Towards a Scalable and Transformative Cure for HIV

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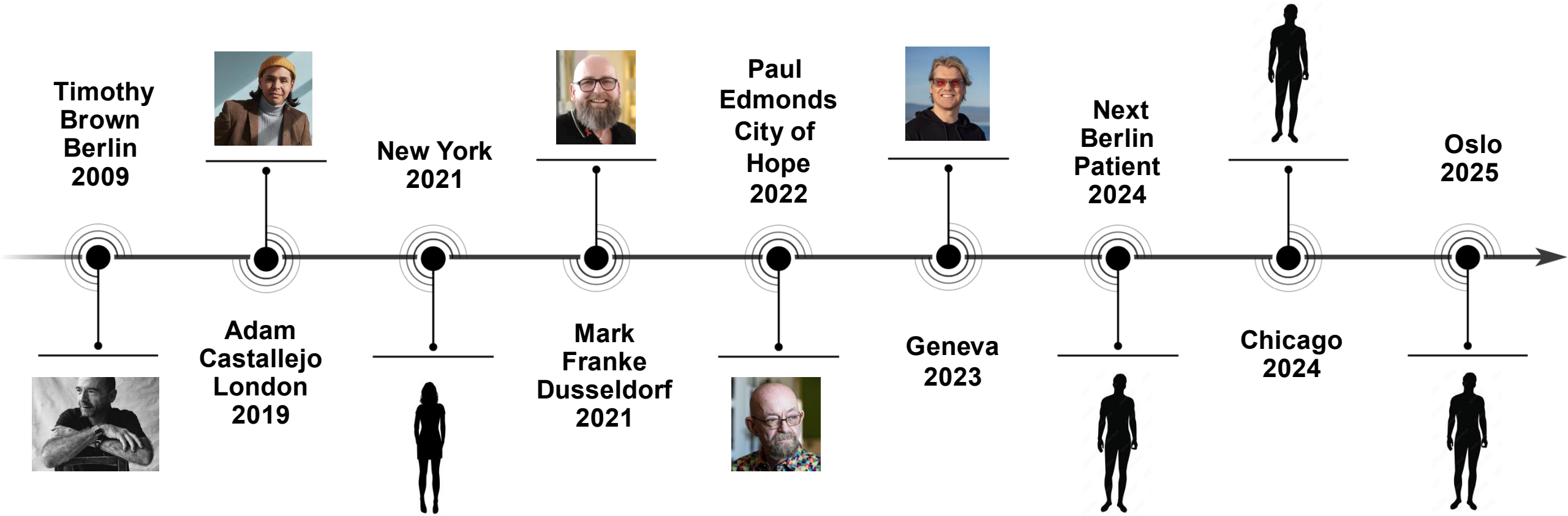
D&RE

Complete eradication has now been achieved in 9 allogenic stem cell transplants

In vivo gene editing of CCR5 in stem cells is in pre-clinical development



Administration of bNAbs during states of high antigen induces partial virus control in some (~ 2000 cpm or lower for months)

nature medicine 4/11

Early intervention with 3BNC117 and romidepsin at antiretroviral treatment initiation in people with HIV-1: a phase 1b/2a, randomized trial

nature medicine 4/11

Impact of a TLR9 agonist and broadly neutralizing antibodies on HIV-1 persistence: the randomized phase 2a TITAN trial

nature medicine 5/12

Safety and antiviral effect of a triple combination of HIV-1 broadly neutralizing antibodies: a phase 1/2a trial

nature 2/9

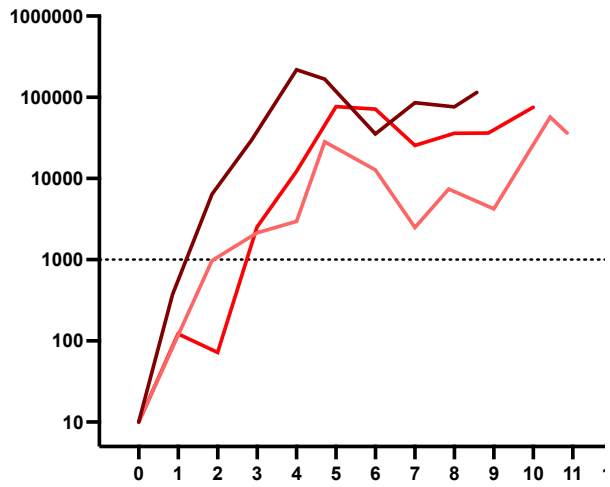
Combination therapy with anti–HIV–1 antibodies maintains viral suppression

RIO ROCKEFELLER | IMPERIAL | OXFORD ~50%, CROI 2025

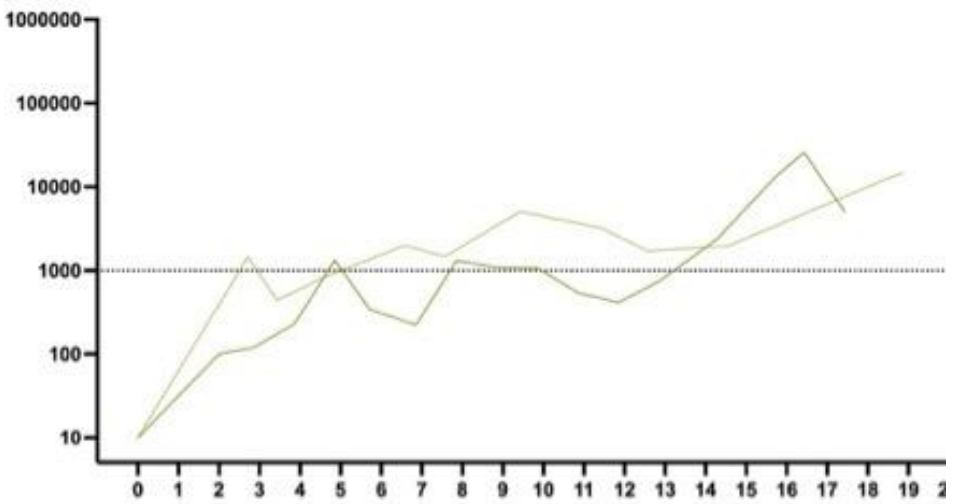
FRESH-Gilead ~40%, CROI 2025

UCSF amfAR Combination Study

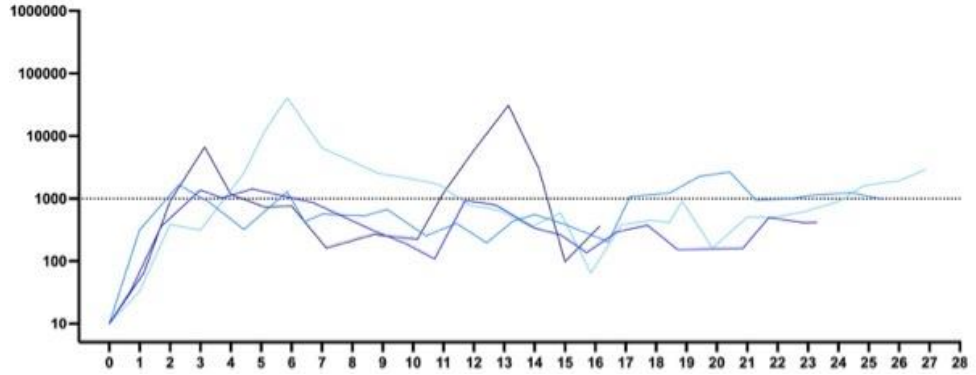
3 stage combination regimen resulted in sustained control(~1000 copies/mL or less) in 7/10 participants



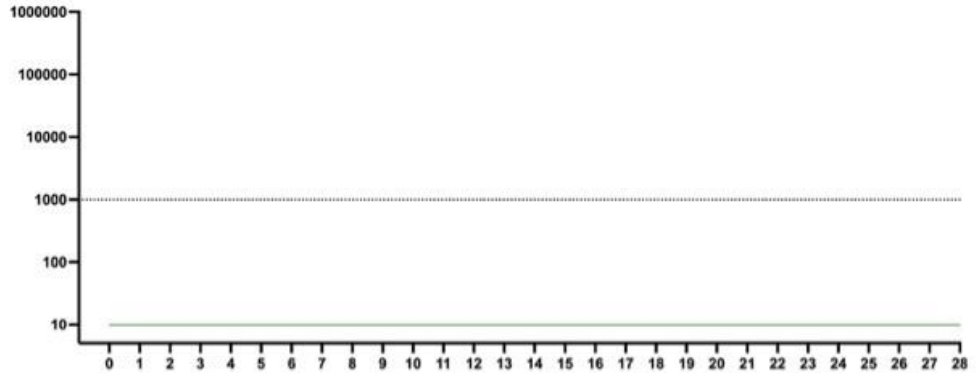
Typical rebound (n=3)



✓ **VL ~ 1000; slow rebound (n=3)**



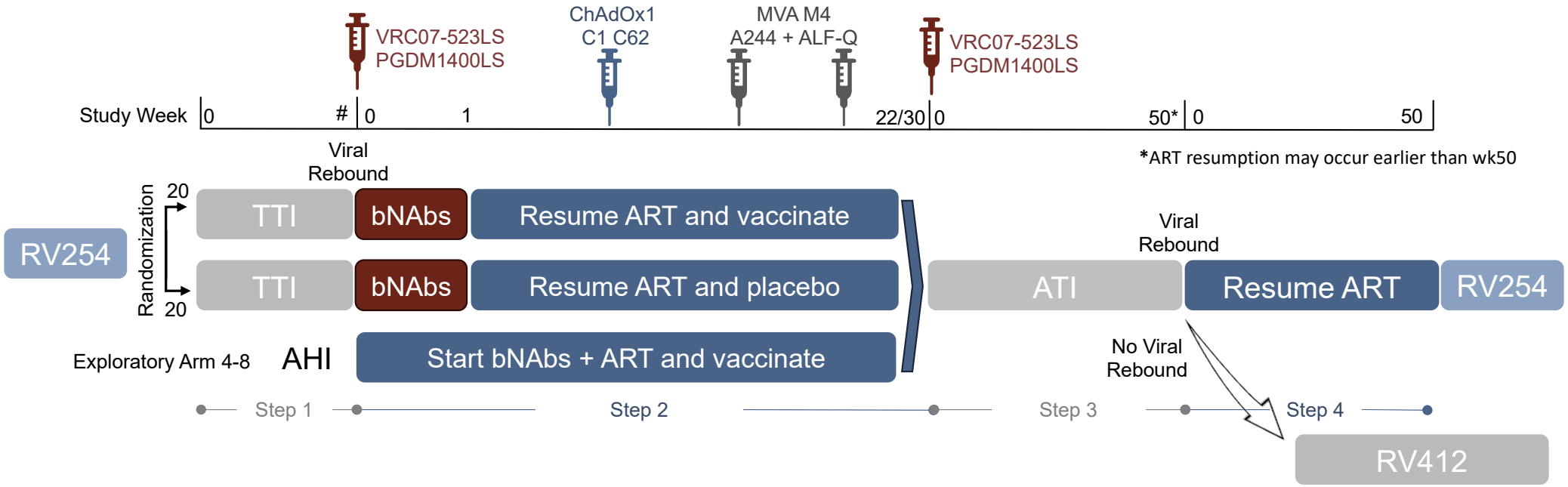
VL ~ 1000; stable (n=4)



No rebound (n=1)

Multiple complex combination approaches now being studied in well-powered, controlled studies

Lydie Trautmann



MHRP
U.S. MILITARY HIV RESEARCH PROGRAM

In the meantime, ART is getting even better, with safe, well-tolerated options that work in nearly everyone, and which may soon be as simple as a single injection given every 6 to 12 months

THE LANCET
Infectious Diseases

Switch to long-acting cabotegravir and rilpivirine in virologically suppressed adults with HIV in Africa (CARES): week 48 results from a randomised, multicentre, open-label, non-inferiority trial

*Cissy Kityo, Ivan K Mambule, Joseph Musaazi, Simiso Sokhela, Henry Mugerwa, Gilbert Ategeka, Fiona Cresswell, Abraham Siika, Josphat Kosgei, Reena Shah, Logashvari Naidoo, Kimton Opiyo, Caroline Otike, Karlien Möller, Arvind Kaimal, Charity Wambui, Veerle Van Eygen, Perry Mohammed, Fafa Addo Boateng, Nicholas I Paton, for the CARES trial team**

Cabotegravir/rilpivirine maintenance therapy: ~100% effective

The NEW ENGLAND JOURNAL of MEDICINE

Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women

L.-G. Bekker, M. Das, Q. Abdool Karim, K. Ahmed, J. Batting, W. Brumskine, K. Gill, I. Harkoo, M. Jaggernath, G. Kigozi, N. Kiwanuka, P. Kotze, L. Lebina, C.E. Louw, M. Malahleha, M. Manentsa, L.E. Mansoor, D. Moodley, V. Naicker, L. Naidoo, M. Naidoo, G. Nair, N. Ndlovu, T. Palanee-Phillips, R. Panchia, S. Pillay, D. Potloane, P. Selepe, N. Singh, Y. Singh, E. Spooner, A.M. Ward, Z. Zwane, R. Ebrahimi, Y. Zhao, A. Kintu, C. Deaton, C.C. Carter, J.M. Baeten, and F. Matovu Kiweewa, for the PURPOSE 1 Study Team*

Lenacapavir PrEP: 100% effective

What will a cure need to do to achieve regulatory approval? What will it need to do to address unmet needs with ART?

- What is the goal?
  - Providing more options for people on ART?
  - Providing options for those who for whatever reason are not on ART, or who cannot remain on ART indefinitely, or who are failing ART?
- Will a cure strategy need to be as effective and safe as standard-of-care?
  - Is this even possible?
- What kind of cures do people want? What will they take?
- What will be the regulatory framework?
- How will we decide which strategies to move forward? Do we need to focus?

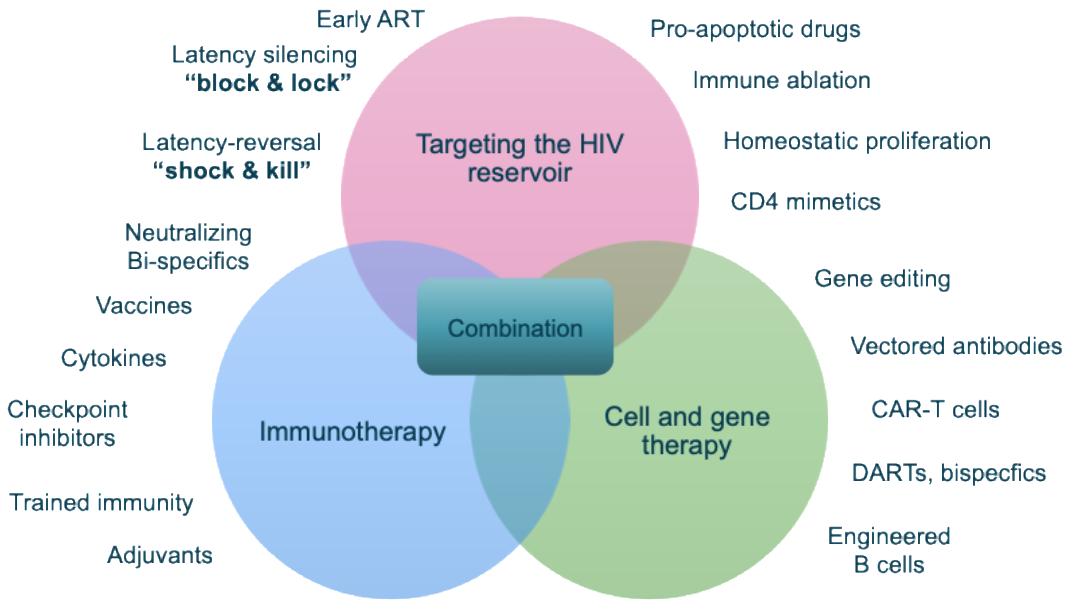


Figure: Afam Okoye

HIV Cure: The Public Health Argument

nature Review

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

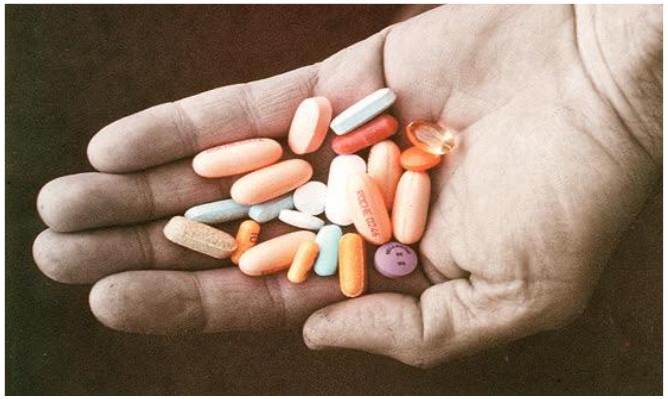
https://doi.org/10.1038/s41586-019-1841-8

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

To address the unmet needs in prevention and treatment, a curative intervention will need to be <u>safe, affordable, scalable, effective</u> in those populations that are not currently doing well on ART (for any reason) and (ideally) <u>prevent re-infection</u>

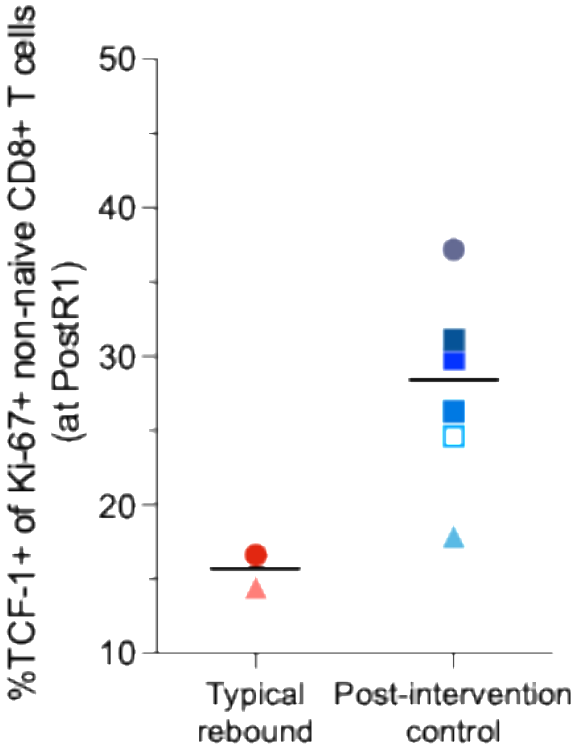
The ideal cure, one that would be truly transformative, are strategies that need to be given over a very brief period of time ("one shot cures")

There are several promising pathways toward a cure, but they are complex and not without risk. How might they be optimized?



AZT provided proof-of-concept for ART, inspiring others to develop better options, a process that continues to this day

Post-bNAb HIV control linked to early *in vivo* CD8+ T cell proliferative and effector responses




Demi Sandel


Rachel Rutishauser

nature medicine

Combination anti-HIV-1 antibody therapy is associated with increased virus-specific T cell immunity

Julia Niessl[1,2,3], Amy E. Baxter[1,2,3,9], Pilar Mendoza[4], Mila Jankovic[4], Yehuda Z. Cohen[4], Allison L. Butler[4], Ching-Lan Lu[4,10], Mathieu Dubé[1], Irina Shimeliovich[4], Henning Gruell[5,6,7], Florian Klein[5,7,8], Marina Caskey[4], Michel C. Nussenzweig[4,11]* and Daniel E. Kaufmann[1,2,3,11]*

nature

Early antibody therapy can induce long-lasting immunity to SHIV

Yoshiaki Nishimura[1], Rajeev Gautam[1], Tae-Wook Chun[2], Reza Sadjadpour[1], Kathryn E. Foulds[3], Masashi Shingai[1], Florian Klein[4,5], Anna Gazumyan[6], Jovana Golijanin[6], Mitzi Donaldson[3], Olivia K. Donau[1], Ronald J. Plishka[1], Alicia Buckler-White[1], Michael S. Seaman[7], Jeffrey D. Lifson[8], Richard A. Koup[3], Anthony S. Fauci[2], Michel C. Nussenzweig[6,9] & Malcolm A. Martin[1]

nature COMMUNICATIONS

Administration of broadly neutralizing anti-HIV-1 antibodies at ART initiation maintains long-term CD8$^+$ T cell immunity

Published online: 29 October 2022
Check for updates

Miriam Rosás-Umbert[1], Jesper D. Gunst[1,2], Marie H. Pahus[1], Rikke Olesen[1], Mariane Schleimann[2], Paul W. Denton[3], Victor Ramos[4], Adam Ward[5,6], Natalie N. Kinloch[7,8], Dennis C. Copertino[5,6], Tuixent Escribà[9], Anuska Llano[9], Zabrina L. Brumme[7,8], R. Brad Jones[5,6], Beatriz Mothe[9,10,11], Christian Brander[9,11,12], Julie Fox[13,14], Michel C. Nussenzweig[4,15], Sarah Fidler[16,17], Marina Caskey[4], Martin Tolstrup[1,2] & Ole S. Søgaard[1,2]

CROI 2025

HIV-Specific CD8+ T Cell Stemness Predicts Post-Intervention Control of Viremia

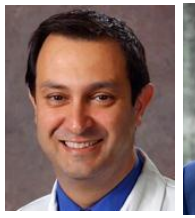
Zahra Kiani[1], Mpho Olatotse[1], Jonathan Urbach[1], Mathias Lichterfeld[1], Jesper D. Gunst[2], Ole S. Søgaard[3], Marina Caskey[4], Michel Nussenzweig[4], Bruce Walker[1], David R. Collins[1]

Lymph Node HIV-Specific CD8 T Cells of HIV Controllers Harbour a Specific Transcriptomic Signature

Erica Lana[1], Mathilde Foglierini-Perez[1], Philippe Guillaume[2], Riddhima Banga[1], Francesco Procopio[1], Matthias Cavassini[3], Sébastien Déglise[1], Alexandre Harari[2], Giuseppe Pantaleo[1], Matthieu Perreau[1], Andrea Mastrangelo[1]

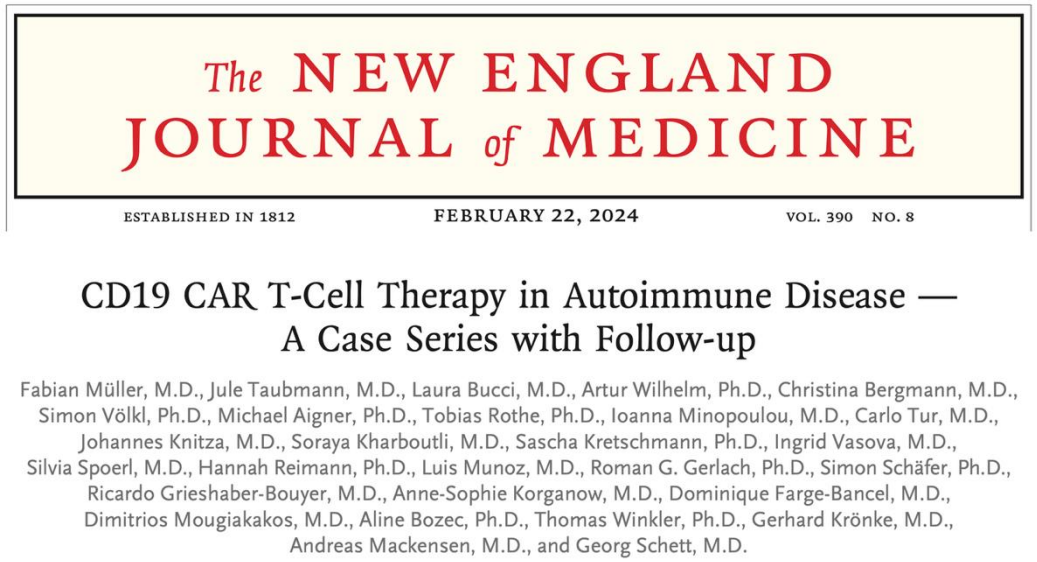
CAR-T cells recognizing vulnerable epitopes within HIV are now being studied; efforts to induce desirable phenotypic characteristics are making progress

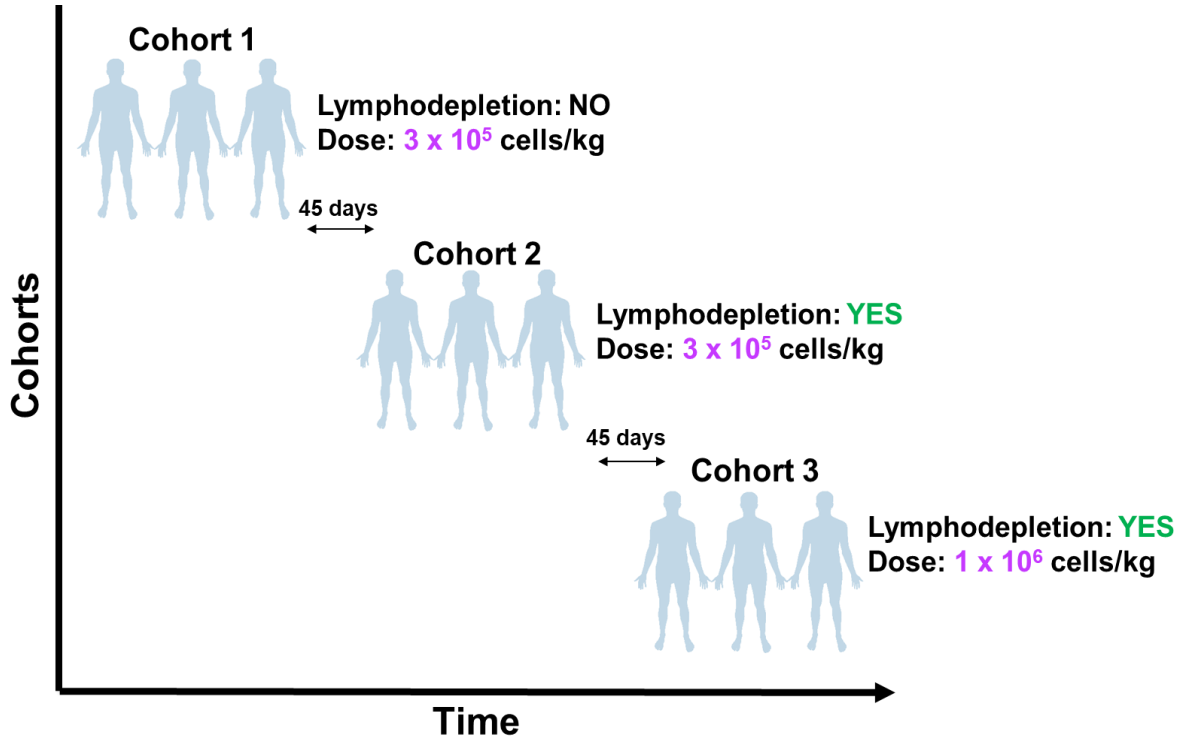
Revolution in autoimmunity (SLE, others) provides rationale that this approach can be safe and scalable



Mehrdad Abedi

Boro Dropulic





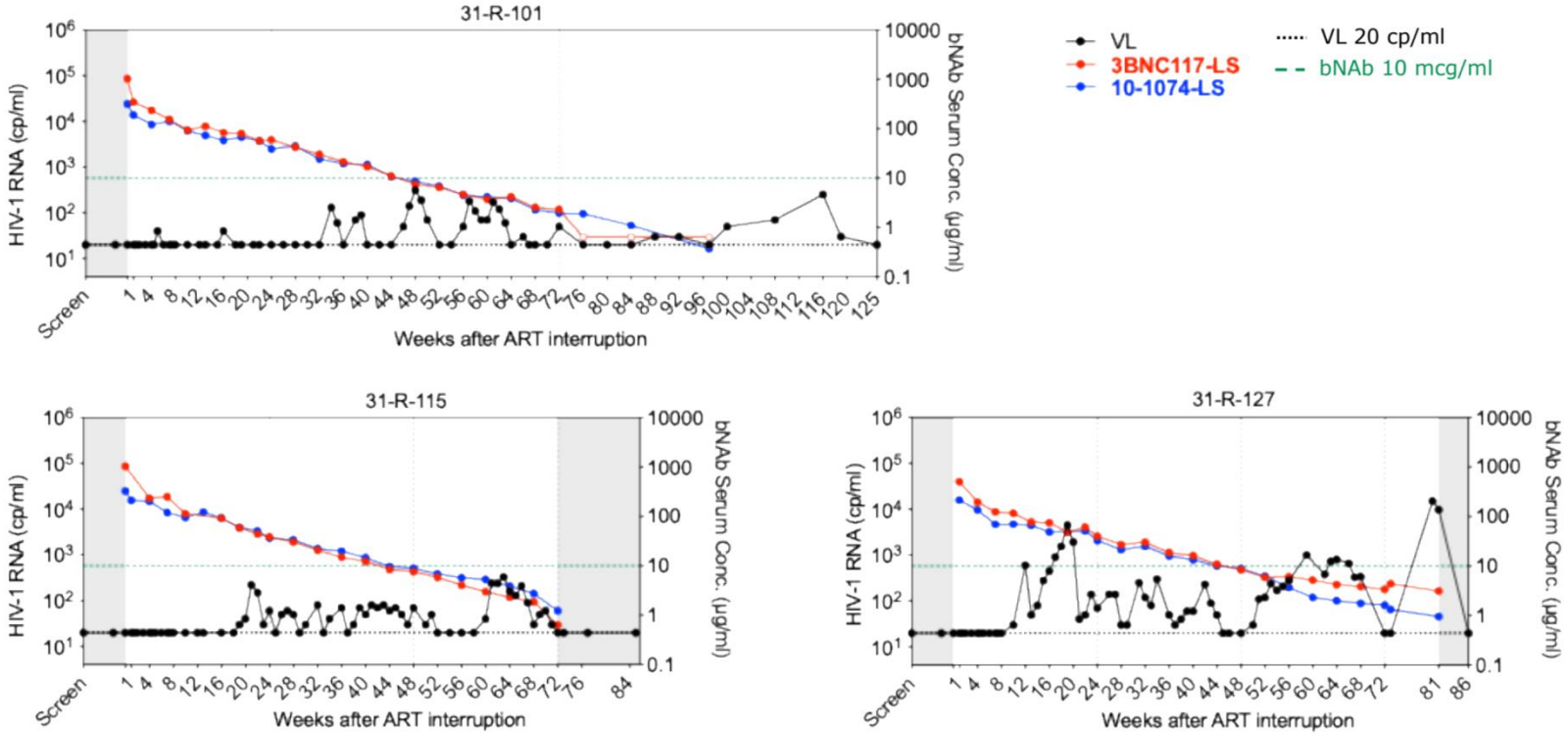
CaringCross

CIRM
CALIFORNIA'S STEM CELL AGENCY

HIV and CAR-T cells: Multiple barriers, all addressable

- Escape in HIV envelop protein
  - Used combination CARs
- Not enough antigen during ART
  - LRAs (to reduce reservoir)
  - Novel strategies aimed at detecting small amounts of antigen in development (HIT)
  - Focus on post-ART control
- Need for a durable (life-long) responses
  - HIV CAR-T cells studies 1990s: Cells persists for decades
- Cost and scalability
  - *Ex vivo*: Short-term processing in the clinic (“gene therapy is a box”, COG ~ 10K)
  - *In vivo*: Scalable and potentially affordable (COG ~2K)
- Toxicity and safety
  - CRS, ICANs assumed to be related to target cell burden/density; rare outside of cancer
  - Malignant transformation: "safe harbors”, Non-integrating approaches (AAV)

Post-bNAb control may also be due to low-levels of antibody
Direct antiviral activity, selection for poorly fit virus



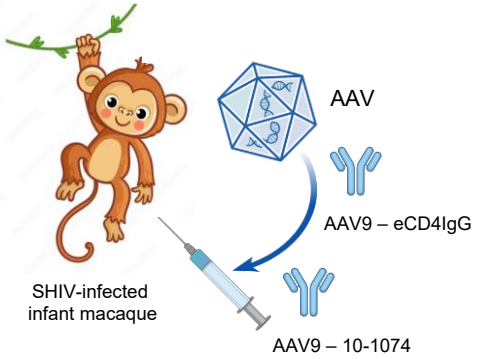
- 28 individuals on ART (chronic)
- 3BNC117 + 10-1074 at ATI
- IL-15 q3 wks during ATI (8 doses)
- 7 had “fluctuating” low levels of viremia for months, 3 of whom reached week 72

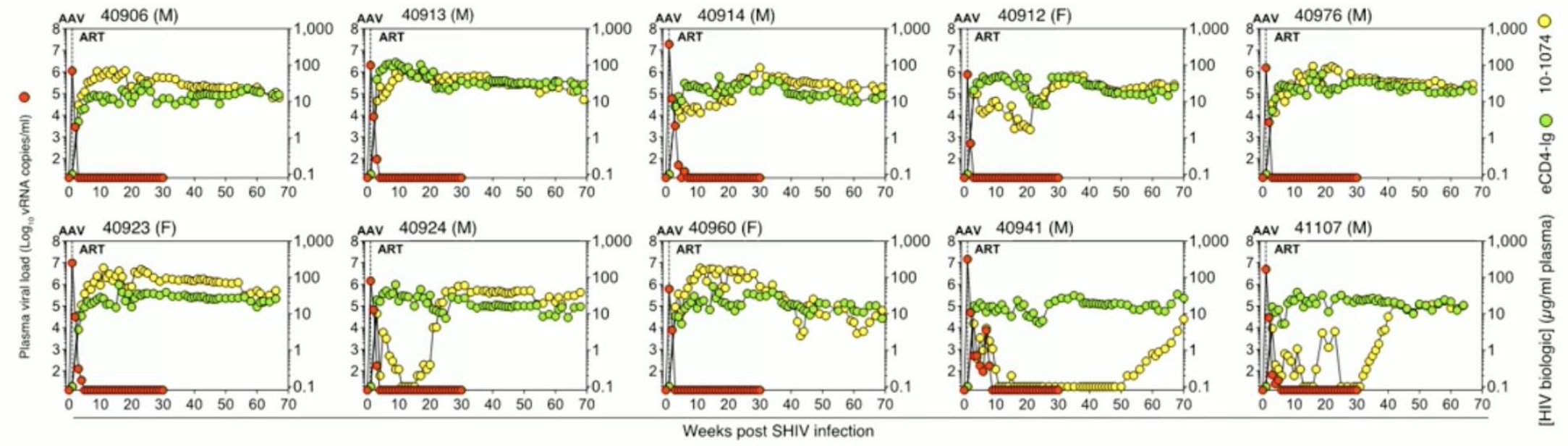
Marina Caskey, IAS 2025

CROI 2024
Conference on Retroviruses and Opportunistic Infections
March 3-6 | Denver, Colorado

AAV-Expressed HIV IgG Biologics Enable Durable ART-Free Viral Control in Infant Macaques

Daniel O'Hagan[1], Tracy Ordonez[2], Lucas Costa[1], Shilpi Pandey[2], Siddhartha Shandilya[1], Jeremy Smedley[2], Diogo M. Magnani[3], Deborah Persaud[4], Ann Chahroudi[5], Matthew R. Gardner[5], Michael D. Alpert[6], Ann J. Hessell[2], Michael Farzan[7], Nancy L. Haigwood[2], Mauricio A. Martins[1]





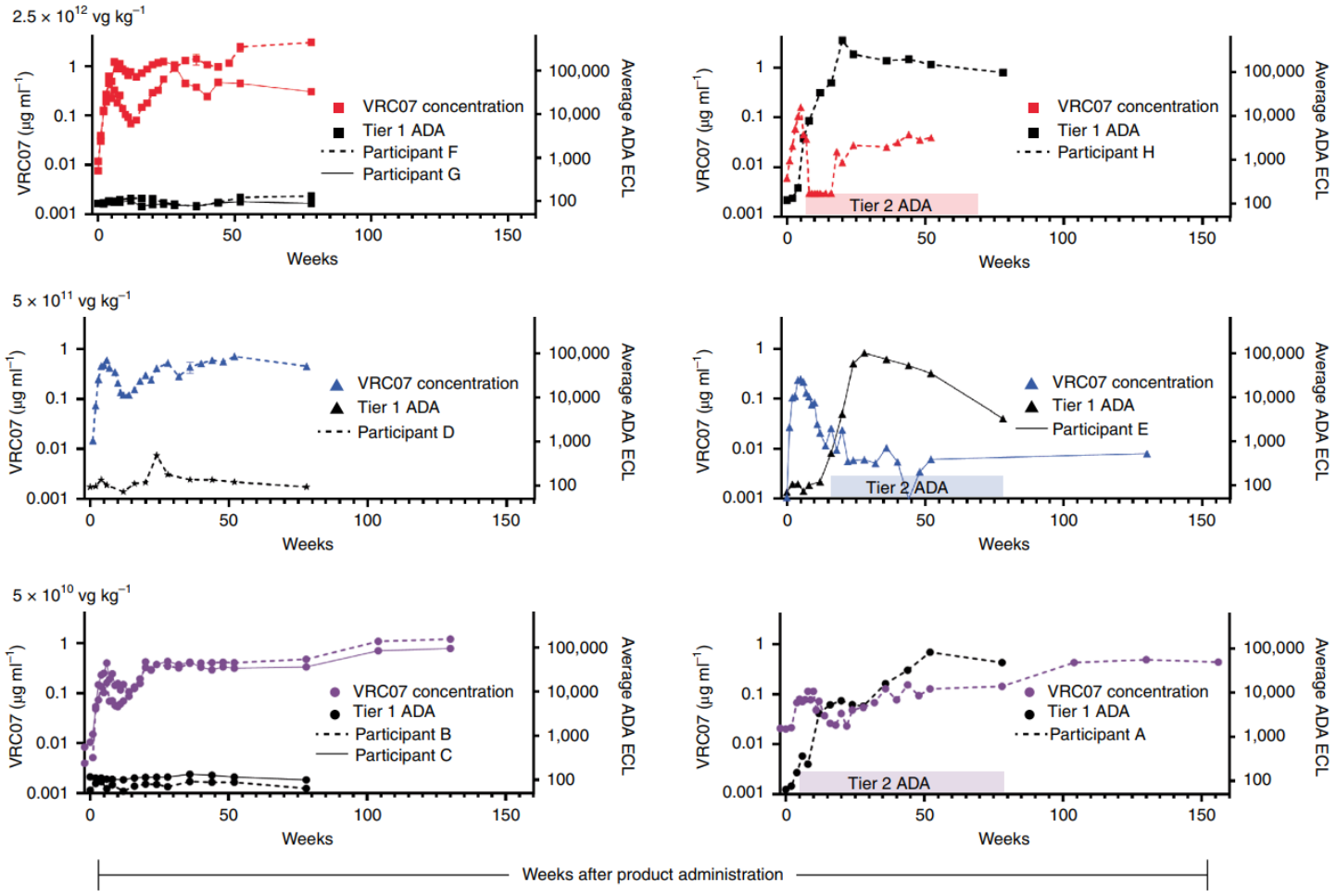
A single shot of a vector (AAV) that delivered to muscle cells the genes for two antibodies (eCD4, 10-1074) resulted in sustained production of antibodies (years/decades?) and post-ART control

Scalable cure strategies

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*



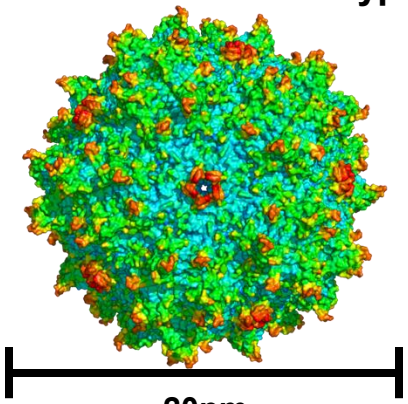
AAV8 delivery of a gene for VRC-07 was safe and resulted in sustained expression, albeit at low levels

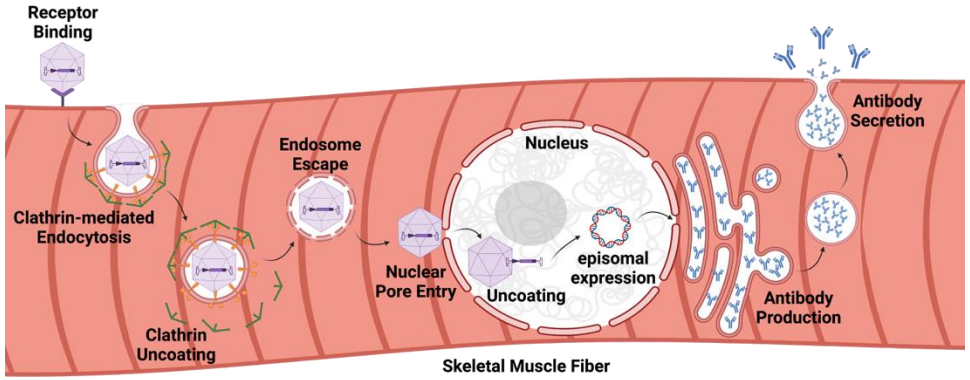
A5430, “Administration of AAV8-VRC07 as Vectored ImmunoTherapy against HIV"



Michael Peluso, Kara Chew, Alex Balazs

Adeno Associated Virus Serotype 8 (AAV8)





- Small Trials RFA (n=30)
- Goals
  - Identify strategies to prevent ADA and enhance expression
  - Explore impact of bNAbs on size and distribution of intact reservoir
- Three strategies
  - Single-dose AAV8-VRC07
  - Split dose AAV8-VRC07
  - Brief immune suppression

Acknowledgements

UCSF SCOPE Team

UCSF University of California San Francisco

D&RE

ZUCKERBERG SAN FRANCISCO GENERAL Hospital and Trauma Center

UCSF-BAY AREA CFAR CENTER FOR AIDS RESEARCH

NIH National Institutes of Health

amfAR MAKING AIDS HISTORY

BILL & MELINDA GATES foundation