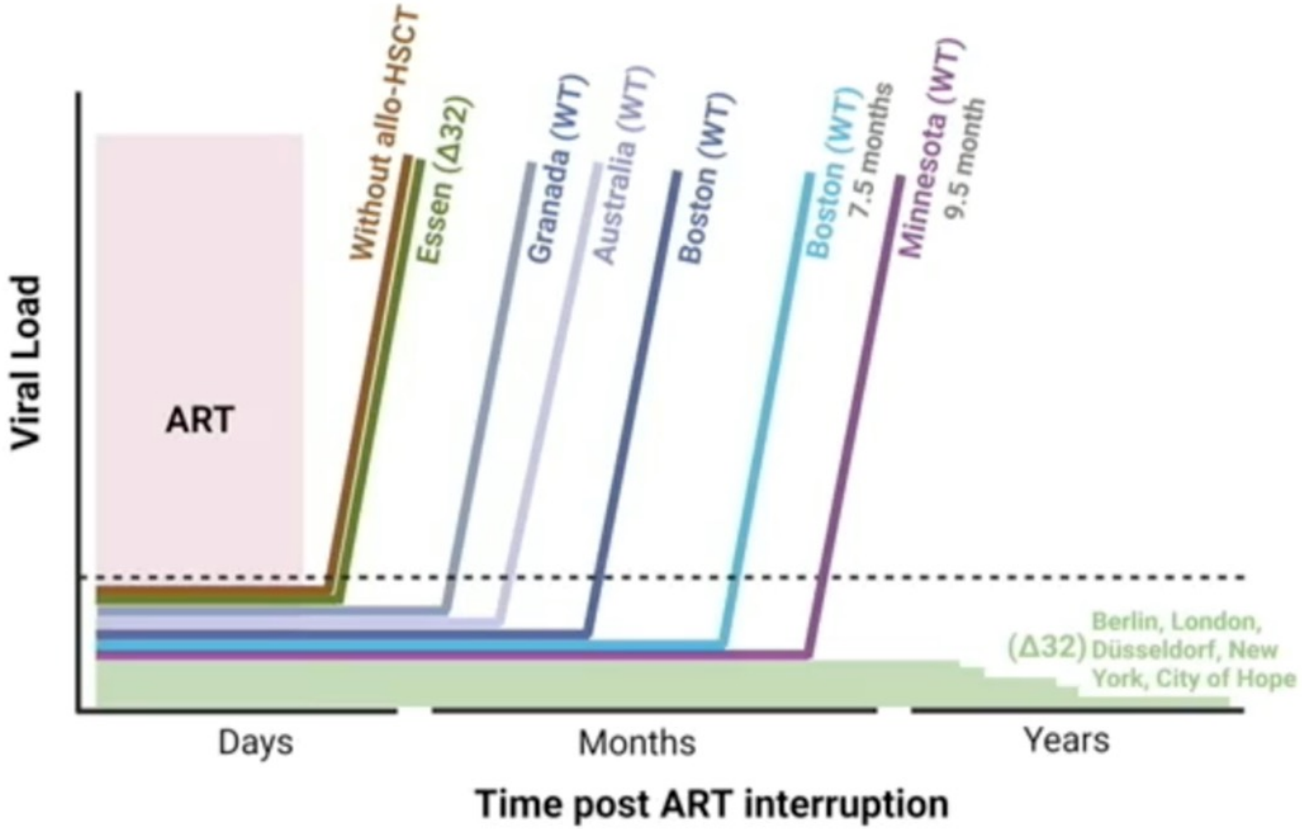
- **Case reports of an HIV cure**
- **New concepts in understanding HIV latency**
- **Clinical strategies for an HIV cure and new studies**
  - Latency reversal
  - Combination immunotherapy
  - Gene therapy
- **Implementation of an HIV cure**

HIV cure is extremely rare but possible: transplantation



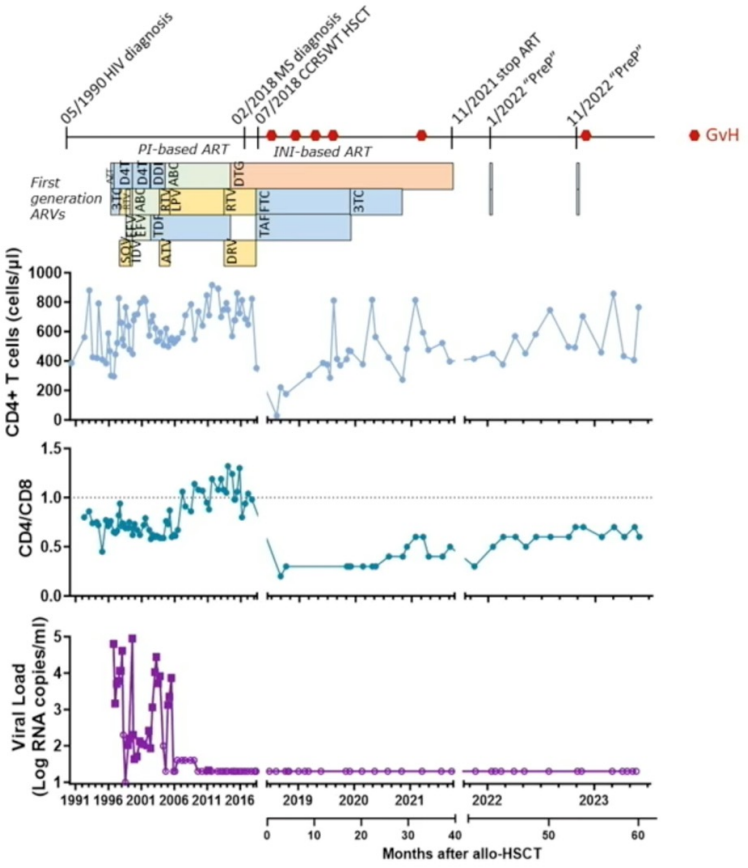
Hutter, N Engl J Med 2010; Gupta, Nature 2019; Gupta, Lancet HIV 2019; Jensen Nature Med 2023; Bryson, CROI 2022; Dickter IAS2022

Wild type donors for transplantation have not resulted in viral control beyond 9 months



Henrich Ann Int Med 2014; Kordelas NEJM 2014; Koelsch JAIDS 2017; Cummins Plos Med 2017; Eberhard Sci Tranl Med 2022; Salgado IAS2023

The Geneva patient: viral control post wild type HSCT



- Male diagnosed with HIV in 1990
- Continuous viral suppression since 2005
- Biphenotypic sarcoma (extramedullary myeloid tumor) in 2018
- Total body irradiation + chemotherapy + allo-HSCT July 2018
- Acute and chronic **graft versus host disease**
- Complex immunosuppression (including **ruxolitinib**, a JAK1-2 inhibitor)
- Stopped ART November 2021 with
  - No viral load rebound
  - No intact virus in blood or GI tract
  - Using on-demand PREP for prevention

Salgado et al IAS2023, Brisbane, Australia July 24-27th., 2023

HIV cure is extremely rare but possible: natural control

VISCONTI
SPARTAC
CHAMP

Post treatment control (remission)

Timothy Brown
Berlin
2009

2010

Adam Castallejo
London
2019

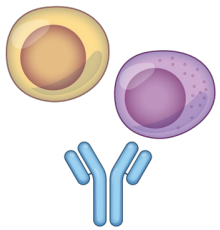
2020

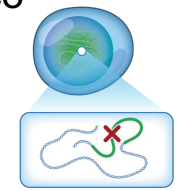
Lorraine
Willenberg
San Francisco

2021

The Esperanza
patient

The New York
patient
2022

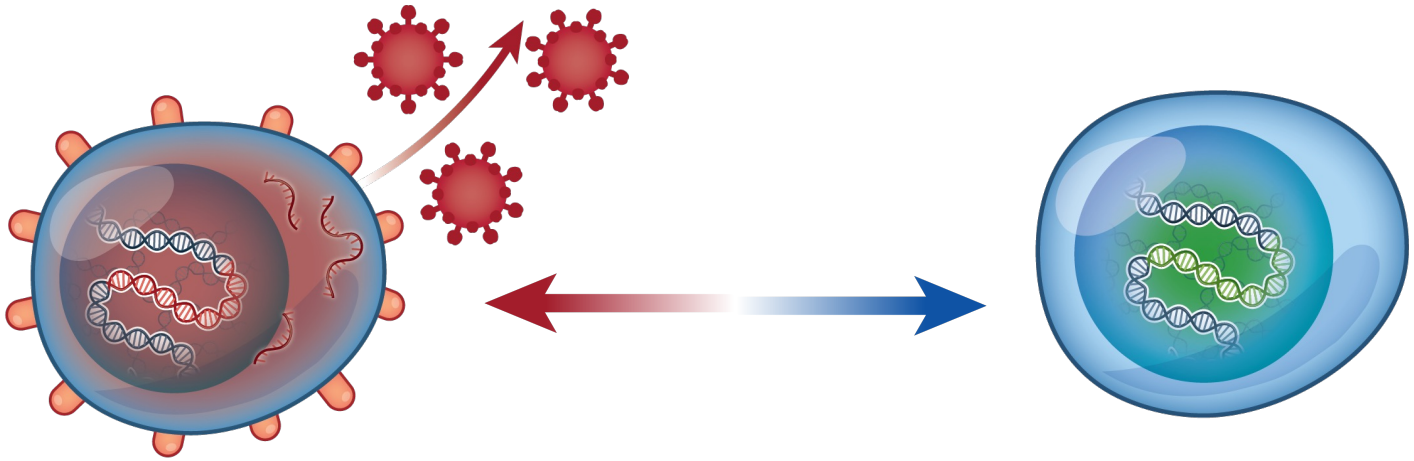




Hutter, N Engl J Med 2010; Gupta, Nature 2019; Gupta, Lancet HIV 2019; Bryson, CROI 2022; Jiang Nature 2020; Turk Annals Int Med 2021

New concepts in understanding HIV latency

Two major forms of HIV infected cells



Productive infection

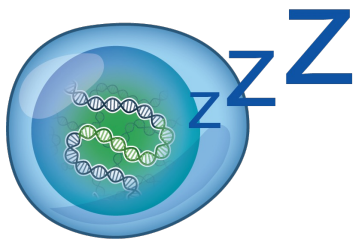
DNA positive
RNA positive
HIV protein positive
DEATH

Latent infection

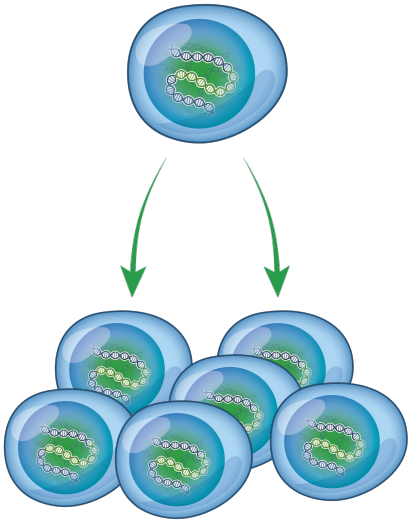
DNA positive
RNA negative
HIV protein negative
SURVIVAL

New concepts in HIV persistence and latency

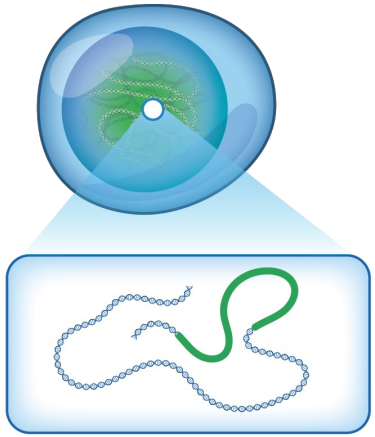
1.
Reservoir ‘activity’



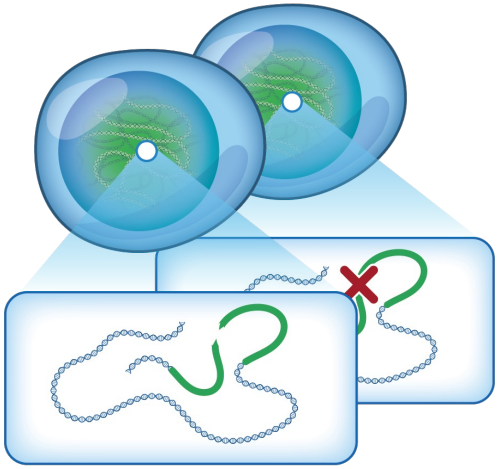
2.
Proliferation



3.
Position matters

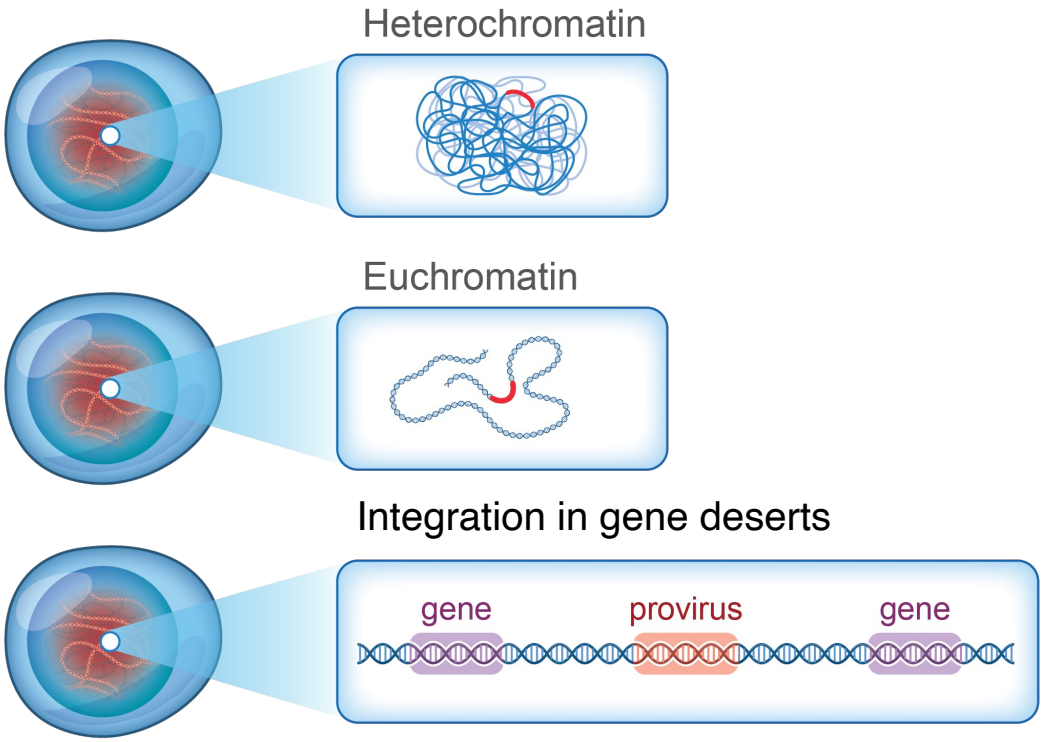


4.
Defective and
intact virus



Bekker LG, Nat Rev Primer 2023

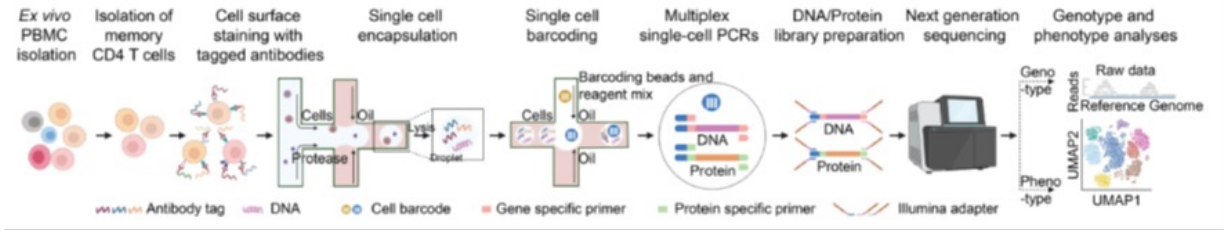
Position matters: HIV integration is important for virus transcription…..allowing it to stay silent or activate



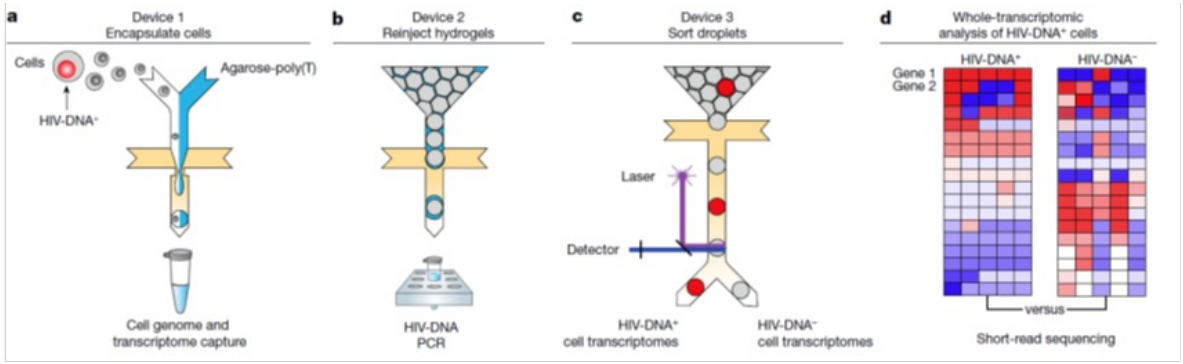
- Integration sites determine the likelihood of a virus being active or silent[1,2]
- In elite controllers, intact virus more commonly found in gene deserts ie limited or no transcription[3,4]
- Over prolonged ART, there is loss of transcriptionally active cells, leaving more deeply latent cells – some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

Single cell technologies are transforming our understanding of HIV latency

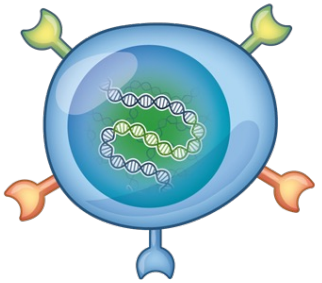


Phenotypic and proviral sequencing (**PheP-Seq**)
Sun et al Nature 2023

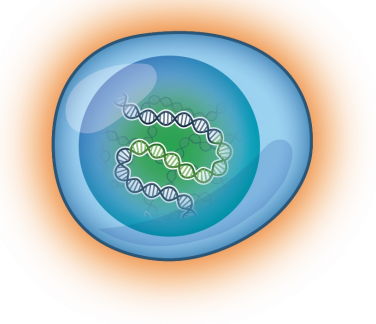


Focused interrogation of cells by nucleic acid detection and sequencing (**FIND-seq**)
Clarke Nature 2023

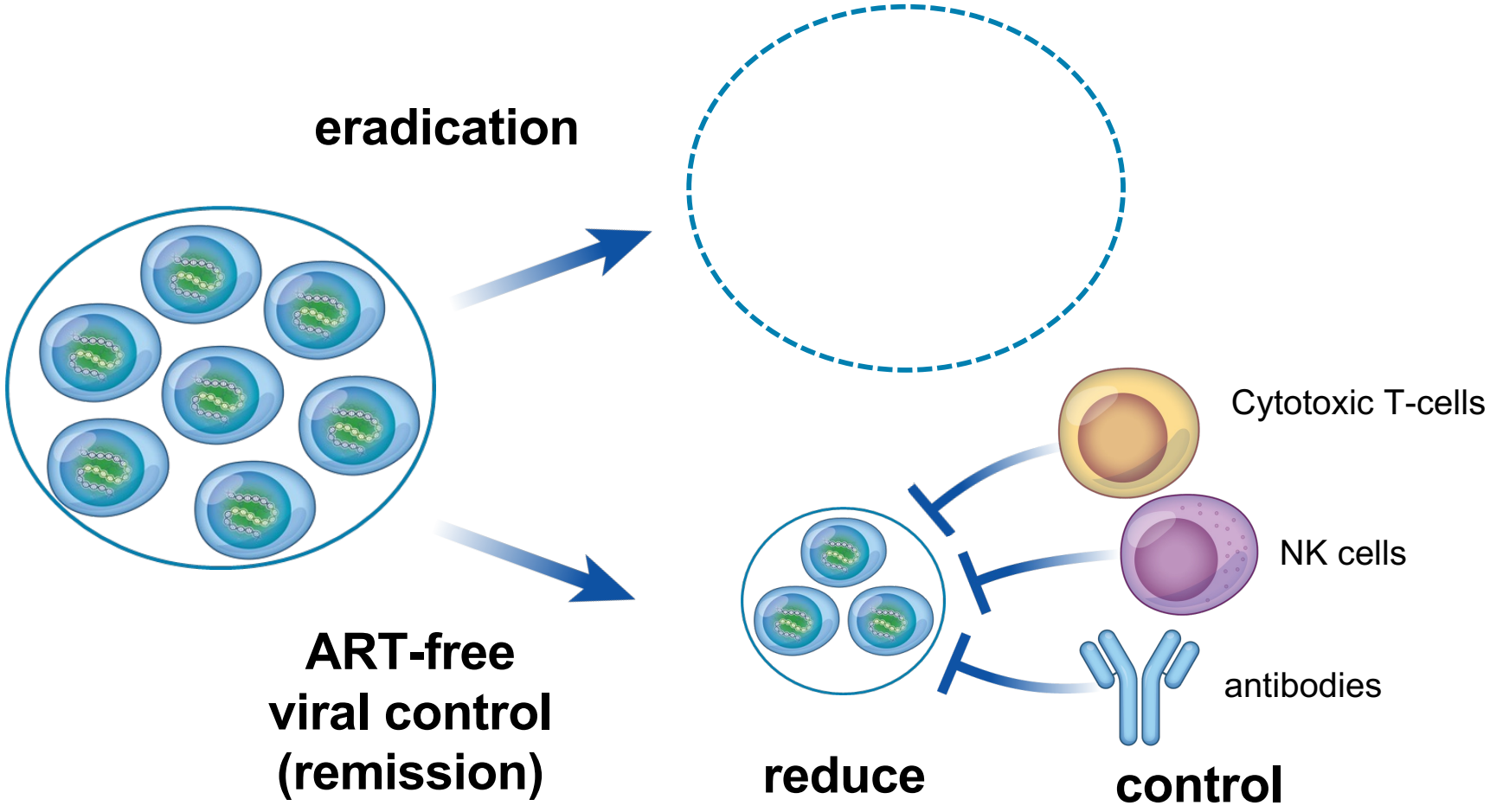
5. Evade immunity



6. Primed to survive

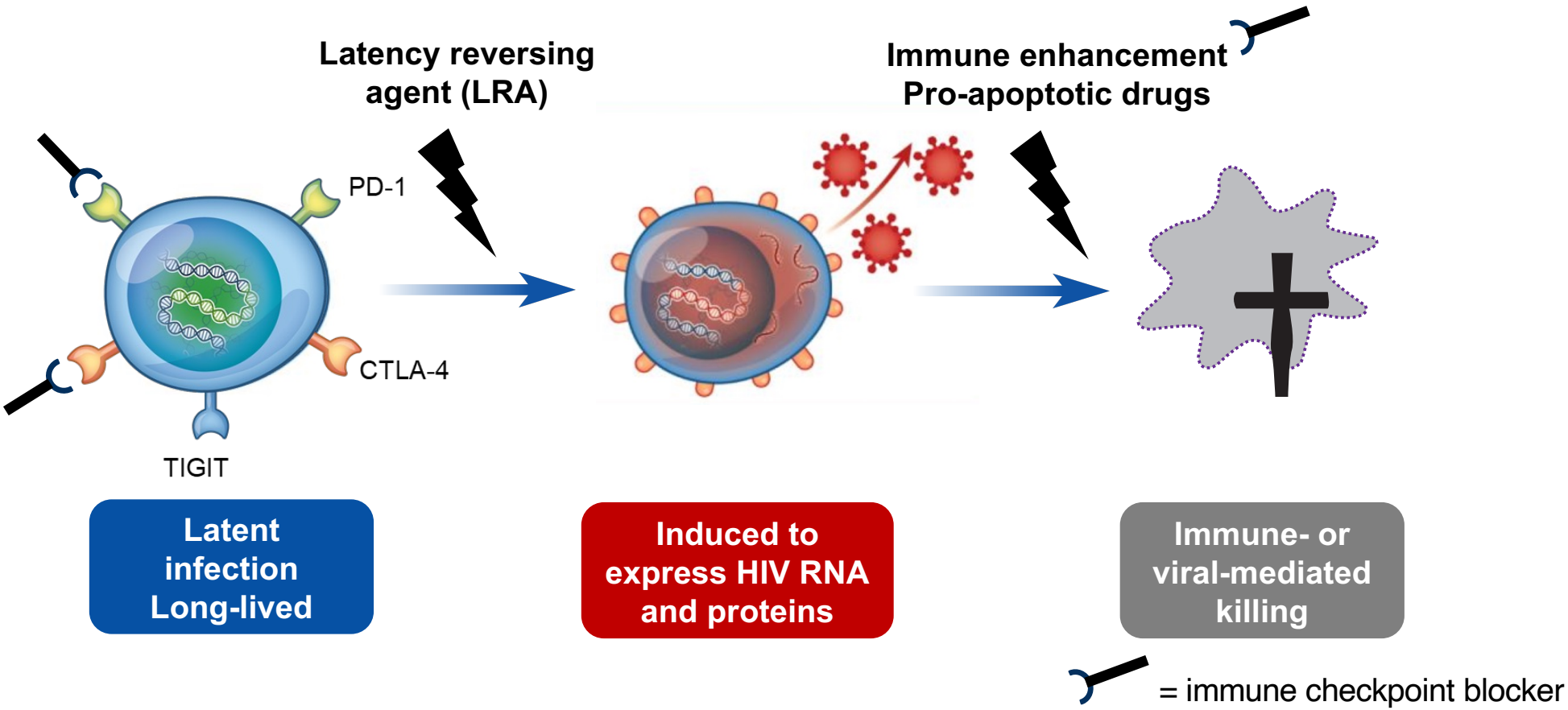


Overarching goals of cure strategies



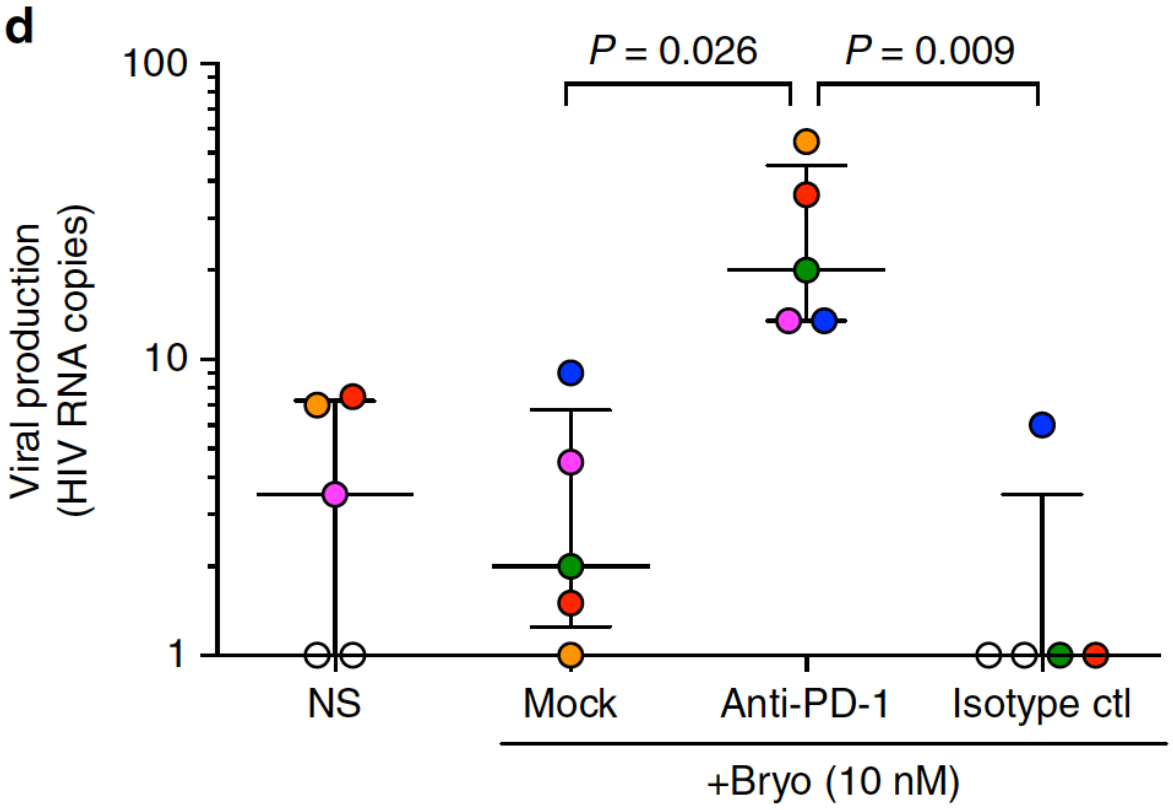
Latency reversal: shock and kill

HIV latency reversal: shock and kill



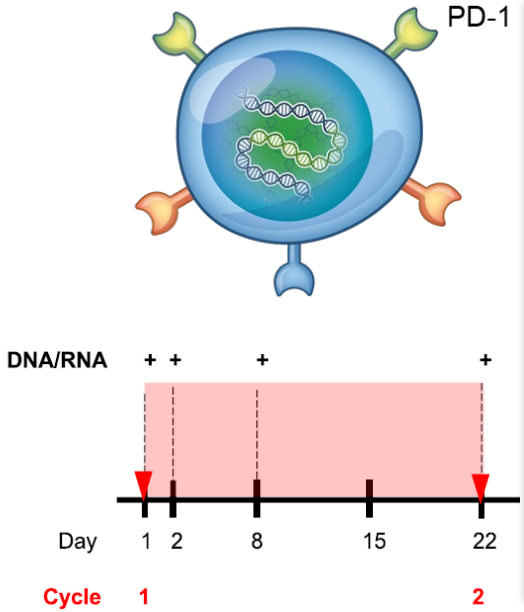
Chomont Nat Med 2010; Fromentin PLoS Pathogens 2015; Fromentin Nat Comms 2018; Rasmussen Cell Rep Med 2022

Anti-PD-1 enhances latency reversal *ex vivo*



Fromentin, Chomont et al, Nature Communication 2019

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



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

HIV

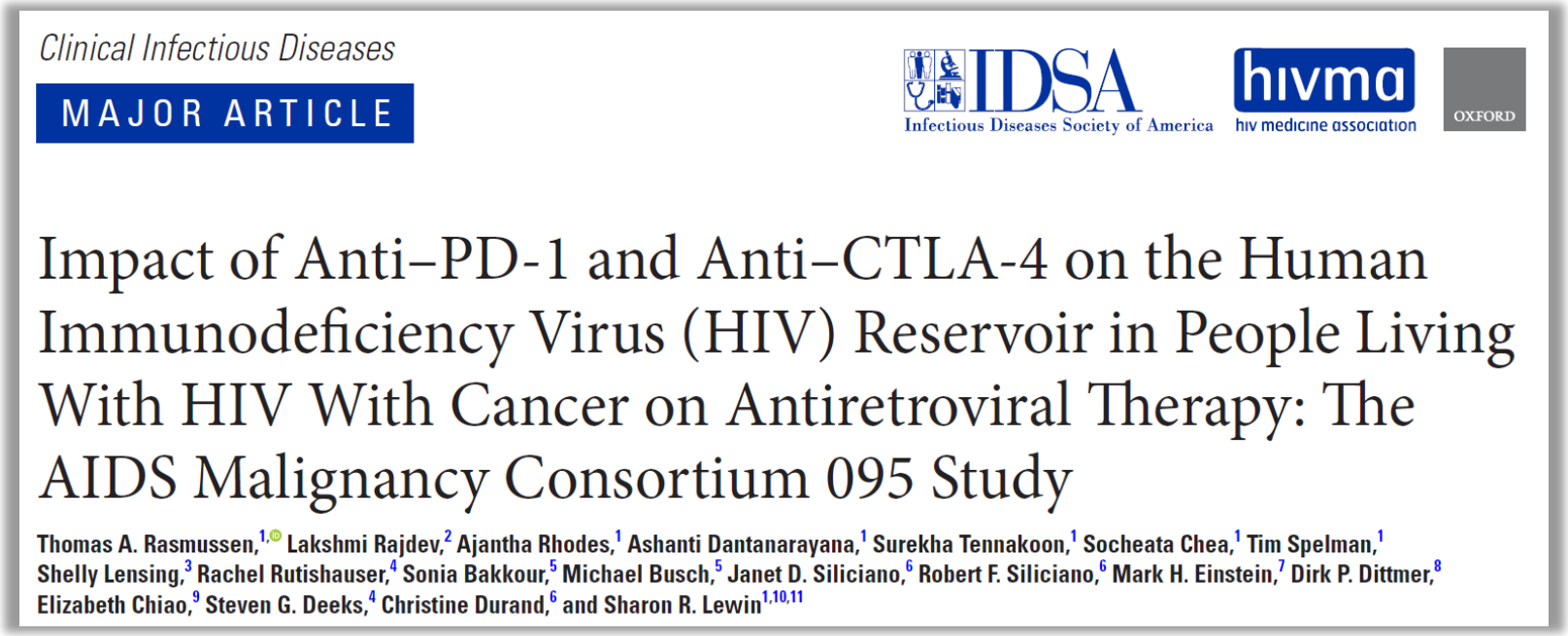
Pembrolizumab induces HIV latency reversal in people living with HIV and cancer on antiretroviral therapy

Thomas S. Uldrick[1,2,3]*, Scott V. Adams[1], Remi Fromentin[4], Michael Roche[5,6], Steven P. Fling[1], Priscila H. Gonçalves[3], Kathryn Lurain[3], Ramya Ramaswami[3], Chia-ching Jackie Wang[7], Robert J. Gorelick[8], Jorden L. Welker[8], Liz O'Donoghue[1], Harleen Choudhary[1], Jeffrey D. Lifson[8], Thomas A. Rasmussen[6,9], Ajantha Rhodes[6], Carolin Tumpach[6], Robert Yarchoan[3], Frank Maldarelli[3], Martin A. Cheever[1]†, Rafick Sékaly[10], Nicolas Chomont[4], Steven G. Deeks[7], Sharon R. Lewin[6,11,12]*

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

Anti PD1 with anti CTLA4 has greater potency in latency reversal



Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

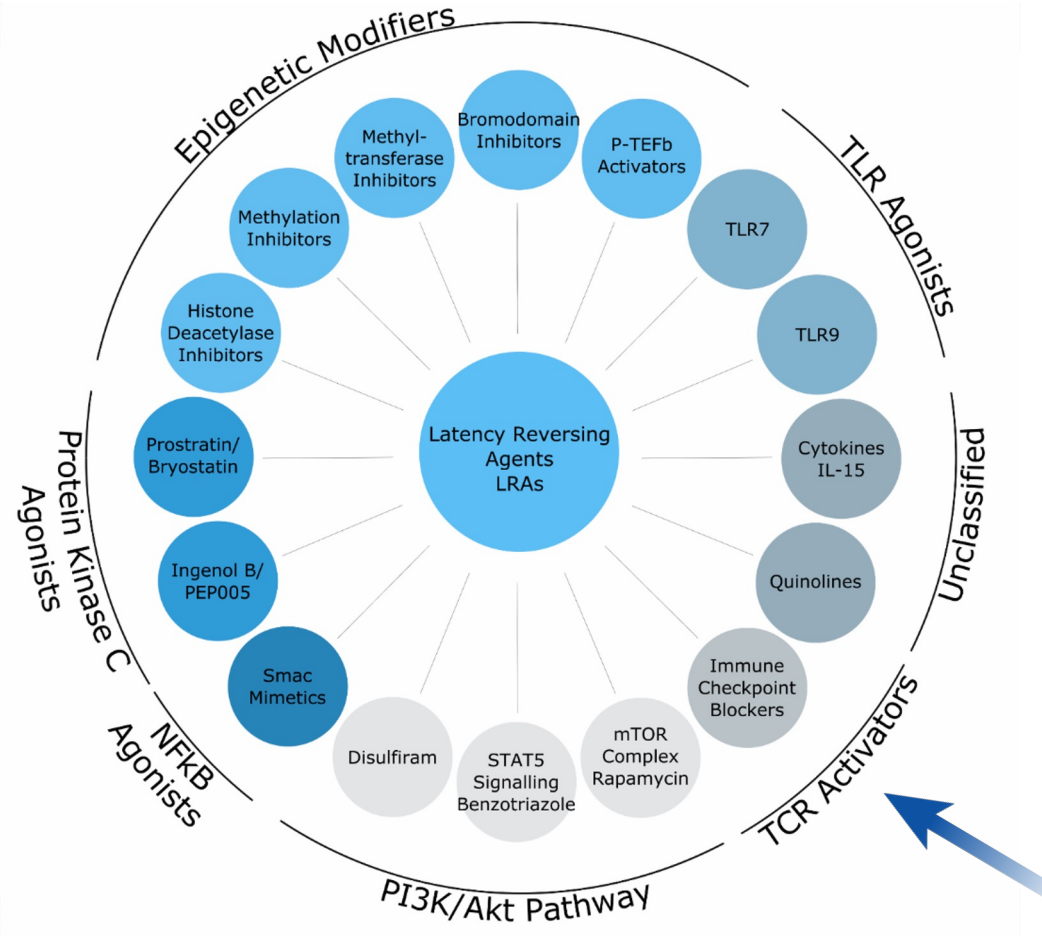
Impact of Anti–PD-1 and Anti–CTLA-4 on the Human Immunodeficiency Virus (HIV) Reservoir in People Living With HIV With Cancer on Antiretroviral Therapy: The AIDS Malignancy Consortium 095 Study

Thomas A. Rasmussen,[1] Lakshmi Rajdev,[2] Ajantha Rhodes,[1] Ashanti Dantanarayana,[1] Surekha Tennakoon,[1] Socheata Chea,[1] Tim Spelman,[1] Shelly Lensing,[3] Rachel Rutishauser,[4] Sonia Bakkour,[5] Michael Busch,[5] Janet D. Siliciano,[6] Robert F. Siliciano,[6] Mark H. Einstein,[7] Dirk P. Dittmer,[8] Elizabeth Chiao,[9] Steven G. Deeks,[4] Christine Durand,[6] and Sharon R. Lewin[1,10,11]

Significant **increase in cell associated unspliced HIV RNA** in participants receiving ant1-PD1 and anti-CTLA4 with **reduction in the HIV reservoir** (frequency of cells with infectious virus) after multiple doses in two participants. Toxicity of anti-CTLA4 means this cant be further progressed.

Rasmussen et al Clin Infect Dis 2021

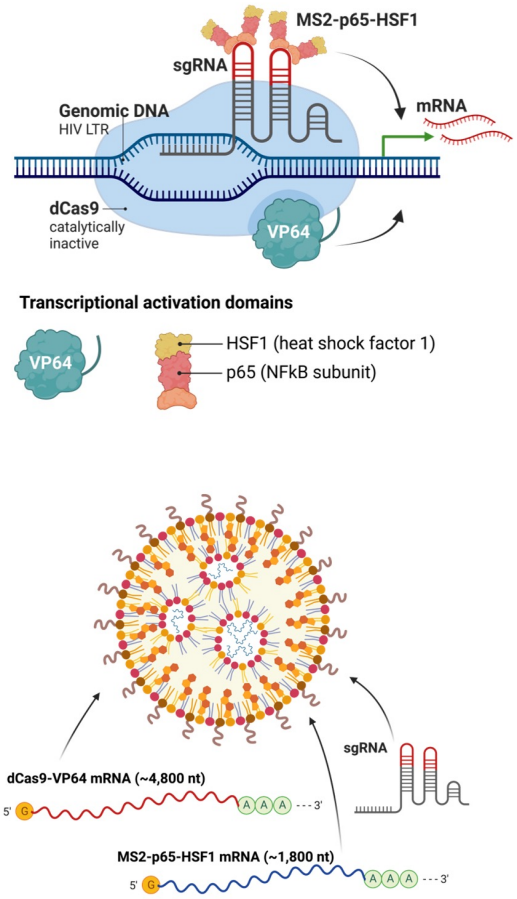
Latency reversing agents (LRA): can ‘shock’ but not ‘kill’

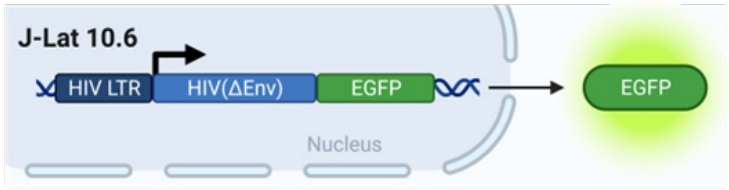


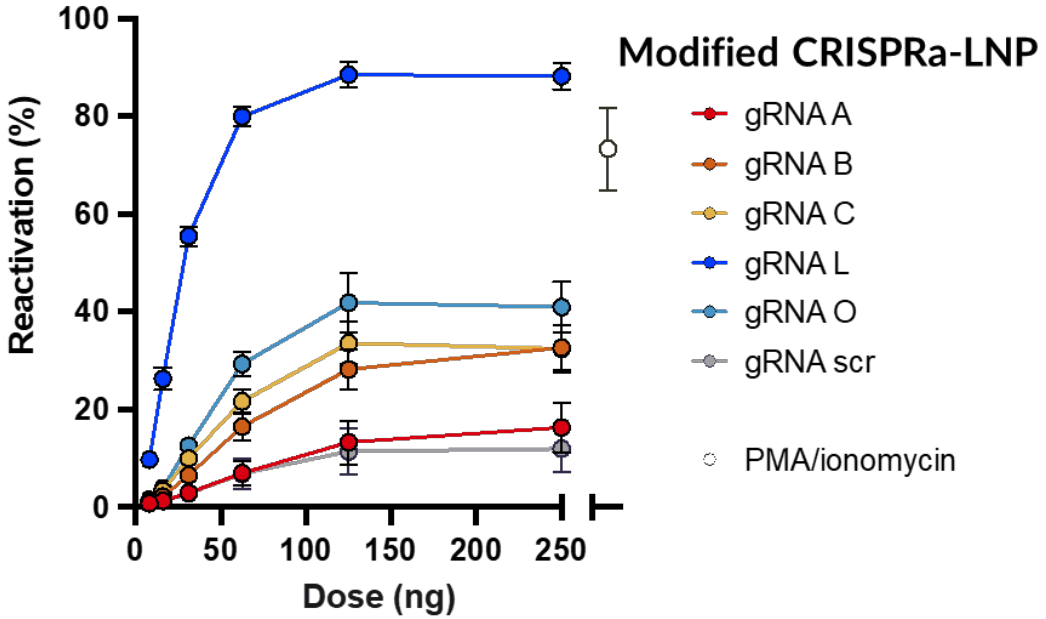
- In vivo, **LRAs increase transcription** but no decline in the number of infected cells
- Next generation LRAs need **greater specificity** and **lower toxicity**
- Need to get the ‘kill’ into shock and kill: **pro-apoptotic drugs**

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

Next generation LRAs: using CRISPR and mRNA

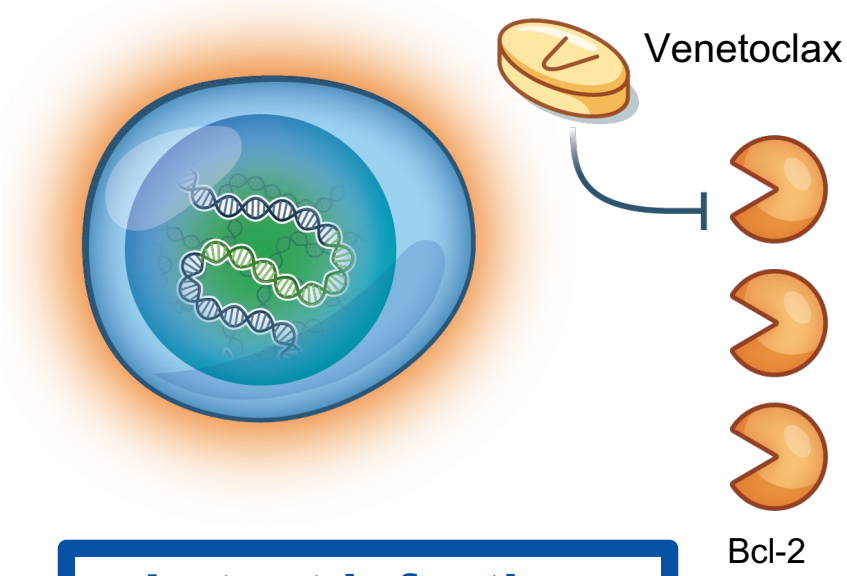






Cevaal et al., IAS 2023, Brisbane July 21, 2023

Pro-apoptotic drugs: BCL-2 antagonists



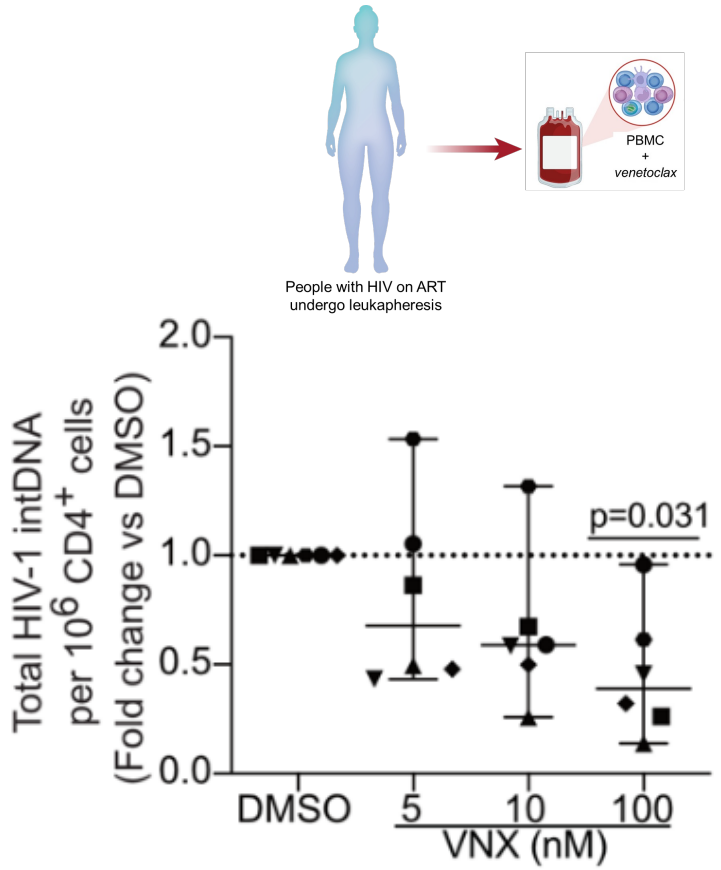
Latent infection

DNA positive

RNA negative

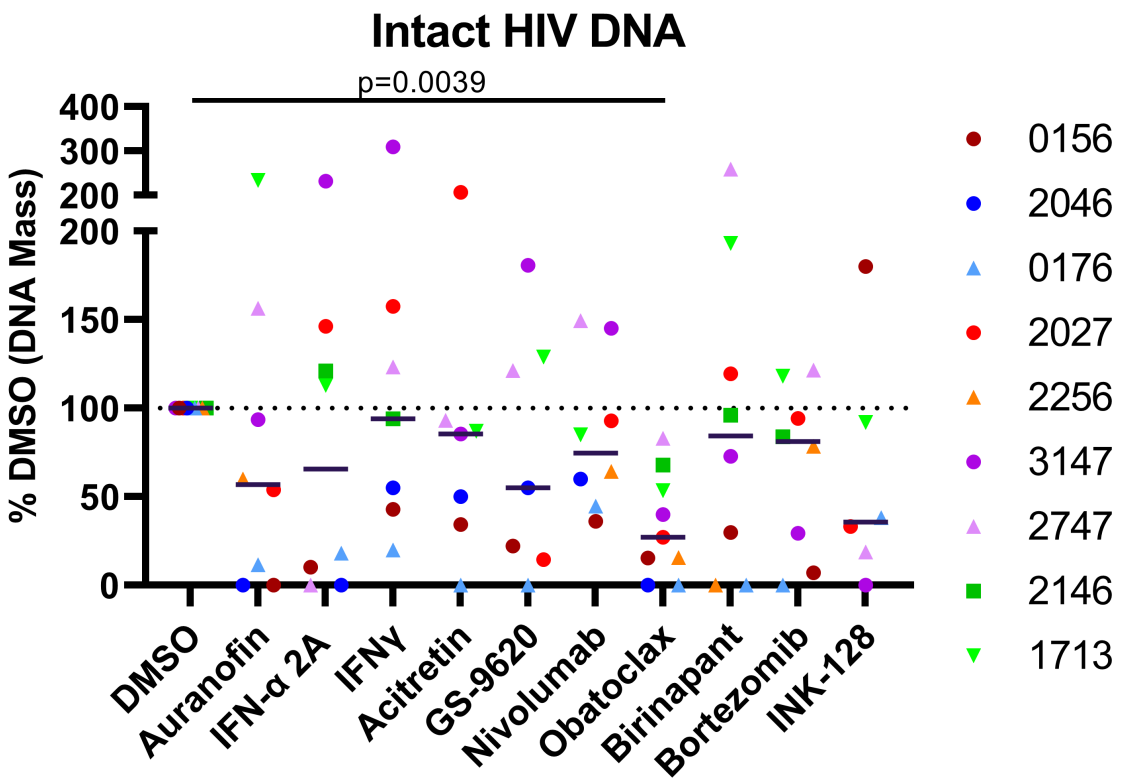
HIV protein negative

SURVIVAL



Roberts et al., N Engl J Med 2016; Cummins et al., J Virol 2017; Ren at al., J Clin Inv 2020; Arandjelovic et al., Cell Rep Med 2023

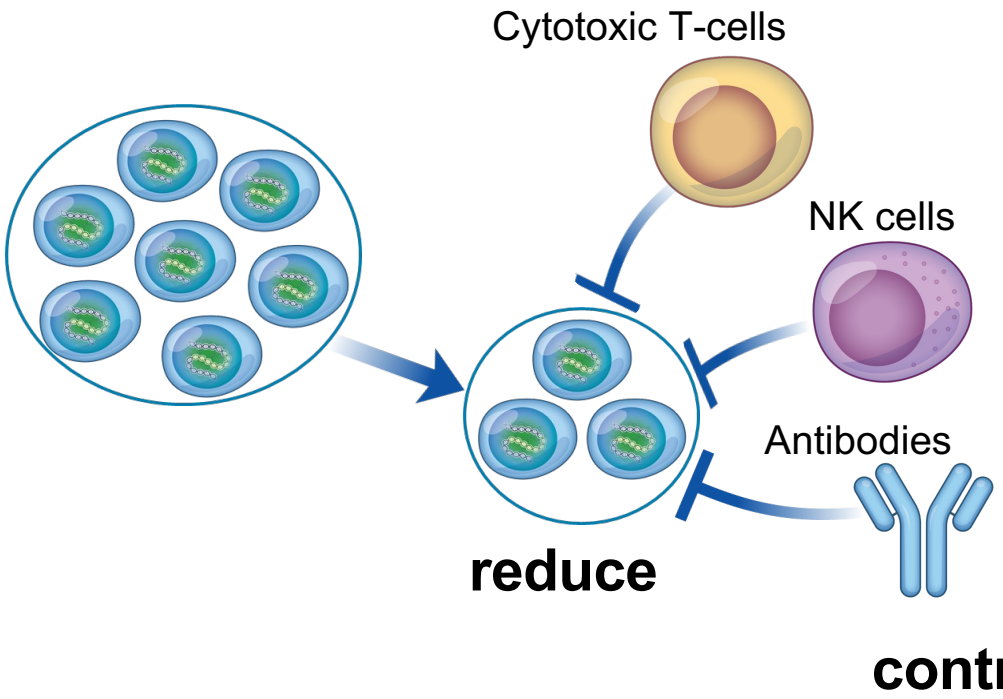
Similar findings with Obatoclax (a BCL2 inhibitor)



Yukl et al., IAS2023, Brisbane, Australia July 23-26., 2023

Combination immunotherapy

Immunotherapies under investigation for HIV cure



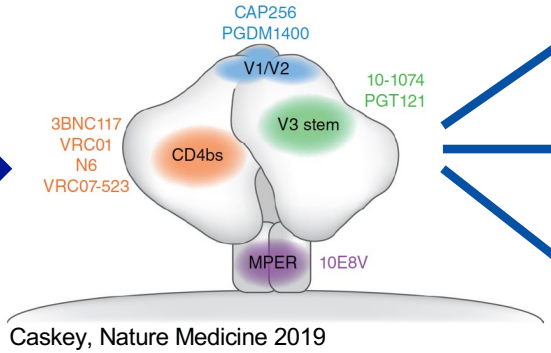
- Broadly neutralising antibodies
- Therapeutic HIV vaccines
- Immune checkpoint blockade
- Toll-like receptor agonists
- Immunomodulatory drugs
- CAR T-cells
- Interferon therapy
- Cytokines: IL-15, anti-IL-10

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

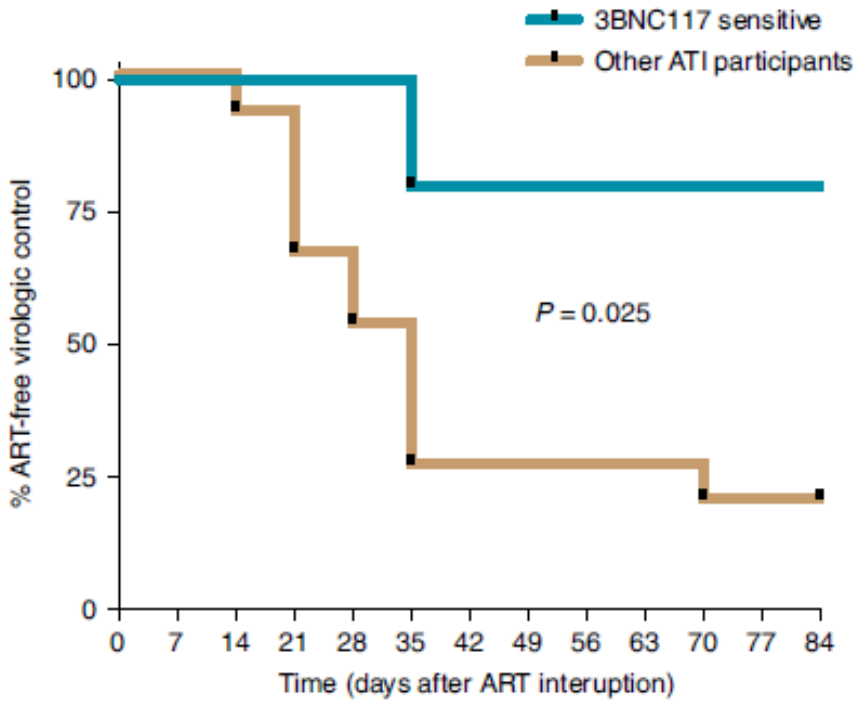
Combination immunotherapy: larger and/or randomised clinical trials showing viral control in some participants

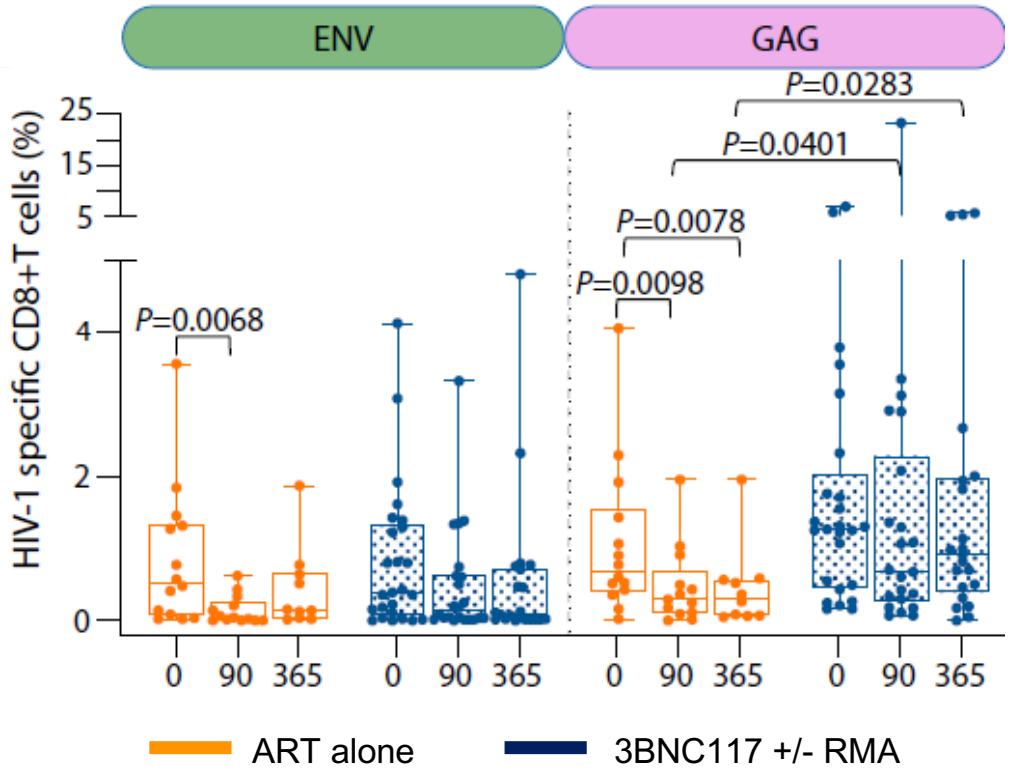
name	Reduce and control		Reservoir
ROADMAP [1]	romidepsin	bNAb (3BNC)	No change
eCLEAR**[2]	romidepsin	bNAb (3BNC)	No change
JAWS*[3]	TRL9 agonist	bNab (VRC07-523LS +10-1074) DNA/MVA vaccine	Not reported
TITAN*[4]	TLR9 agonist	bNAb (3BNC+10-1074)	No change

* During ATI = antiretroviral treatment interruption ** At time of ART initiation

1 Gruell Lancet Microbe 2022; 2 Gunst Nat Med 2022; 3 Peluso CROI 2023; 4 Gunst Nat Med 2023 (in press)

eCLEAR: romidepsin with 3BNC117 (bNab)

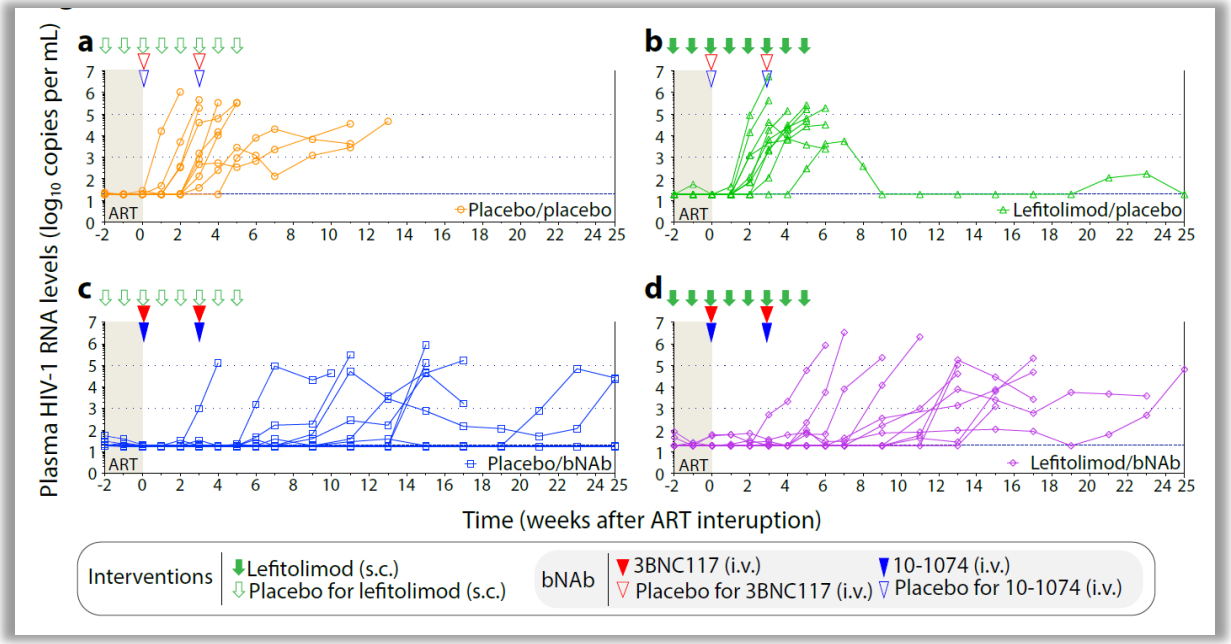


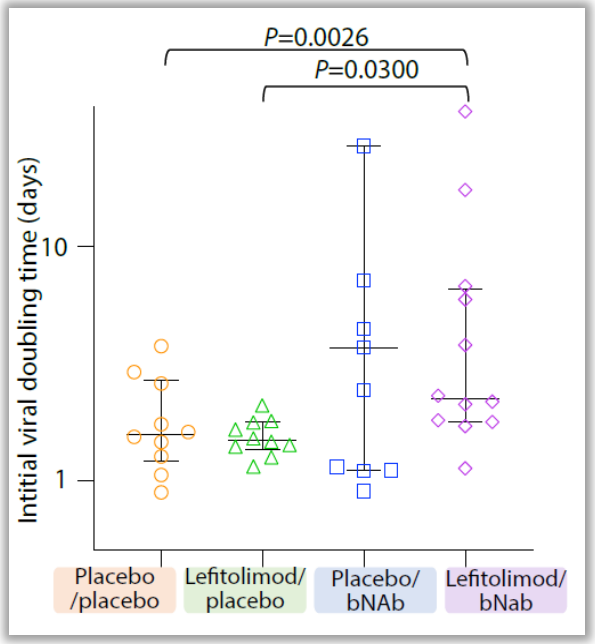


Gunst et al., Nat Med 2022; Rosas-Umbert et al., Nat Comms 2022

TITAN: TLR9 agonist with 3BNC117 and 10-1074 (bNAbs)

Phase 2a, placebo-controlled, double-blinded international trial, PWH on long-term suppressive ART were randomized to one of four groups: treatment with a toll-like receptor 9 agonist, lefitolimod, or placebo followed by two broadly neutralizing anti-HIV-1 antibodies (bNAbs), 3BNC117 and 10-1074, or placebo.

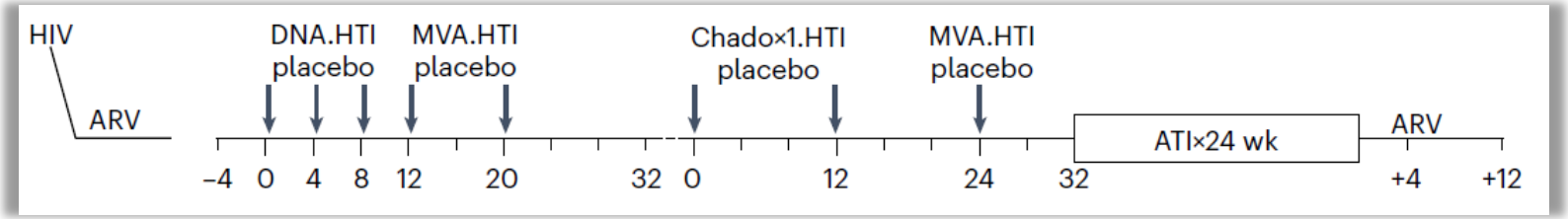




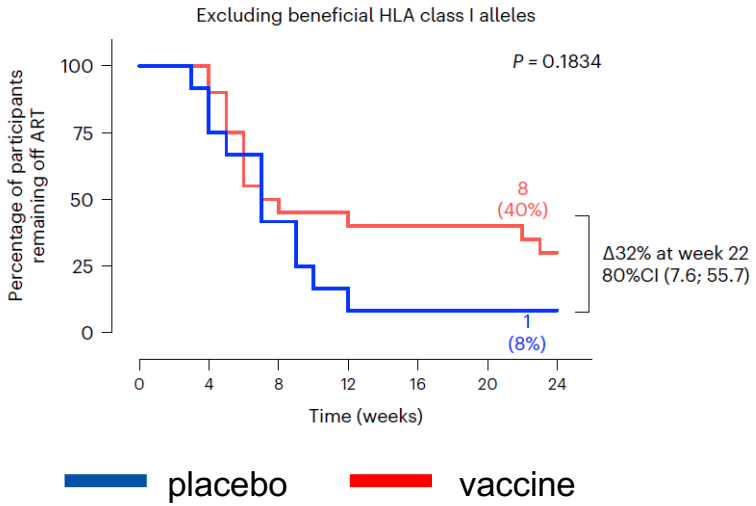
Primary endpoint was time to loss of virologic control (defined as 4 weeks >1,000 HIV RNA copies/mL or 2 measurements >100,000 copies/mL) during ART interruption (ATI).

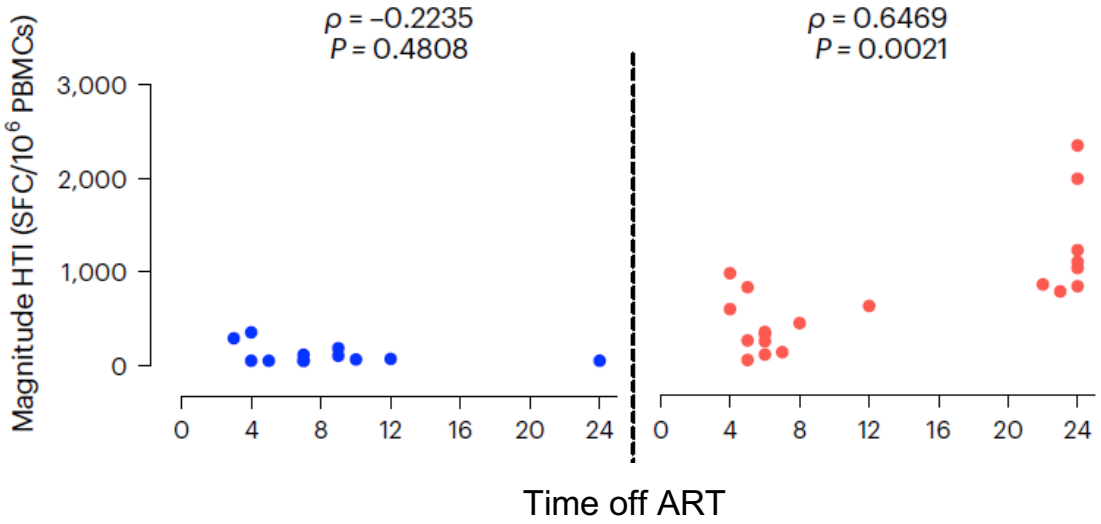
Gunst et al., Nature Med 2023 (in press)

T-cell vaccination can also induce ART-free virological control in some participants



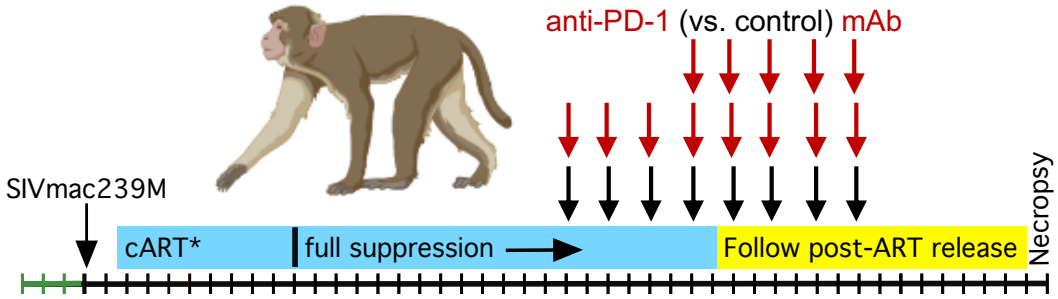
AELIX-002: a phase I, first-in-human, randomized, double blind, placebo-controlled study to evaluate the safety, immunogenicity and effect on viral rebound of DNA.HTI, MVA.HTI and ChAdOx1.HTI HIV-1 vaccines (n=45)





Balion et al., Nat Med 2022

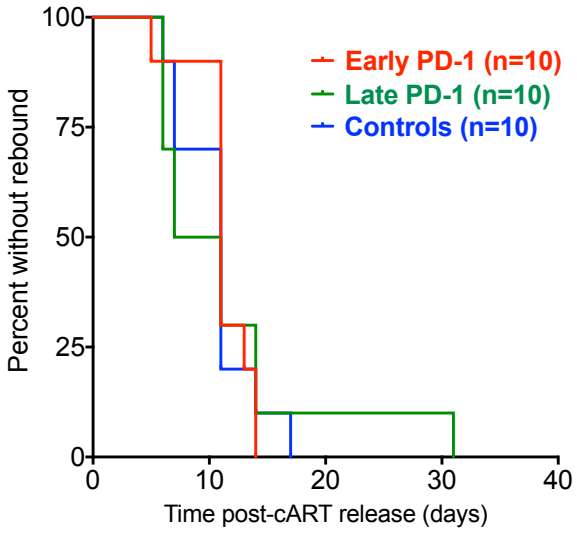
Anti-PD1 induces virus ‘control’ off ART in a monkey model

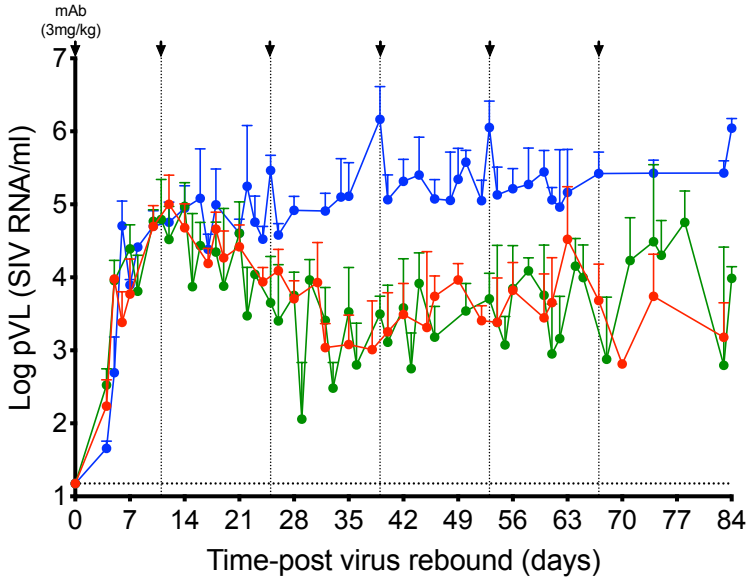


control Ab

early anti-PD1

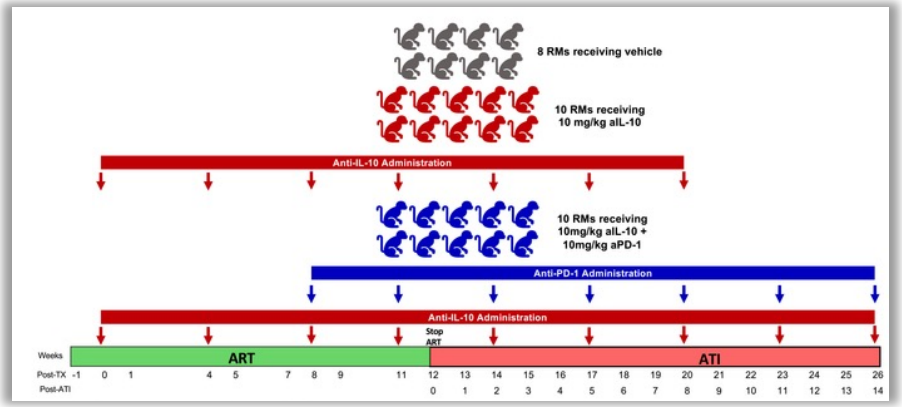
late anti-PD1

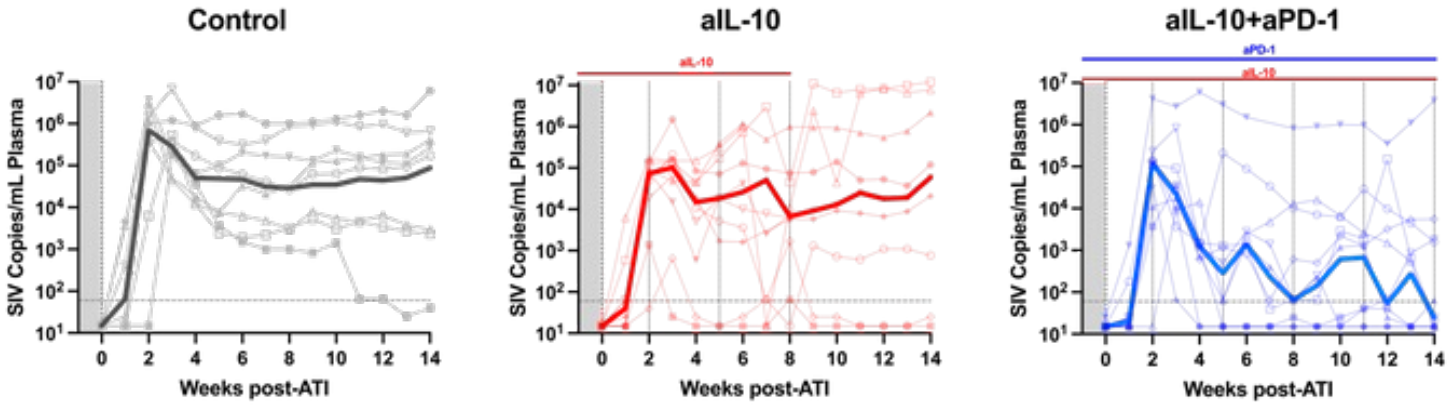




Okoye et al., CROI 2021 virtual

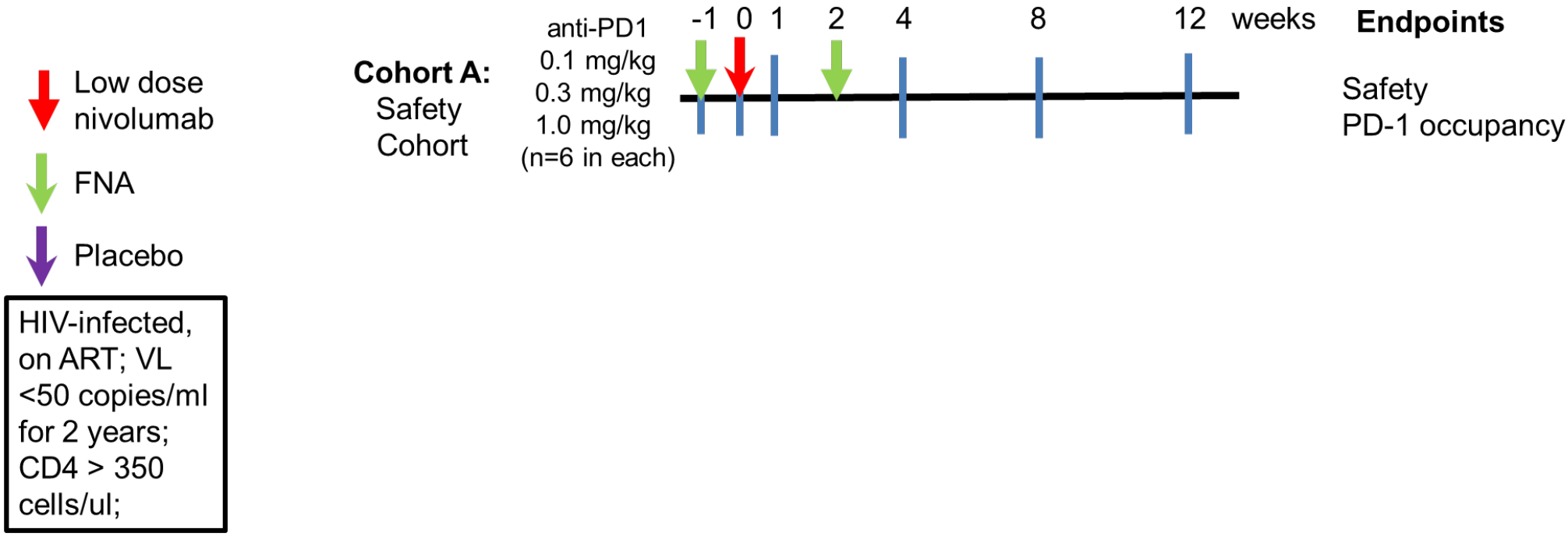
Anti-PD1 with anti-IL10 enhanced post treatment control





Strongin et al., IAS2021 virtual, late breaker

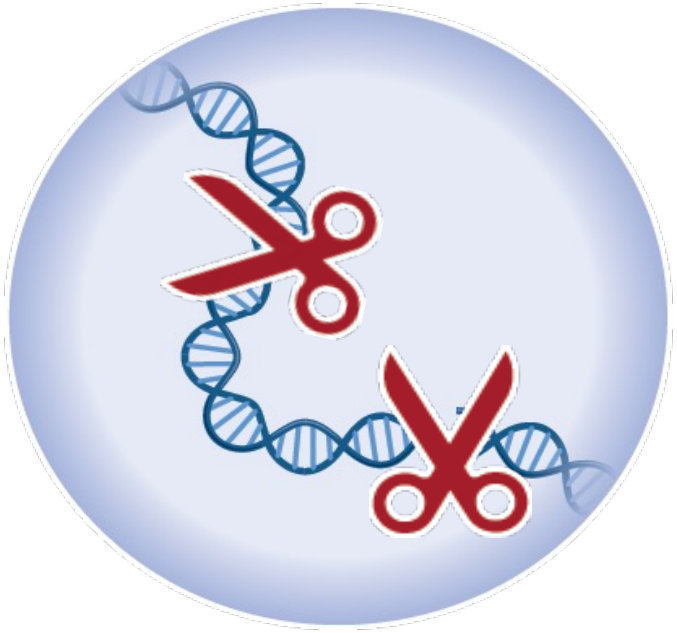
NIVO LD: A two-step dose finding phase 1b trial in adults living with HIV on suppressive ART (NCT05187429)



Enrolling in Melbourne, Australia. Cohort B will also enrol in Melbourne and the National Centre for Infectious Disease in Singapore

Gene therapy

Gene therapy: targets and strategies



Attack: enhance anti-HIV immune responses

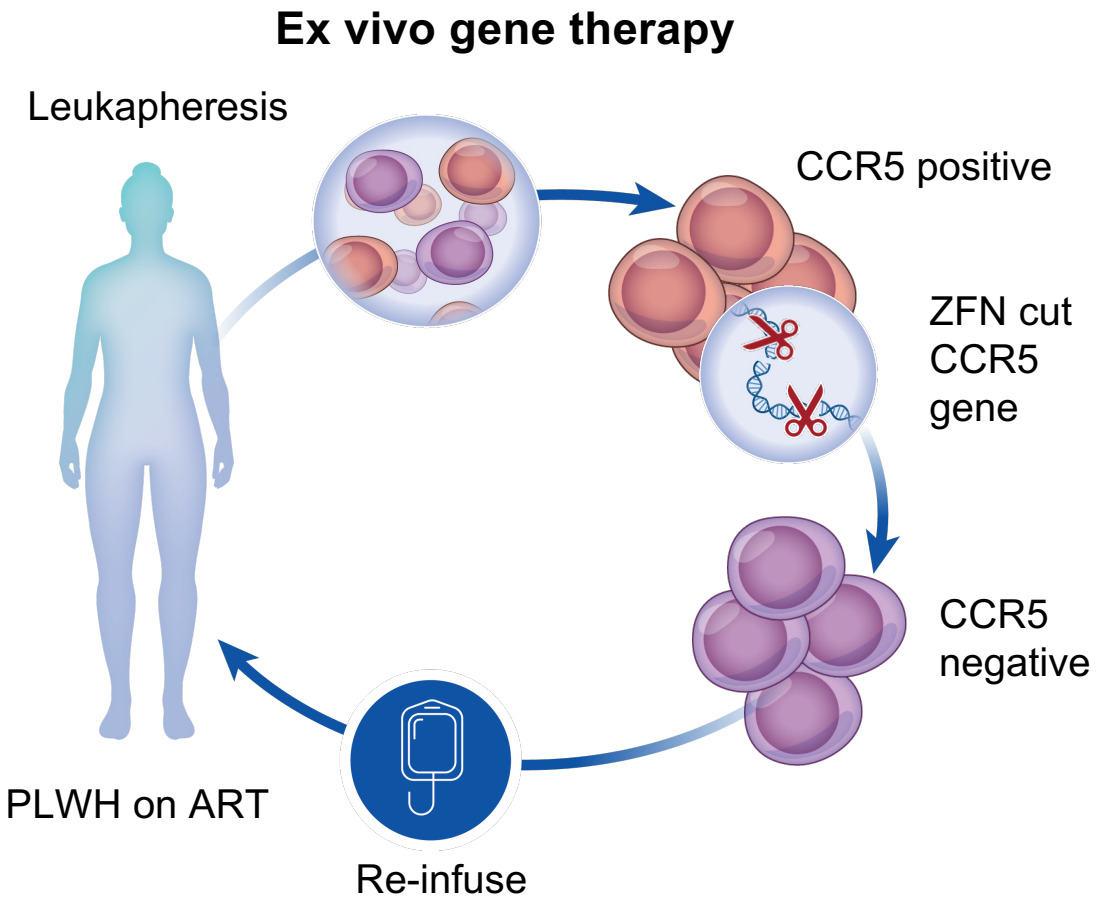
Protect: engineer uninfected cells to be resistant to HIV

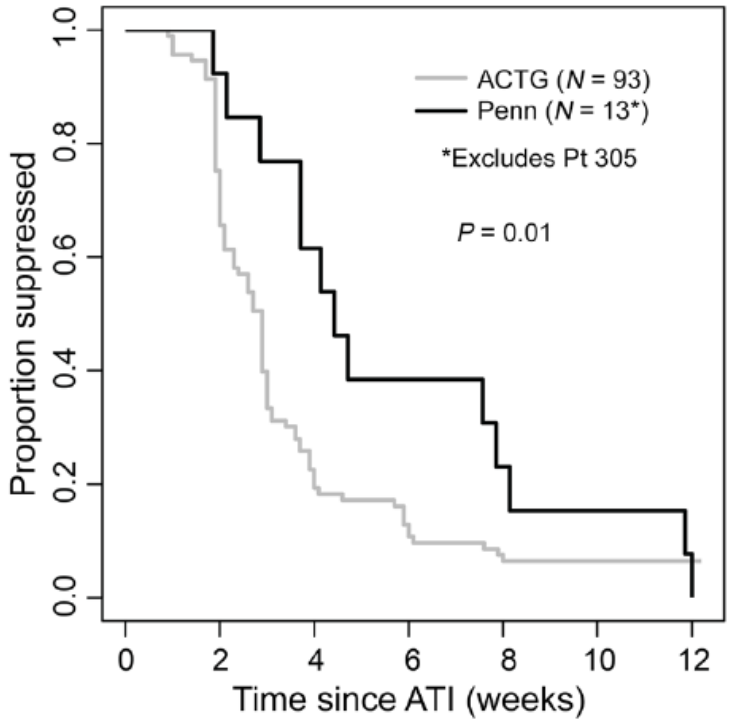
Purge: directly eliminate the virus itself

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

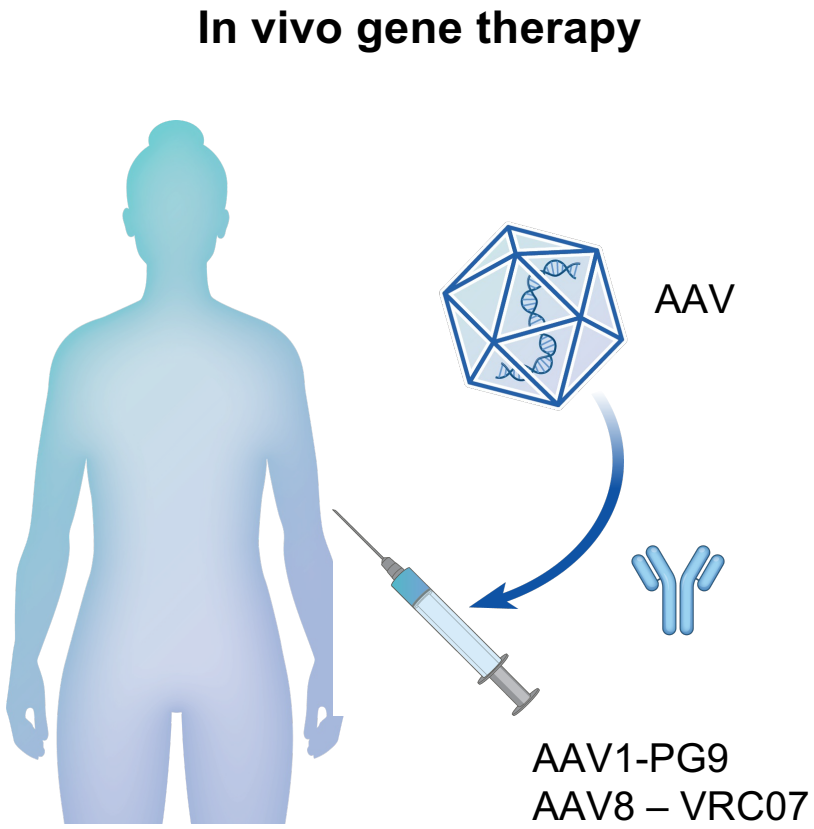


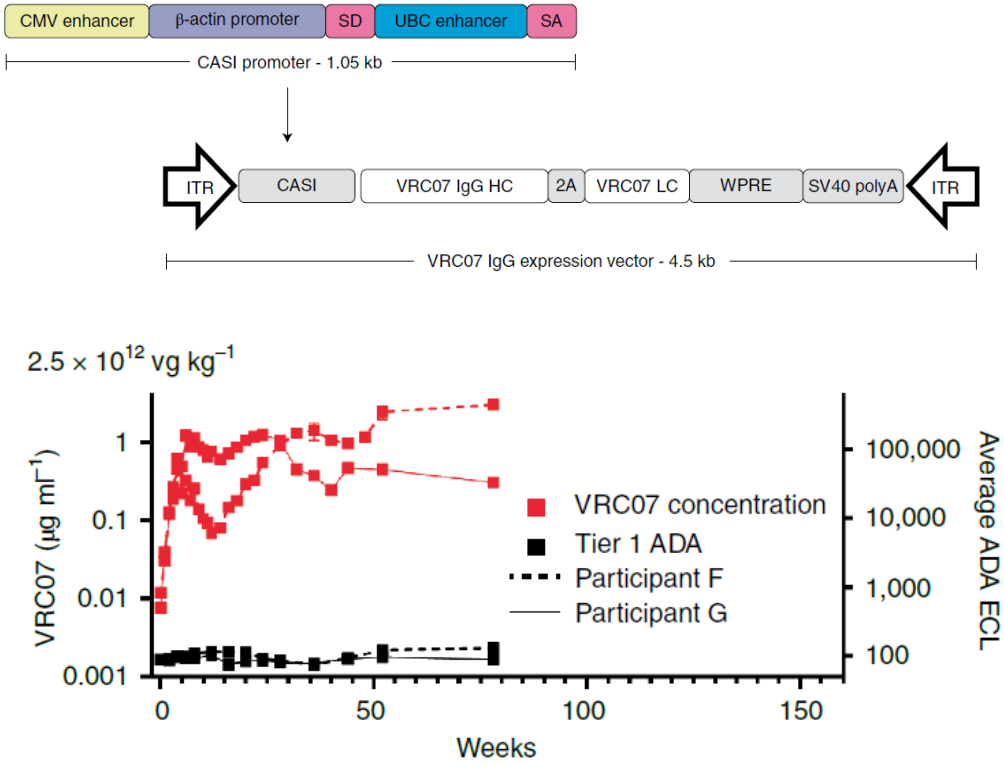


Participants were PLWH on ART who received ex vivo CCR5-modified cells (SB-728mRT) ± cyclophosphamide had delayed time to viral load rebound after interruption of ART

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

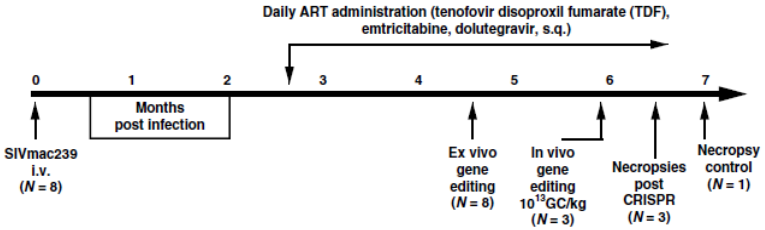
ARTICLE

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.

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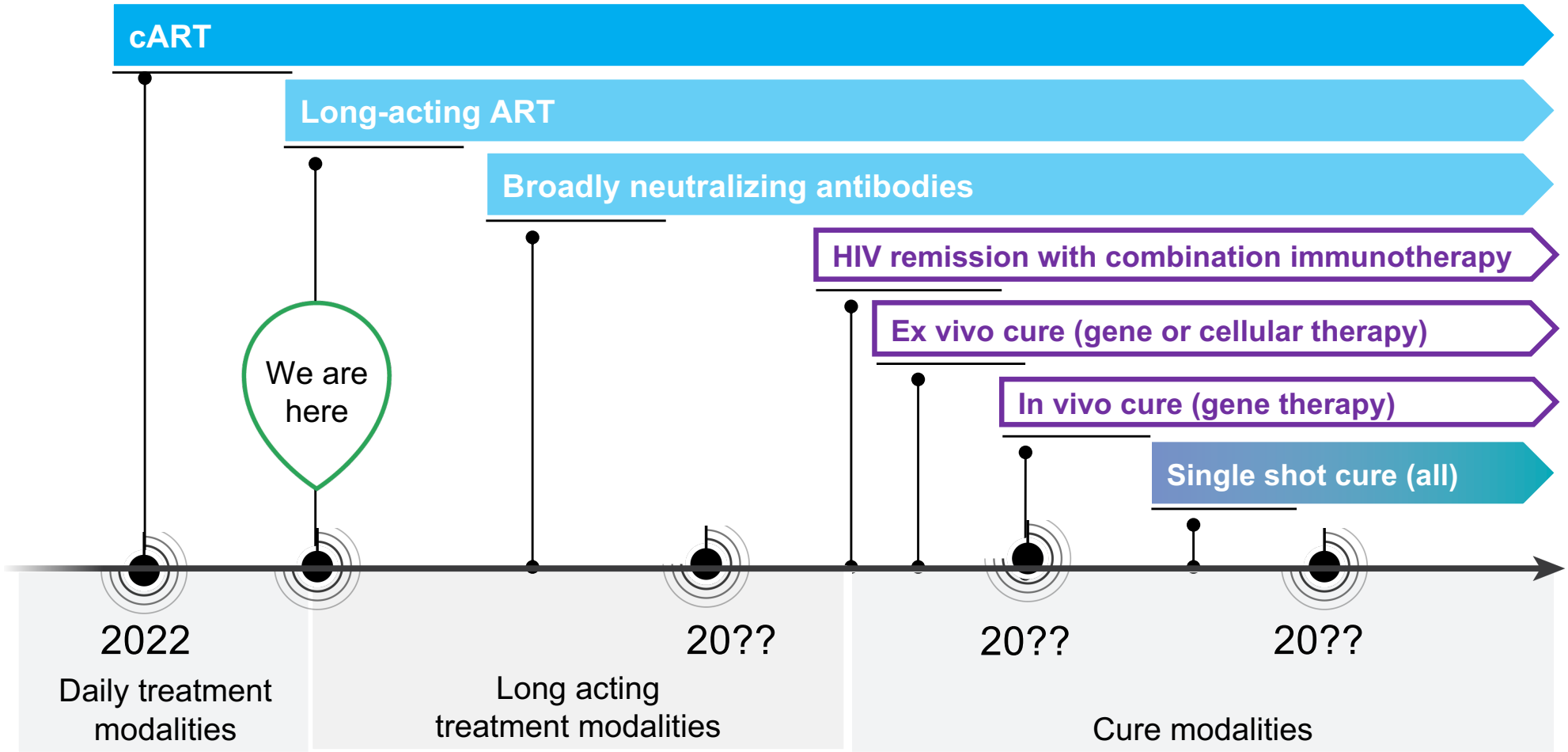
Excision Biotherapeutics: first-in-human Phase I/II trial to evaluate the safety, tolerability and efficacy of EBT-101 in healthy individuals living with HIV. EBT-101 uses Adeno Associated virus (AAV), CRISPR-Cas9 plus 2 x gRNAs

First patient enrolled in September 2022

Mancuso Nat Comms 2020; Burdo Gene Therapy 2023

Current and future landscape for HIV treatment



Target Product Profile (TPP) for an HIV Cure

- An agreed set of **minimally-acceptable** and **optimal** characteristics of a new product informed by all stakeholders including PWH
- These criteria should be **universal** and not classified according to high and low income settings
- The TPP should not inhibit **innovation** and discovery
- Critically important for **global equity** and successful **implementation** of a cure

Review

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

Developing a cure for HIV is a global priority. Target product profiles are a tool commonly used throughout the drug development process to align interested parties around a clear set of goals or requirements for a potential product. Three distinct therapeutic modalities (combination therapies, ex-vivo gene therapy, and in-vivo gene therapy) for a target product profile for an HIV cure were identified. Using a process of expert face-to-face consultation and an online Delphi consultation, we found a high degree of agreement regarding the criteria for the optimum target product profile. Although the minimum attributes for a cure were debated, the broad consensus was that an acceptable cure need not be as safe and effective as optimally delivered antiretroviral therapy. An intervention that successfully cured a reasonable fraction of adults would be sufficient to advance to the clinic. These target product profiles will require further discussion and ongoing revisions as the field matures.

Lancet HIV 2020
Published Online November 30, 2020 https://doi.org/10.1016/S2352-3018(20)30234-4
See Online/Viewpoint https://doi.org/10.1016/S2352-3018(20)30232-0

*Working group co-chairs and joint corresponding authors

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Lewin et al., Lancet HIV 2020

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, evade immunity and primed to survive.

- **Latency reversal agents alone** 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 immune checkpoint blockers. Early signs that immunotherapy with **antibodies while viremic** can induce viral control.

- 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

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ACH2 Australian Centre for HIV and Hepatitis Virology Research

Medical Research Future Fund

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