

Towards an HIV cure: what's happening in recent clinical trials?

—
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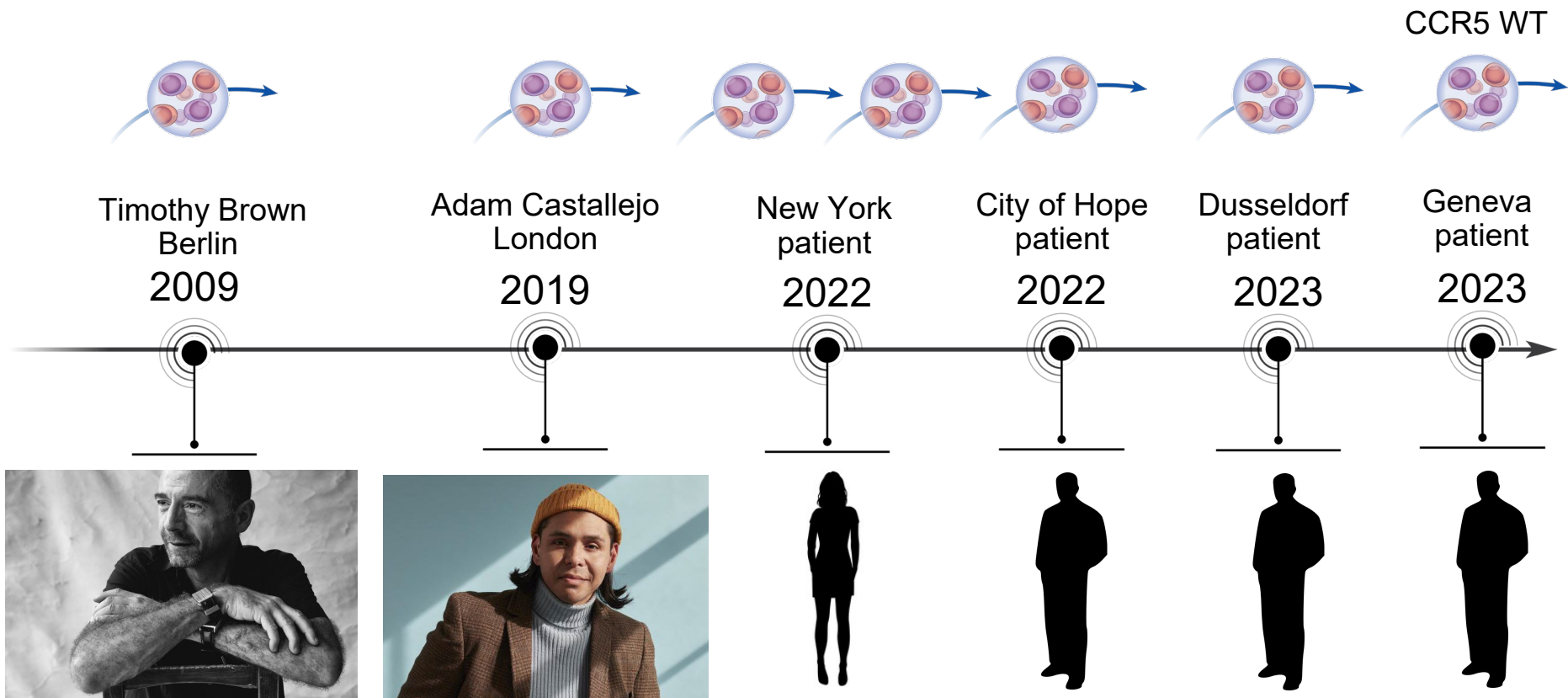
ANRS/MIE Vietnam

Hai Phong, Vietnam, November 15-16, 2023

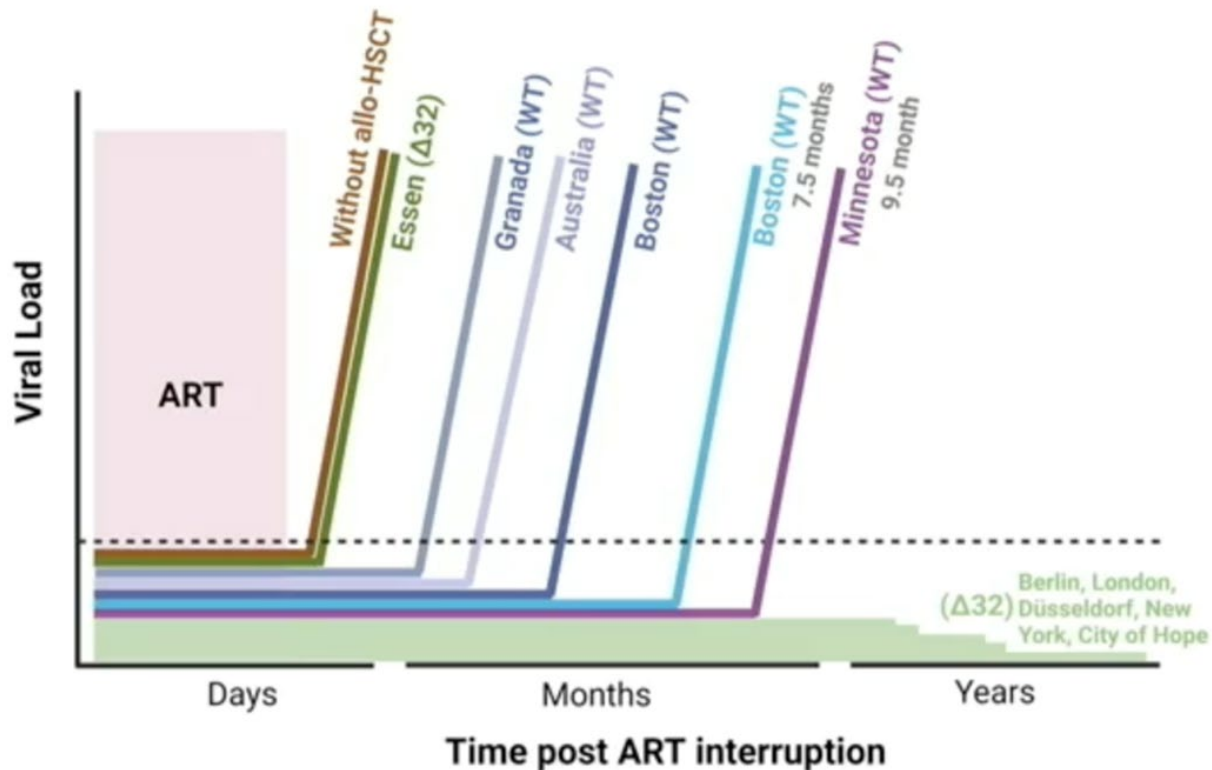
Outline

- **Case reports of an HIV cure**
- **Recent clinical trials**
 - Combination immunotherapy
 - Antibodies
 - Anti-PD1
 - Gene therapy
- **Potential considerations for Vietnam**

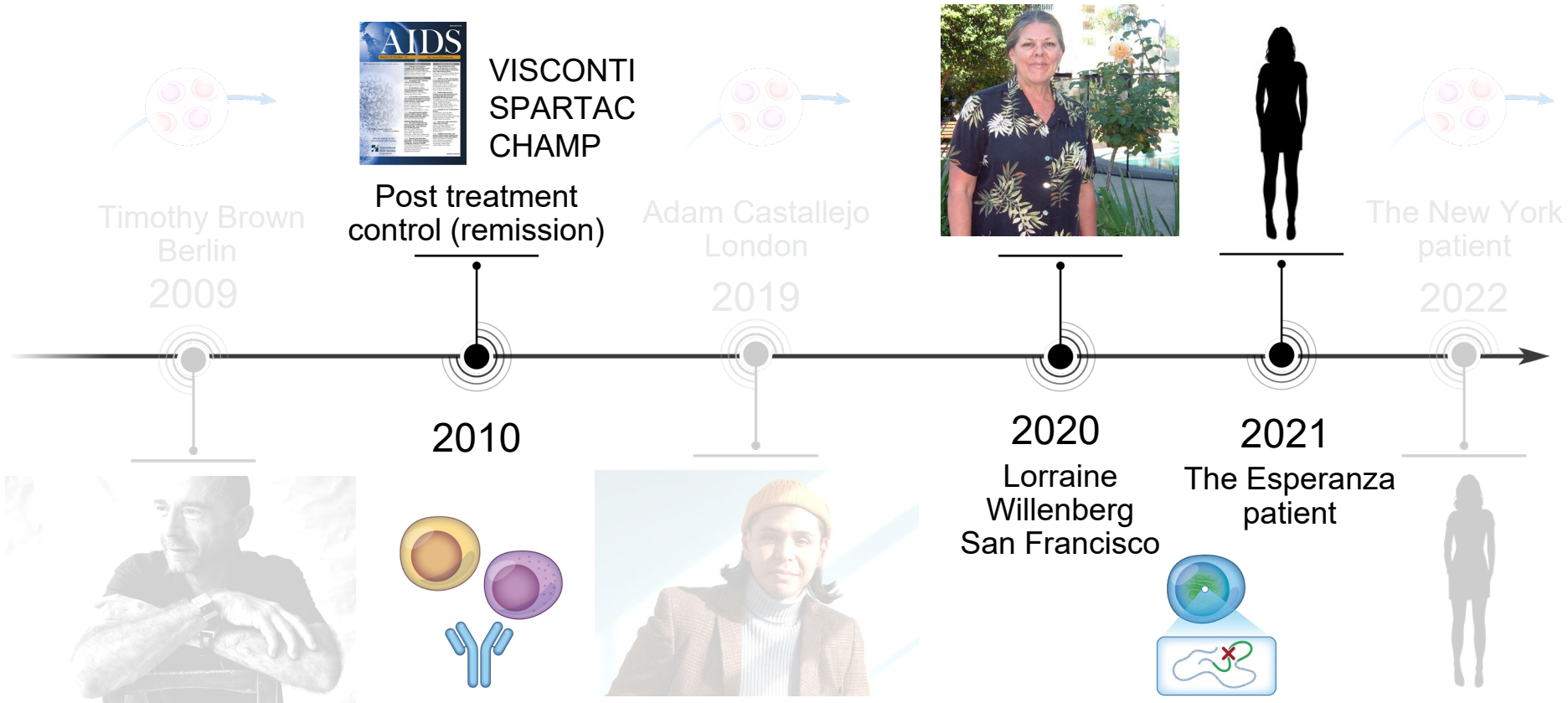
HIV cure is extremely rare but possible: transplantation



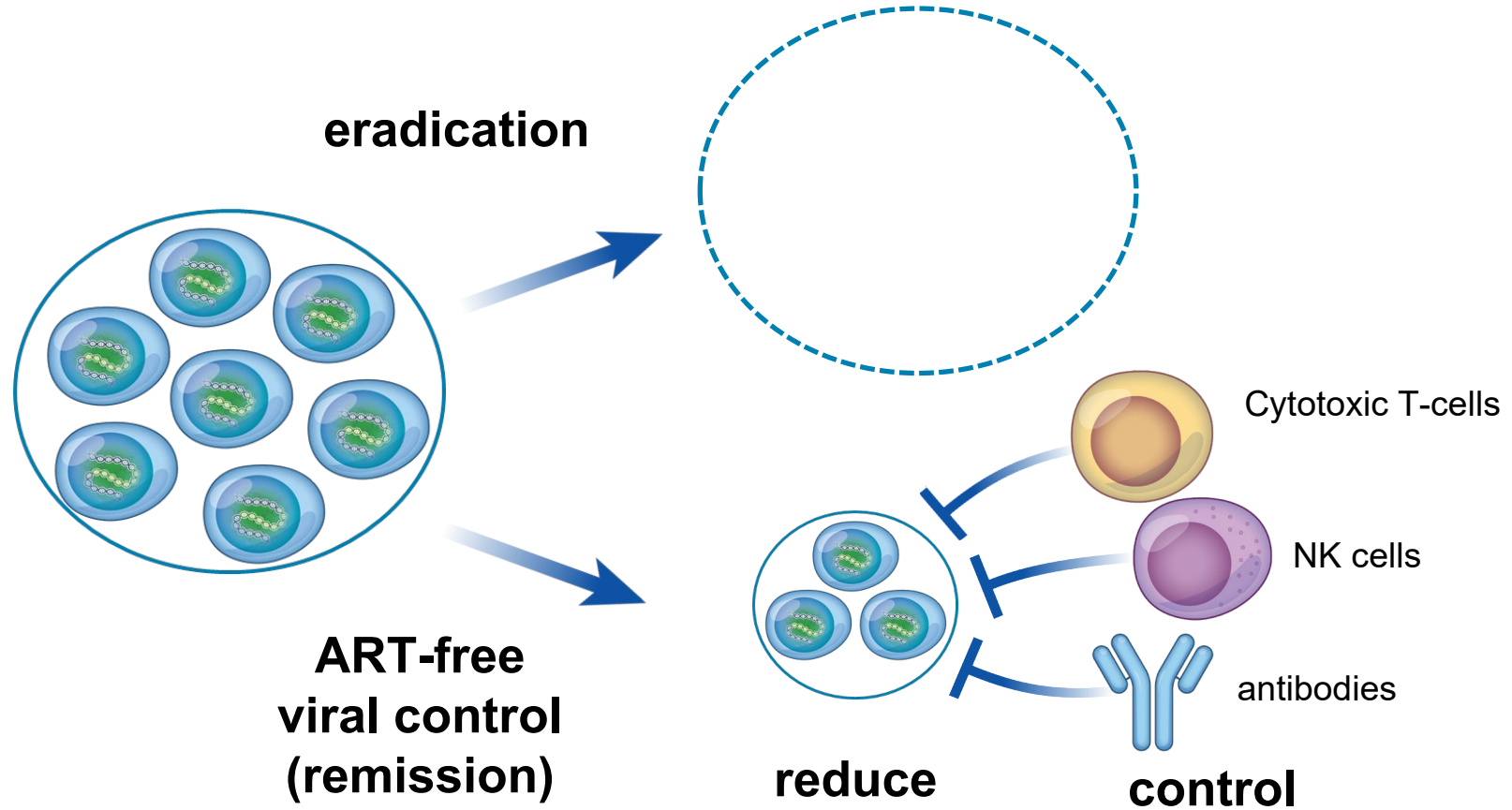
Wild type donors for transplantation have not resulted in viral control beyond 9 months



HIV cure is extremely rare but possible: natural control

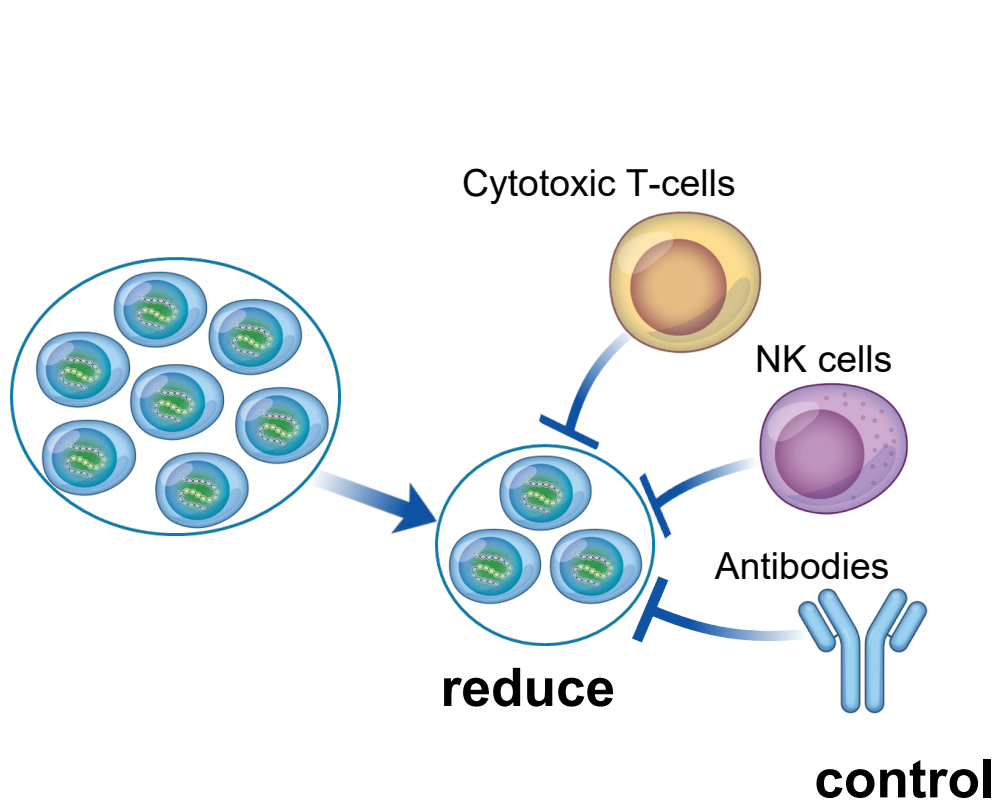


Overarching goals of cure strategies



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

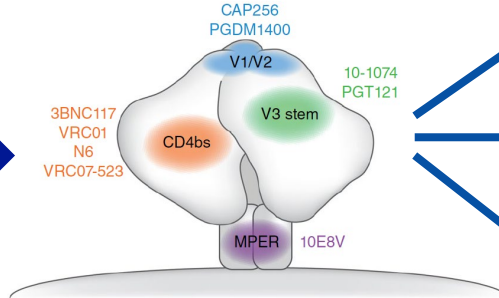
Broadly neutralising antibodies

Broadly neutralising antibodies (bNAbs) against HIV



Technological advances in B-cell cloning → bNAb production

Isolation of bNAbs in a minority of HIV-infected individuals



Caskey, Nature Medicine 2019

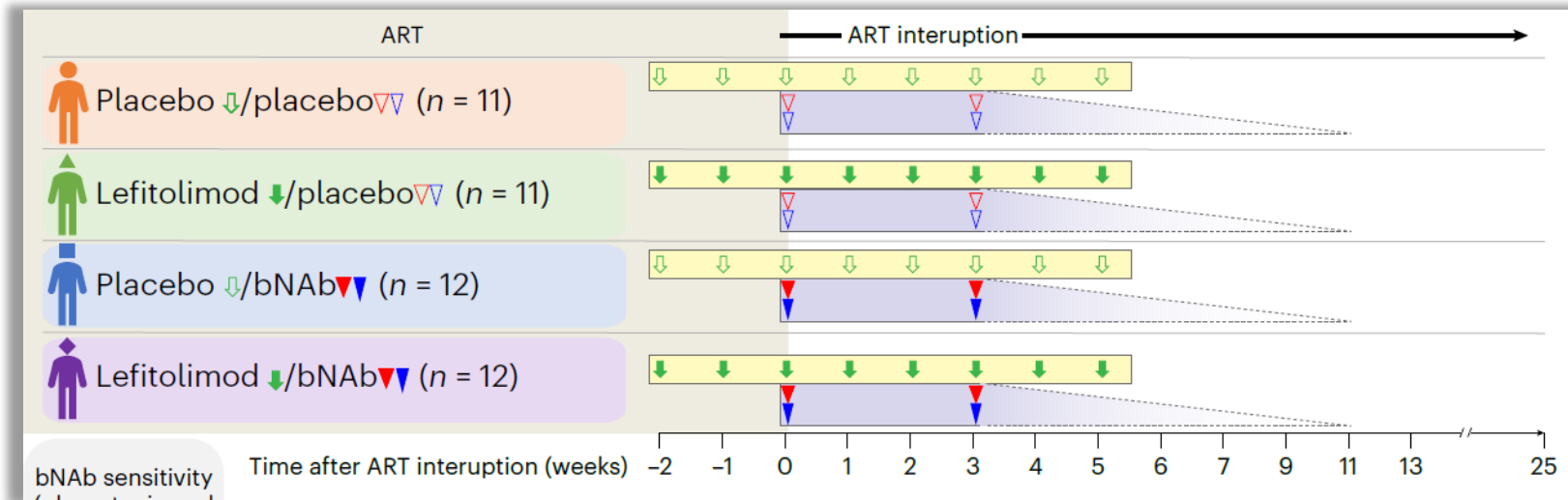
Many bNAbs identified and produced for clinical applications

HIV prevention

HIV treatment

HIV cure

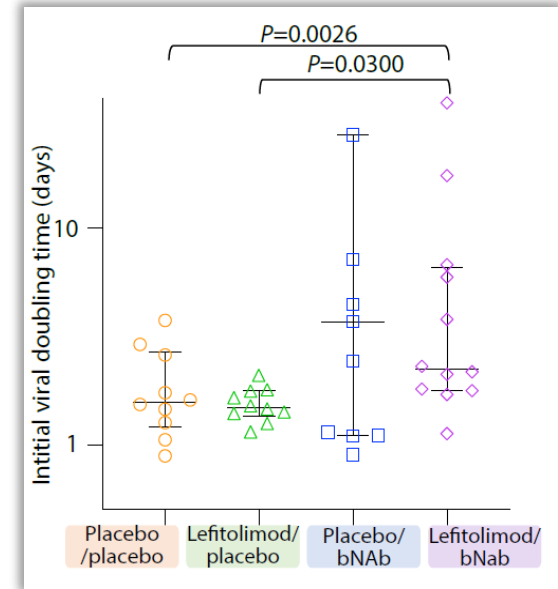
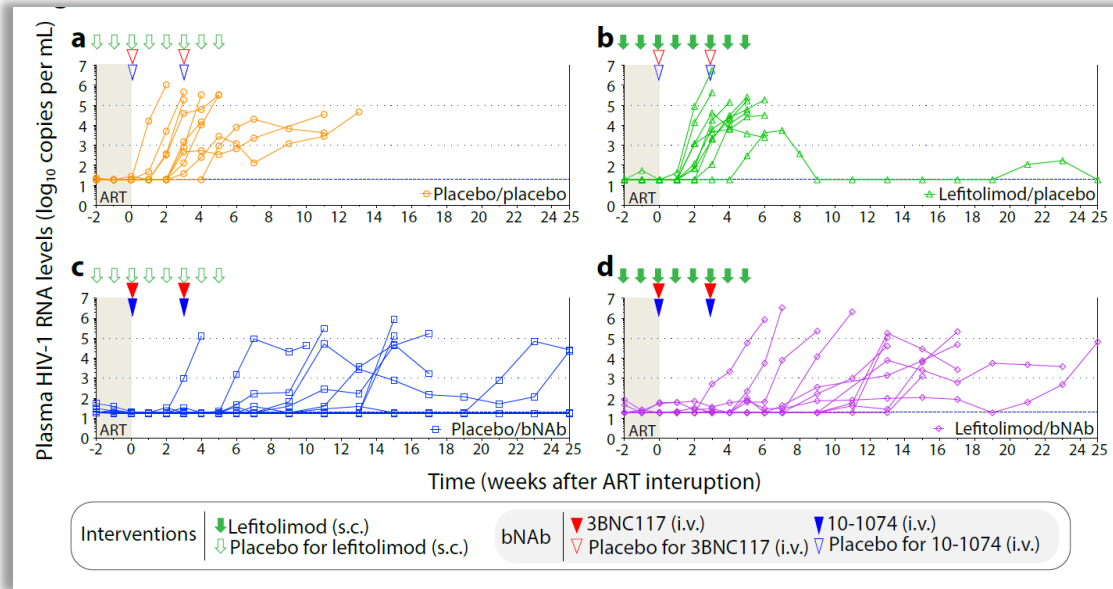
TITAN: TLR9 agonist with two broadly neut antibodies



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).

Significant delay to viral rebound in arms that received bNAbs and 30% maintaining viral control at week 24



- Time to rebound longer in the arms that received bNAbs. No effect of TLR9 agonist
- Despite subtherapeutic plasma bNAb levels, 36% (4/11) in the placebo/bNAb group compared to 0% (0/10) in the placebo/placebo group maintained virologic control after the 25-week ATI

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

Trial name	Reduce and control		Viral control off ART
TITAN ^{1*}	TLR9 agonist	bNAb (3BNC + 10-1074)	Yes ~33%

Immune checkpoint blockade

Anti-PD-1: studies in people with HIV and cancer



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. Adams¹, Remi Fromentin⁴, Michael Roche^{5,6}, Steven P. Fling¹, Priscila H. Gonçalves³, Kathryn Lurain³, Ramya Ramaswami³, Chia-ching Jackie Wang⁷, Robert J. Gorelick⁸, Jordan L. Welker⁸, Liz O'Donoghue¹, Harleen Choudhary¹, Jeffrey D. Lifson⁸, Thomas A. Rasmussen^{6,9}, Ajantha Rhodes⁶, Carolin Tumpach⁶, Robert Yarchoan³, Frank Maldarelli³, Martin A. Cheever^{1†}, Rafick Sékaly¹⁰, Nicolas Chomont⁴, Steven G. Deeks⁷, Sharon R. Lewin^{6,11,12*}

Clinical Infectious Diseases

MAJOR ARTICLE

IDS
Infectious Diseases Society of America

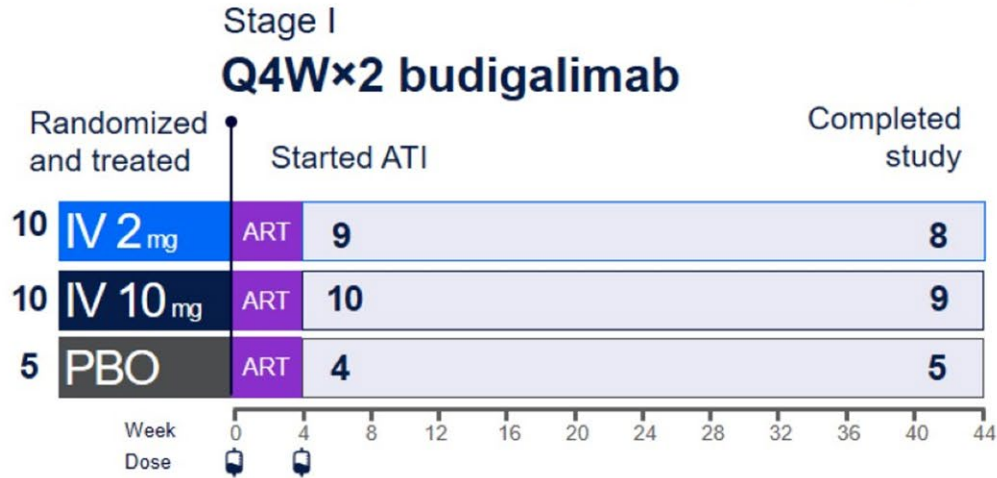
hivma
hiv medicine association

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

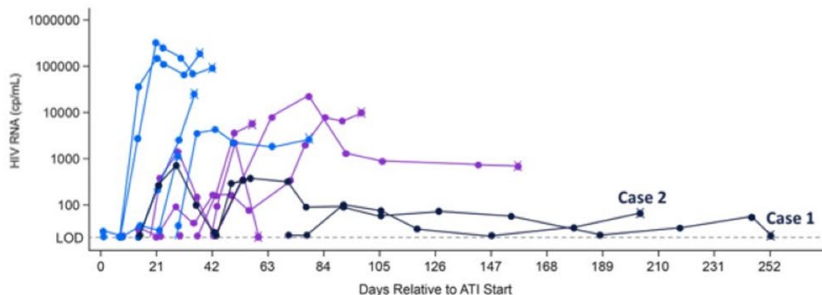
Thomas A. Rasmussen,^{1,9} Lakshmi Rajdev,² Ajantha Rhodes,¹ Ashanti Dantanarayana,¹ Surekha Tennakoon,¹ Socheata Chea,¹ Tim Spelman,¹ Shelly Lensing,³ Rachel Rutishauser,⁴ Sonia Bakkour,⁵ Michael Busch,⁵ Janet D. Siliciano,⁵ Robert F. Siliciano,⁶ Mark H. Einstein,¹ Dirk P. Dittmer,⁸ Elizabeth Chiao,³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

Anti PD1: impact on viral control in people with HIV



Anti PD1 induces viral control in a subset of participants

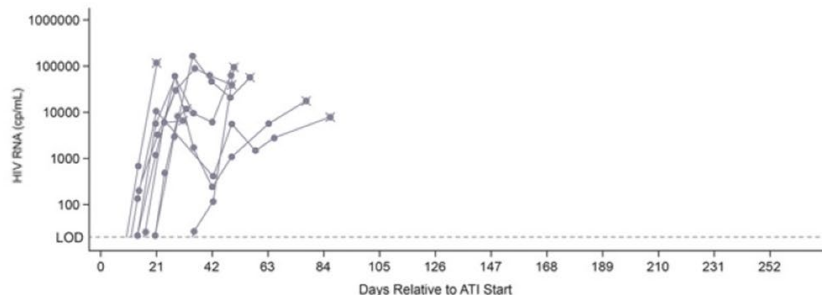
10-mg Q2W×4 Budigalimab (n=11)



Legend

- Case 1 and 2
- With delayed viral rebound or off-ART viral control^a
- Without delayed viral rebound or off-ART viral control^a
- Placebo
- ✕ Last observed data point before ART restart

Pooled Placebo (n=9)

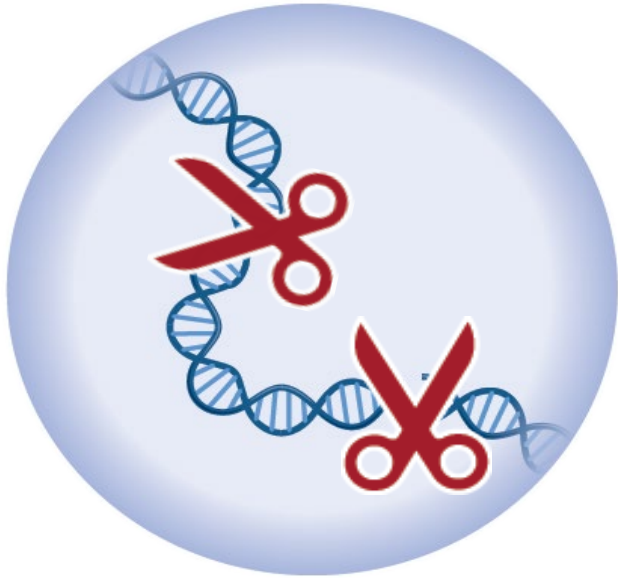


	Pooled Placebo (n=10)	10-mg Q2W×4 Budigalimab (n=11)
Median time to viral rebound (90% CI), days	21 (21–24)	29 (21–49)

Phase 2 trial of low dose anti-PD1 (nivolumab) in PWH on ART underway in Melbourne and Singapore

Gene therapy

Gene therapy: targets and strategies



Attack: enhance anti-HIV immune responses

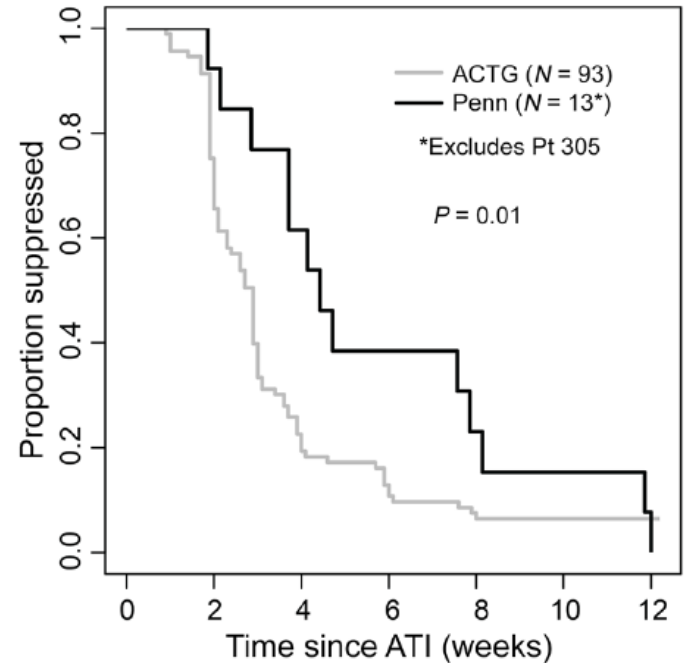
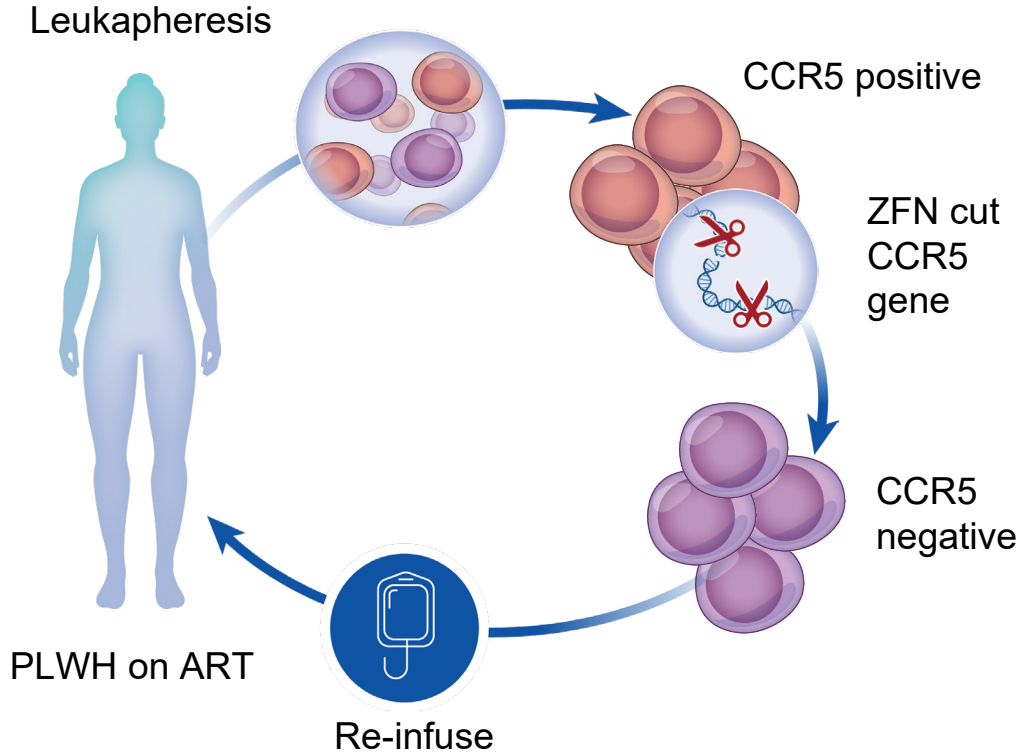
Protect: engineer uninfected cells to be resistant to HIV

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)

Gene therapy: ex vivo gene modification

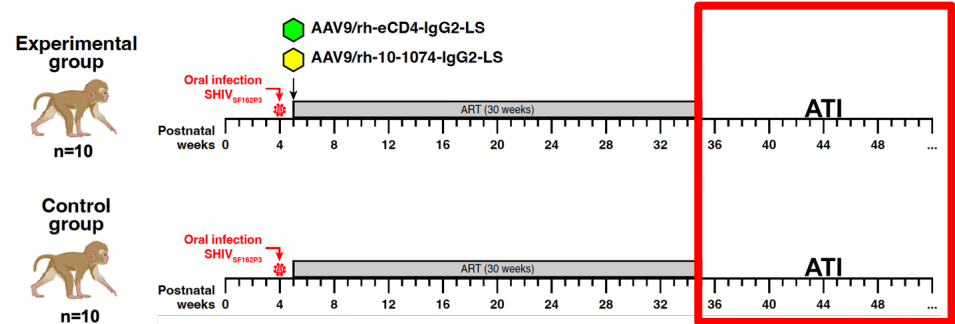
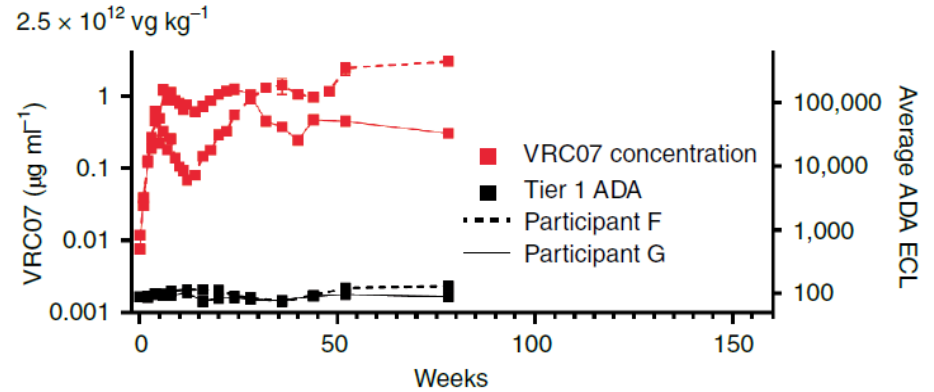
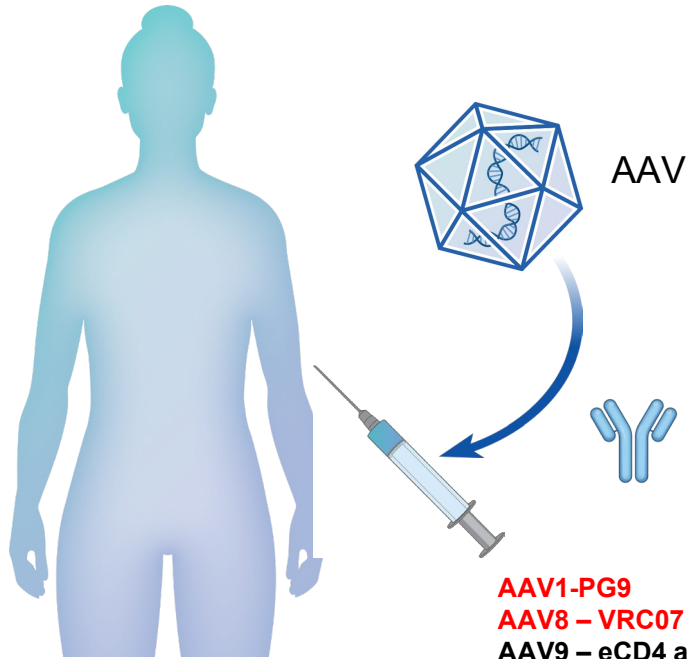
Ex vivo gene therapy



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

Gene therapy: in vivo delivery of antibodies

In vivo gene therapy



No monkey rebounded in the experimental group!

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



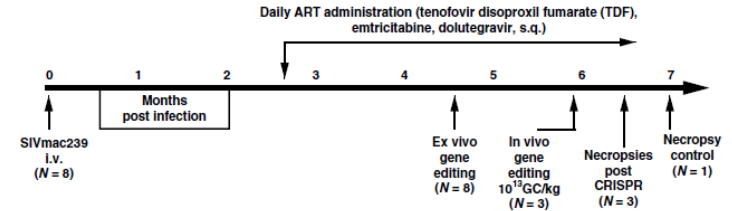
nature COMMUNICATIONS

ARTICLE

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

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

Pietro Mancuso¹, Chen Chen¹, Rafal Kaminski¹, Jennifer Gordon¹, Shuren Liao¹, Mandy D. Smith¹, Hong Liu¹, Ilker K. Sariyer¹, Rahsan Sariyer¹, Tiffany A. Peterson², Jaclyn B. Williams², Summer Siddiqui², Bruce A. Bunnell^{2,3,4,5}, Binhua Ling^{2,6,7}, Andrew G. MacLean^{2,3,6}, Tricia H. Burdo¹ & Kamel Khalili¹



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

No safety concerns in first 3 participants

HIV cure research and considerations for Vietnam

- People living with HIV are very interested in **understanding progress** towards an HIV cure. This gives people hope and can also be a motivation for testing. It is important to understand what is happening to counter balance misinformation



The image is a screenshot of a news article from the Daily Mail website. At the top left is the 'Daily Mail .com' logo. To the right is a graphic of two green leaves with the word 'health' in a teal font. Below the logo is a navigation bar with links for Home, Showbiz, Femal, Royals, Health, Science, Sports, Politics, Money, U.K., Video, Travel, Puzzles, and Shop. A teal bar below the navigation bar contains links for Latest Headlines, Covid-19, Flu, RSV, Monkeypox, Dementia, Cancer, Weight Loss, Diet, CDC, WHO, and a Login button. The main headline reads 'Cure for HIV could be months away as first three patients are injected with new CRISPR therapy that seeks and destroys lingering pieces of virus'. Below the headline is a bulleted list of three points: 'HIV went from certain death sentence to chronic disease people can live with', 'CRISPR uses enzyme to cut large sections of HIV DNA, eliminating it from cells', and 'READ MORE: Researchers make breakthrough in fight against HIV using CRISPR'. At the bottom, it says 'By CASSIDY MORRISON SENIOR HEALTH REPORTER FOR DAILYMAIL.COM' and 'PUBLISHED: 17:13 EDT, 30 October 2023 | UPDATED: 13:25 EDT, 31 October 2023'.

Daily Mail .com

health

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Cure for HIV could be months away as first three patients are injected with new CRISPR therapy that seeks and destroys lingering pieces of virus

- HIV went from certain death sentence to chronic disease people can live with
- CRISPR uses enzyme to cut large sections of HIV DNA, eliminating it from cells
- READ MORE: Researchers [make breakthrough in fight against HIV using CRISPR](#)

By CASSIDY MORRISON SENIOR HEALTH REPORTER FOR DAILYMAIL.COM
PUBLISHED: 17:13 EDT, 30 October 2023 | UPDATED: 13:25 EDT, 31 October 2023

HIV cure research and considerations for Vietnam

- People living with HIV are very interested in **understanding progress** towards an HIV cure. This gives people hope and can also be a motivation for testing. It is important to understand what is happening to counter balance misinformation
- Observational studies remain very important in **understanding the HIV reservoir** e.g., characteristics of the reservoir with AE subtypes; impact of common co-infections such as hepatitis B and tuberculosis; impact of sex and hormones etc
- Interventional studies are **possible in LMIC** (e.g., Thailand, South Africa, Botswana) but clinical trials with a treatment interruption require high engagement and partnership with community to ensure consistent messaging
- The International AIDS society runs a series of **academies and workshops on HIV cure** for researchers and advocates. Three day intensive program in South Africa. All applicants from LMIC. See iasociety.org.



Summary and implications for future directions

- Multiple case reports of HIV cure following **stem cell transplantation** from a CCR5 negative donor but also a wild type donor. Other pathways to cure include **post treatment control** and rare individuals who can **eliminate all intact virus**
- Combination immunotherapy phase 2 studies underway with several studies using **antibodies while viremic** (at ART initiation or during an ATI) showing viral control in a subset of participants. First study of **low dose anti-PD1** shows viral control off ART is possible and adverse events manageable.
- Gene therapy has multiple applications in HIV cure. Delivery of **gene therapy in vivo** means greater options for implementation.
- We remain far from a cure for HIV and ultimately a **combination approach** will be needed. Increasing community literacy and engagement now is important to ensure rapid future implementation of any future product.

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**Australian Centre for
HIV and Hepatitis Virology Research**



amfAR
MAKING AIDS HISTORY

Medical Research
Future Fund



And support for investigator initiated clinical trials from Merck, Viiv and Gilead