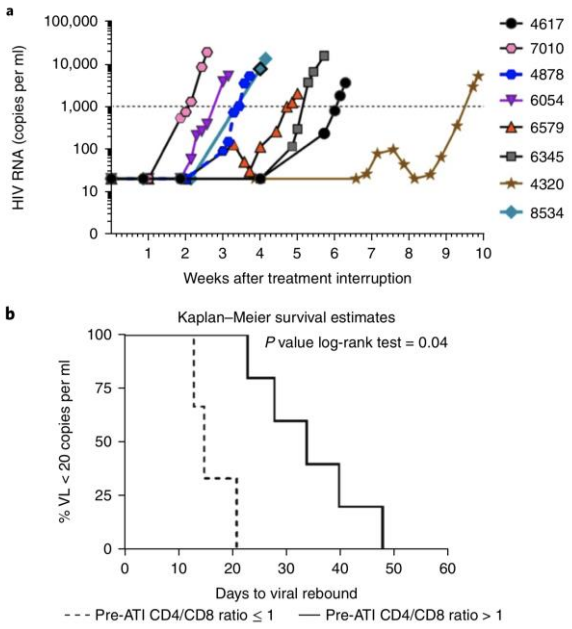
Clinical outcomes of immune therapies in HIV remission

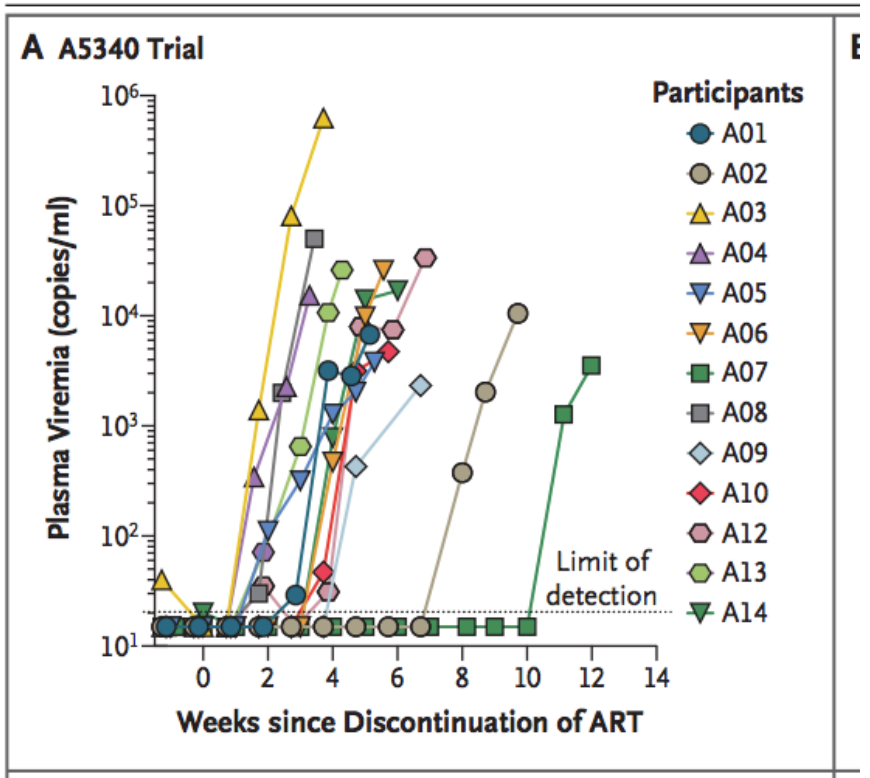
Sarah Fidler Imperial College London

What happens when ART is stopped?
Even if started ART Very early, in acute infection



RV411 Study group Thailand
N = 8 individuals starting ART at Feibig I (first 2 weeks after infection)
On ART median 2.8 years
All experienced rapid viral rebound (>20 cpm x 2) by median 26 days following analytical treatm interruption
None controlled by week 24

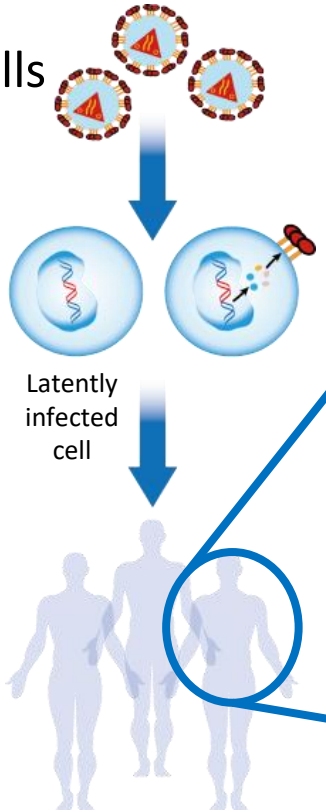
Colby et al Nature Medicine 2018 24 923-926



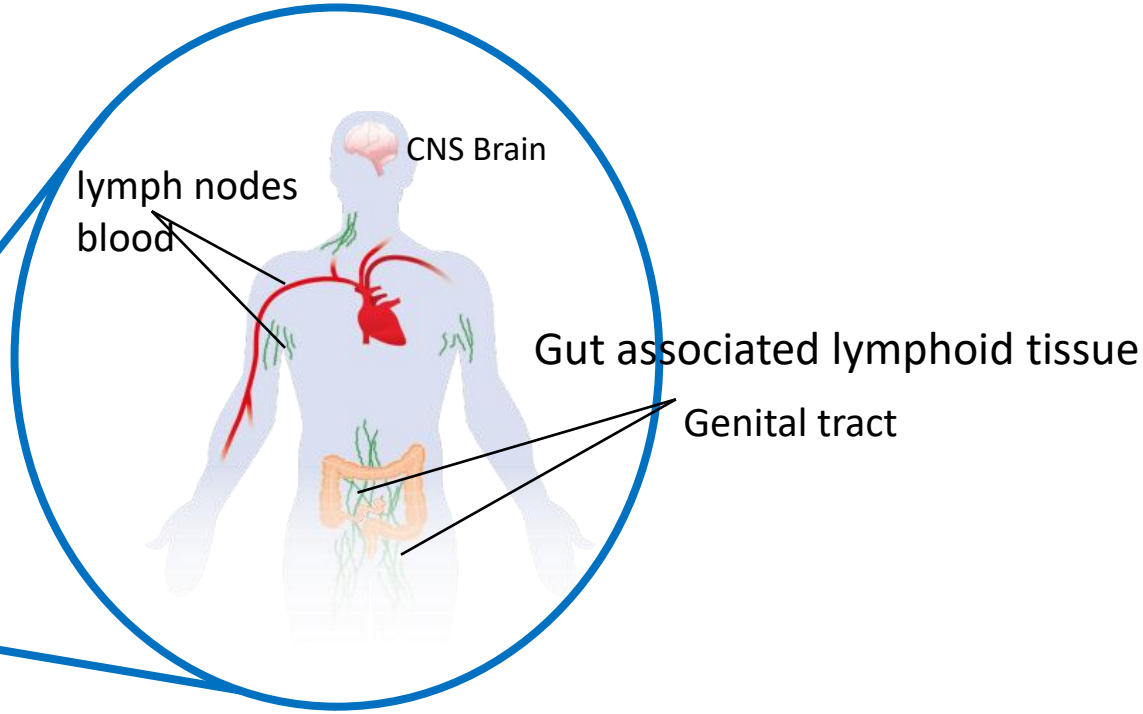
Why can’t ART cure HIV?

HIV infects CD4+ cells

Some CD4+ T-cells become resting memory cells; ‘reservoir’



HIV reservoirs



Larger reservoir size accelerates clinical progression
& predicts time to viral rebound

ART during acute or early HIV infection, leading to:

- Reduced inflammation and immune activation
- Limited viral diversification
- Preserved functional immune responses
- Lower reservoir burden and complexity

Combination interventions:

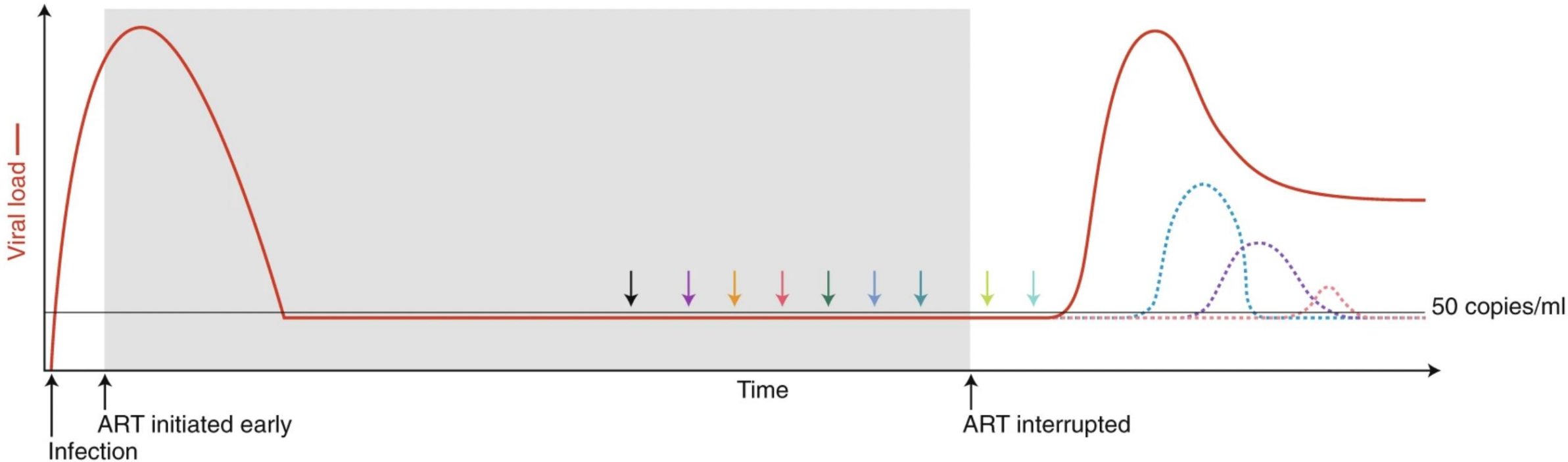
bNAbs Vaccines CAR T cells

Gene therapy LRAs

Immunomodulatory agents, for example cytokines, TLR agonists.

ART interruption followed by:

- Regular monitoring for HIV RNA in plasma
- Additional monitoring: immune responses, reservoir size and composition



Therapeutic vaccine trials

- Goal to focus HIV-specific immune responses that have been shown to enhance viral control towards conserved epitopes
- To provide long term protection against viral reactivation on stopping ART

Therapeutic HIV vaccine trials

Therapeutic vaccination for HIV hopes and challenges. Stephenson, Kathryn E.

Current Opinion in HIV and AIDS: September 2018 - Volume 13 - Issue 5 - p 408-415

Vaccine name	Vaccine design	Year	Latency reversal agent	ATI	Placebo		Immune responses	Impact on viral control	Ref
					Vaccine phase	ATI phase			
MVA.HIVconsv	MVA vector (conserved sequences)	2017	No	No	Yes	–	Minimal	–	[15▪]
DNA/rVSV	DNA (IL-12 + 6 HIV proteins), live attenuated VSV (Gag)	2017	No	Yes	Yes	Yes	Minimal	No	[16▪▪]
DNA	DNA (Gag, Pol, Nef, Env)	2010	No	Yes	Yes	Yes	Minimal	No	[17]
MVA-B	MVA vector (gp120, Gag, Pol, Nef)	2015	Yes Disulfiram	Yes	Yes	Yes	Narrow	No	[18]
rAd5 Gag	Adenovirus serotype 5 vector (Gag)	2010	No	Yes	Yes	Yes	Narrow	No	[19]
TUTI-16	Peptide vaccine (Tat sequences)	2012	No	Yes	Yes	Yes	Narrow	No	[20]
AGS-004	Dendritic cells stimulated with Gag, Nef, Rev, Vpr	2016	No	Yes	Yes	Yes	Narrow	No	[21▪]
ALVAC-HIV, Remune	Canarypox vector (Env, Gag, Pol, Nef), inactivated envelope-depleted virus	2005	No	Yes	Yes	Yes	Narrow	No	[22]
DNA/rAd5	DNA (HIV peptides), Ad5 vector (Gag, Pol, Env)	2015	Yes ART intensification	No	Yes	–	Broad	–	[23]
HIVAX	Attenuated, mutated HIV-1 strain	2016	No	Yes	Yes	No	Broad	Maybe[a]	[24▪]
ALVAC-HIV, Lipo-6T, IL-2	Canarypox vector (Env, Gag, Pol, Nef), lipopeptide vaccine (Nef, Gag, Pol, IL-2)	2005	No	Yes	Yes	Yes	Broad	Yes	[25]
ALVAC-HIV, Lipo-6T, IL-2	Canarypox vector (Env, Gag, Pol, and Nef), lipopeptides (Nef, Gag, Pol, IL-2)	2006	No	Yes	Yes	Yes	Broad	Yes	[26]
DC-HIV	Dendritic cells stimulated with autologous HIV	2011	No	Not on ART	Yes	–	Broad	Yes	[27]

ART, antiretroviral therapy; ATI, analytical treatment interruption; Ref, reference.
[a]Definitive efficacy cannot be determined without placebo control during ATI.

nature medicine

Article

https://doi.org/10.1038/s41591-022-02060-2

Safety, immunogenicity and effect on viral rebound of HTI vaccines in early treated HIV-1 infection: a randomized, placebo-controlled phase 1 trial

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A list of authors and their affiliations appears at the end of the paper

Aelix Vaccine conferred period of PTC off ART vs placebo

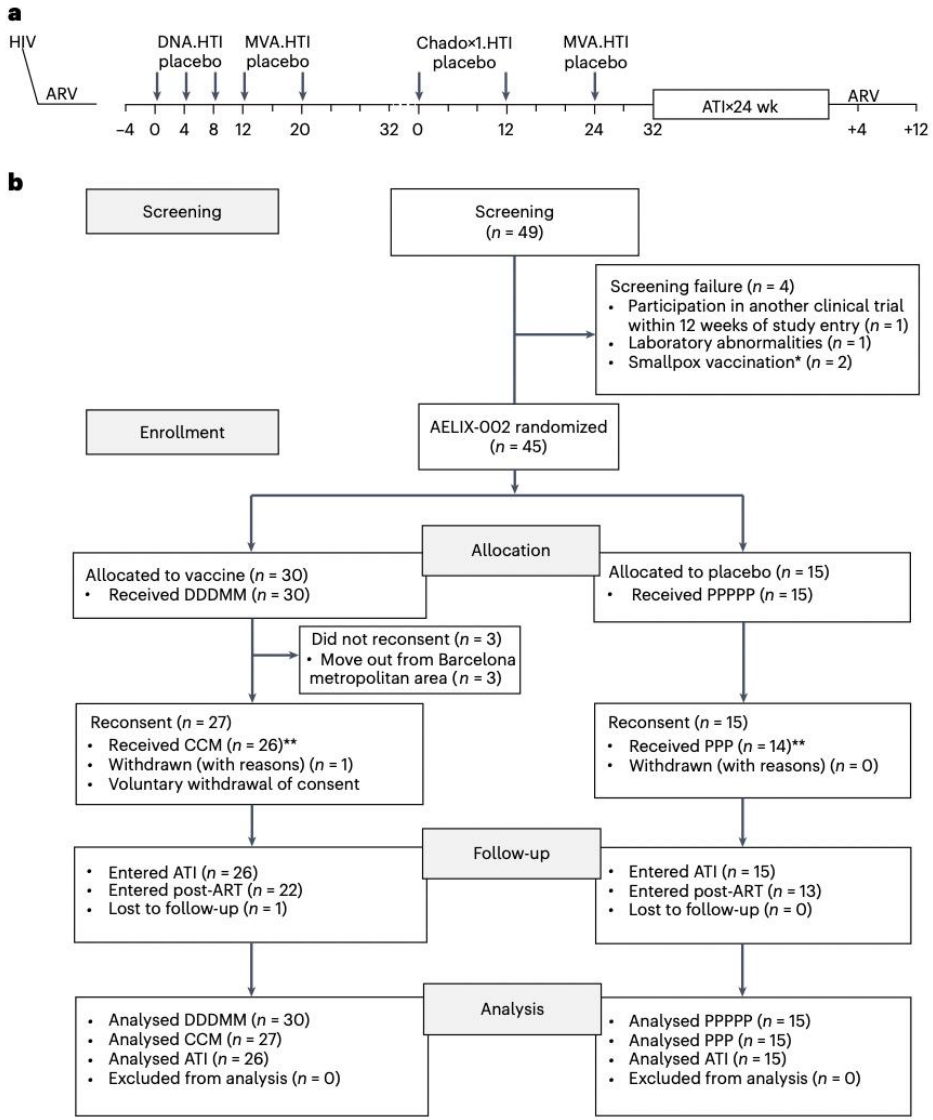


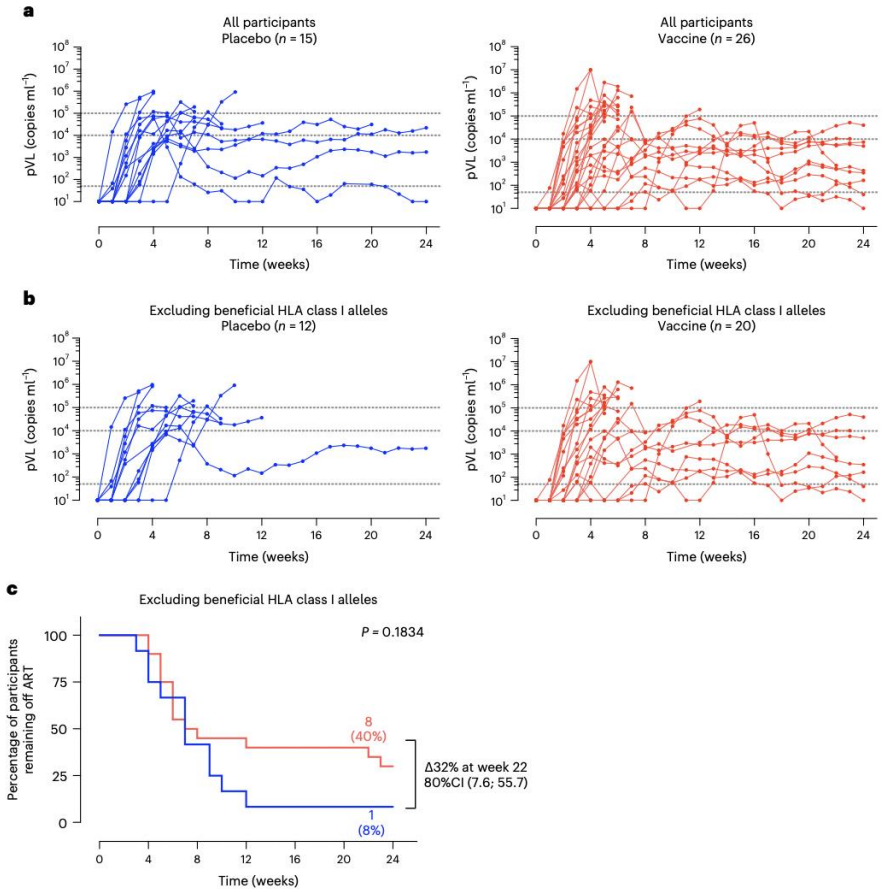
Fig. 1 | Trial design. a, Schematic trial design and study visits. **b**, Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the trial. HIV, human immunodeficiency virus; ARV, antiretroviral therapy; ATI, analytical treatment interruption; D, DNA.HTI; M, MVA.HTI; C, ChAdOx1.HTI; P, placebo.

N = 45 2:1 vaccine vs placebo 30 :15

HTI immunogen DNA vector at weeks 0,4,8 plus 2 doses of HTI Immunogen in MVA vector weeks 12 and 20 vs placebo

Primary outcome: Safety and immunogenicity

Viral rebound dynamics by study arm
Vaccine (red) vs placebo (blue)



ATI: n = 41/45

Viral load rebounded within 2-3 weeks after ATI BUT to lower levels than pre-ART

8 stayed off ART out to 24 weeks in vaccine arm, VL < 2,000

Combined Immunotherapy: Proof-of-concept in monkeys

nature

Immune clearance of highly pathogenic SIV infection

Scott G. Hansen[1]*, Michael Piatak Jr[2]*, Abigail B. Ventura[1], Colette M. Hughes[1], Roxanne M. Gilbride[1], Julia C. Ford[1], Kelli Oswald[2], Rebecca Shoemaker[2], Yuan Li[2], Matthew S. Lewis[1], Awbrey N. Gilliam[1], Guangwu Xu[1], Nathan Whizin[1], Benjamin J. Burwitz[1], Shannon L. Planer[1], John M. Turner[1], Alfred W. Legasse[3], Michael K. Axthelm[3], Jay A. Nelson[2], Klaus Früh[2], Jonah B. Sacha[2], Jacob D. Estes[2], Brandon F. Keele[2], Paul T. Edlefsen[4], Jeffrey D. Lifson[2] & Louis J. Picker[1]

nature

Ad26/MVA therapeutic vaccination with TLR7 stimulation in SIV-infected rhesus monkeys

Erica N. Borducchi[1], Crystal Cabral[1], Kathryn E. Stephenson[1], Jinyan Liu[1], Peter Abbink[1], David Ng'ang'a[1], Joseph P. Nkolola[1], Amanda L. Brinkman[1], Lauren Peter[1], Benjamin C. Lee[1], Jessica Jimenez[1], David Jetton[1], Jade Mondesir[1], Shanell Mojta[1], Abhishek Chandrashekar[1], Katherine Molloy[2], Galit Alter[3], Jeffrey M. Gerold[3], Alison L. Hill[3], Mark G. Lewis[4], Maria G. Pau[5], Hanneke Schuitemaker[5], Joseph Heeney[6], Roman Gerlach[6], Jerome H. Kim[7,8], Merlin L. Robb[7], Nelson L. Michael[7] & Dan H. Barouch[1,2]

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]

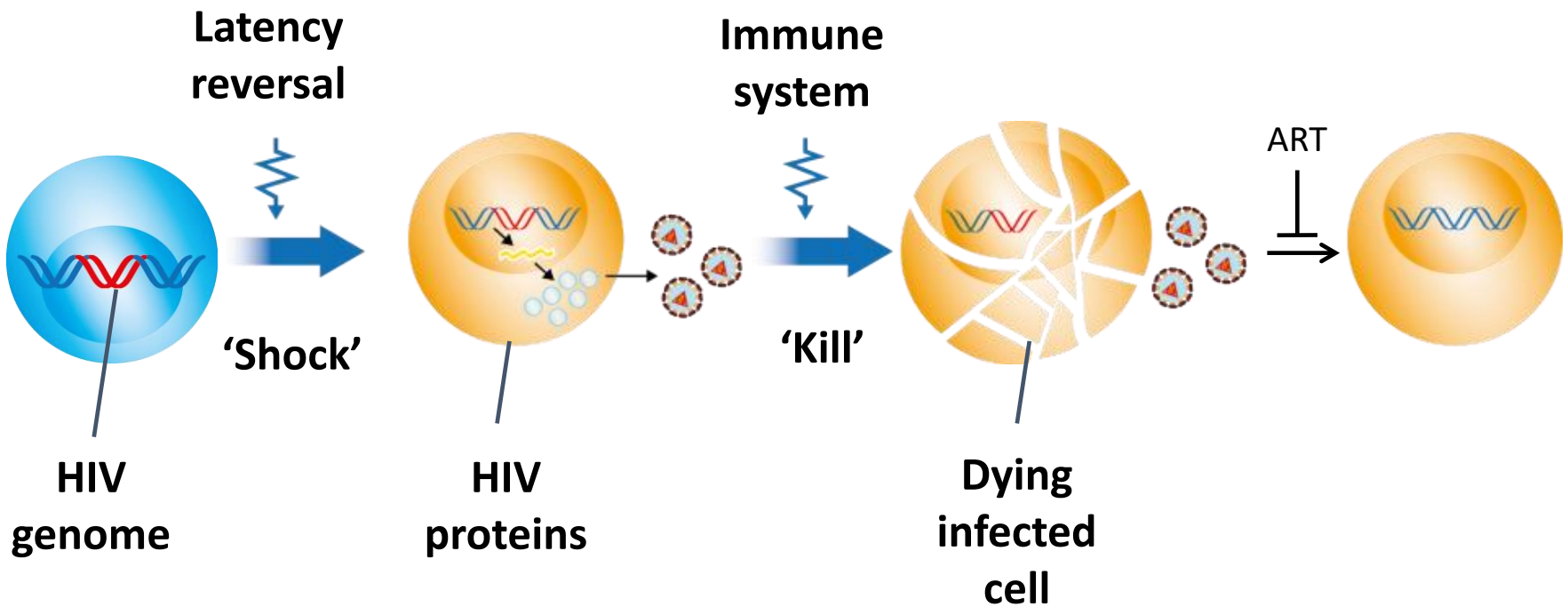
nature

Antibody and TLR7 agonist delay viral rebound in SHIV-infected monkeys

Erica N. Borducchi[1,*], Jinyan Liu[1,*], Joseph P. Nkolola[1,*], Anthony M. Cadena[1,2], Wen-Han Yu[1], Stephanie Fischinger[1], Thomas Broge[1], Peter Abbink[1], Noe B. Mercado[1], Abhishek Chandrashekar[1], David Jetton[1], Lauren Peter[1], Katherine McMahan[1], Edward T. Moseley[1], Elena Bekerman[1], Joseph Heneigouwer[1], Wenjun Li[3], Mark G. Lewis[3], Galit Alter[3], Roman Gelezunas[3] & Dan H. Barouch[1,2,4]

Courtesy of Steve Deeks

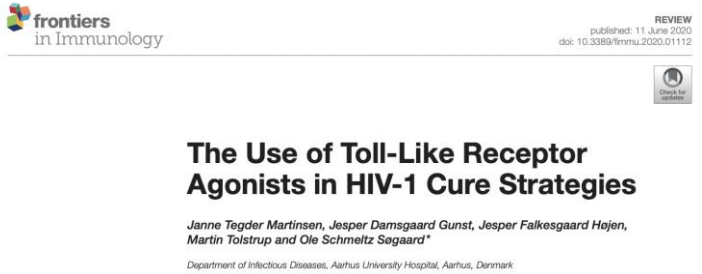
HIV Cure approach “Kick and Kill”



1. Deeks SG. Nature 2012;487:439–40. 2. Walker-Sperling VE, et al. J Virol 2015;89:9631–8.

What is a (Toll-like receptor) TLR-Agonist

- There are 10 different TLRs expressed on immune cells; NK, B-cells and DCs
- TLRs stimulate innate immune cells leading to the activation of humoral and cellular immunity
- They are used as anti-tumour agents in cancer
- They have the capacity to induce the upregulation of IFNg genes
- TLR agonists may reverse HIV latency



Aelix 003
Combination Therapeutic vaccine + TLR-7 agonist

- randomised, double-blind, placebo-controlled
- safety, tolerability, and immunogenicity study
- Intervention: HTI vaccine and Gilead's TLR-7 agonist vesatolimod (GS-9620)
- Early diagnosed, early treated HIV-infected individuals.
- 57 participants and be conducted in 10 sites in Spain.
- After vaccination and TLR-7 agonist treatment, the participants will proceed to an ATI phase to assess their capacity to control viral replication in the absence of anti-retroviral drugs.
- Data from this trial is expected in late 2022.

Antiretroviral therapy alone versus antiretroviral therapy with a kick and kill approach, on measures of the HIV reservoir in participants with recent HIV infection (the RIVER trial): a phase 2, randomised trial

Sarah Fidler, Wolfgang Stöhr, Matt Pace, Lucy Dorrell, Andrew Lever, Sarah Pett, Sabine Kinloch-de Loes, Julie Fox, Amanda Clarke, Mark Nelson, John Thornhill, Maryam Khan, Axel Fun, Mikaila Bandara, Damian Kelly, Jakub Kopycinski, Tomáš Hanke, Hongbing Yang, Rachel Bennett, Margaret Johnson, Bonnie Howell, Richard Barnard, Guoxin Wu, Steve Kaye, Mark Wills, Abdel Babiker, John Frater, on behalf of the RIVER trial study group

Summary

Background Antiretroviral therapy (ART) cannot cure HIV infection because of a persistent reservoir of latently infected cells. Approaches that force HIV transcription from these cells, making them susceptible to killing—termed kick and kill regimens—have been explored as a strategy towards an HIV cure. RIVER is the first randomised trial to determine the effect of ART-only versus ART plus kick and kill on markers of the HIV reservoir.

Methods This phase 2, open-label, multicentre, randomised, controlled trial was undertaken at six clinical sites in the UK. Patients aged 18–60 years who were confirmed as HIV-positive within a maximum of the past 6 months and started ART within 1 month from confirmed diagnosis were randomly assigned by a computer generated randomisation list to receive ART-only (control) or ART plus the histone deacetylase inhibitor vorinostat (the kick) and replication-deficient viral vector T-cell inducing vaccines encoding conserved HIV sequences ChAdV63. HIVconsv-prime and MVA.HIVconsv-boost (the kill; ART + V + V; intervention). The primary endpoint was total HIV DNA isolated from peripheral blood $CD4^+$ T cells at weeks 16 and 18 after randomisation. Analysis was by intention to

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See Online/Comment
https://doi.org/10.1016/S0140-6736(20)30264-6

Department of Infectious Disease, Imperial College London, London, UK
(Prof S Fidler PhD, M Khan BSc, J Thornhill PhD, S Kaye PhD);
NIHR Imperial Biomedical Research Centre, London, UK

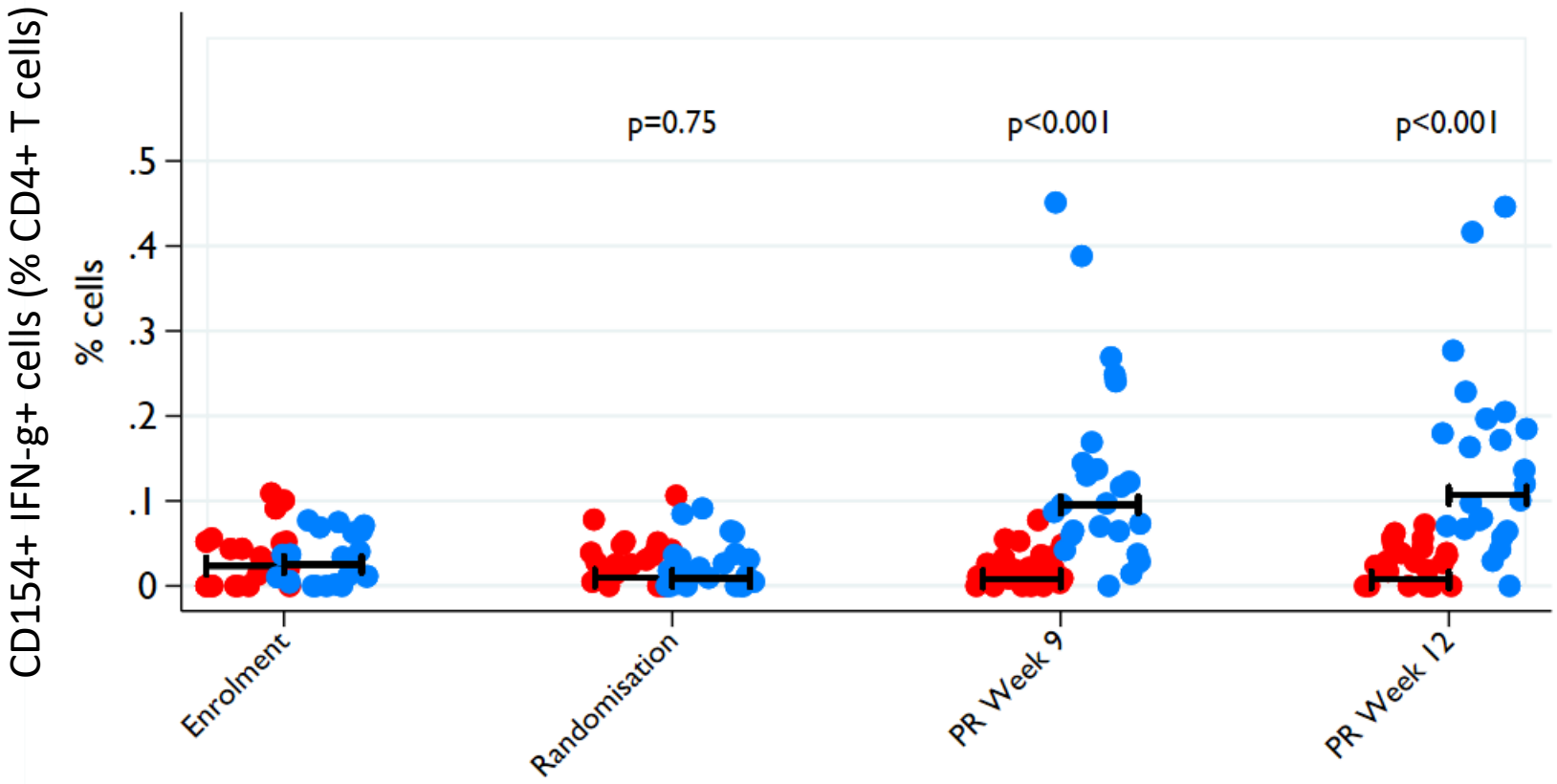
phase 2, open-label, multicentre, randomised, controlled trial was undertaken at six clinical sites in the UK

(the kick) deacetylase inhibitor vorinostat

(the kill) Vaccine: replication-deficient viral vector T-cell inducing vaccines encoding conserved HIV sequences ChAdV63. HIVconsv-prime and MVA.HIVconsv-boost

Primary endpoint: total HIV DNA isolated from peripheral blood $CD4^+$ T-cells at weeks 16 and 18 after randomisation

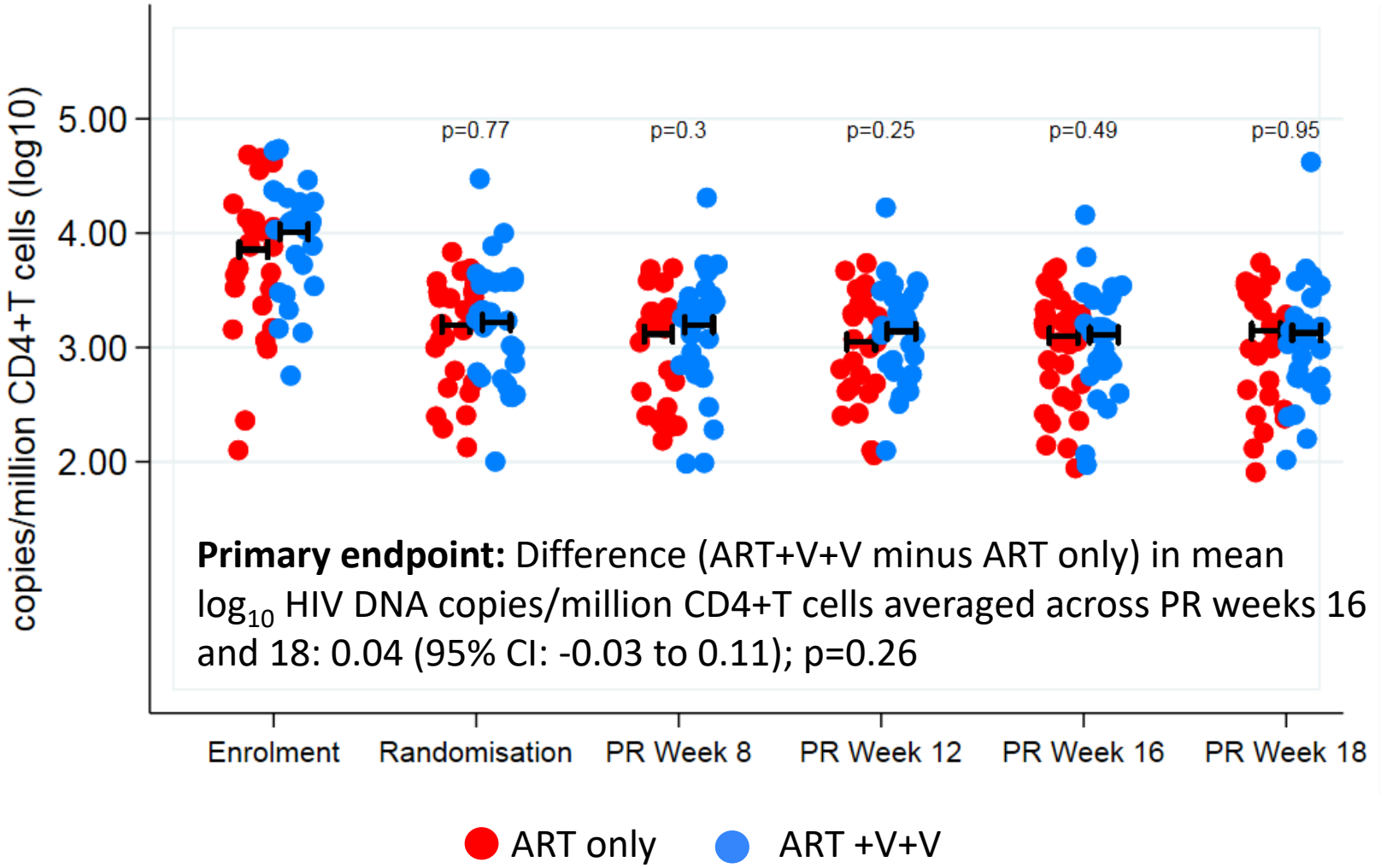
ART + V + V boosts functional HIV-specific CD4+ T cells



p-values: rank tests for difference between groups per time-point

ART only ART +V+V

BUT; the change seen in HIV reservoir (Total HIV DNA) over time, was the same by study group



Primary endpoint: Difference (ART+V+V minus ART only) in mean $\log_{10}$ HIV DNA copies/million CD4+T cells averaged across PR weeks 16 and 18: 0.04 (95% CI: -0.03 to 0.11); p=0.26

The future of HIV therapeutic vaccine approach

No therapeutic vaccine has yet to induce long-term HIV remission following ATI in a randomized controlled trial.

- Which is the best vaccine design?
  - Which epitopes are truly “reservoir epitopes”
  - Are these best to be conserved or individual viral variant specific
- When is the best time to vaccinate?
  - Should we focus to treated acute/early infection in the first place to ensure immune recovery
  - Should we pre-screen for immune recovery prior to enrolment
- At what point and which combination intervention be given?
  - Should we prime vaccine induced responses before after or during immune modulation using other agents?

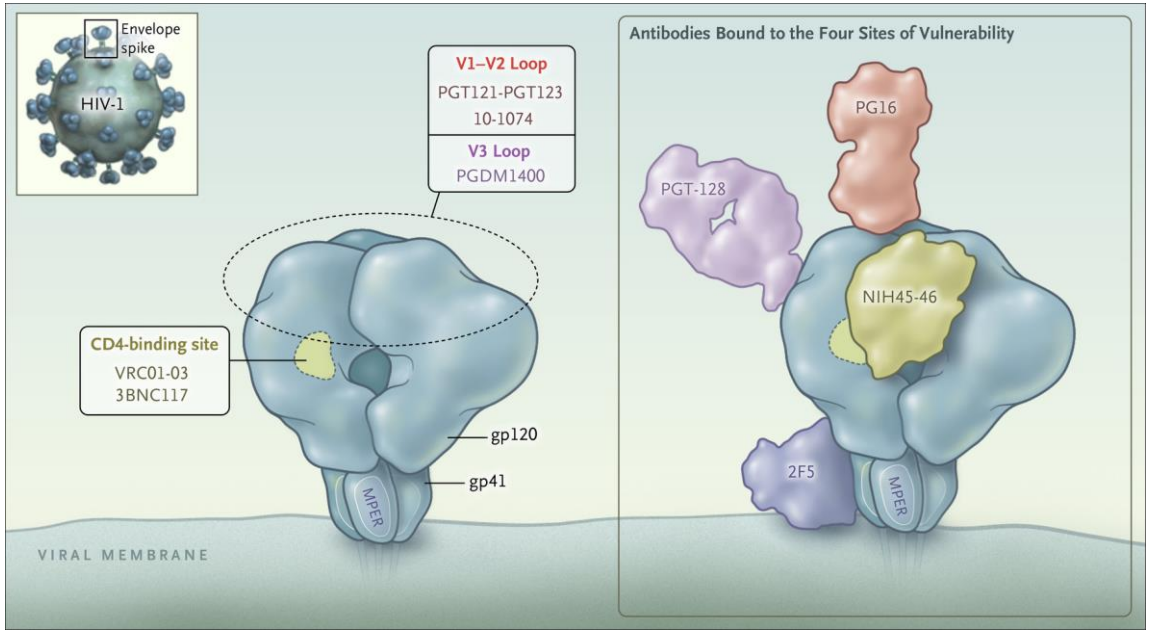
Neutralising Antibodies (bNAbs)

- Neutralising antibodies are antibodies that block pathogens to render them no longer infectious or pathogenic.

- HIV-specific neutralising antibodies target the HIV envelope spike protein

Broadly neutralising antibodies

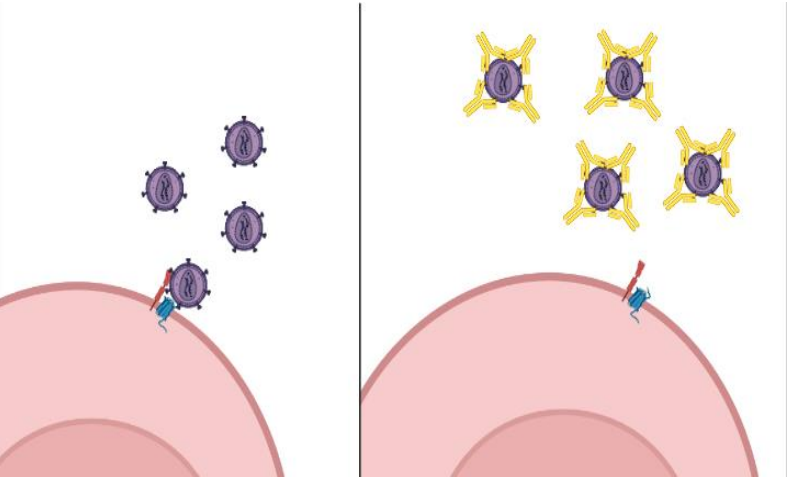
- Most neutralising antibodies developed in people with chronic HIV infection are strain specific,
- ~1% develop antibodies with the neutralising breadth and potency to overcome HIV diversity.
- Highly potent 2nd generation bNAbs now able to be manufactured and studied in clinical trials as novel HIV therapy.



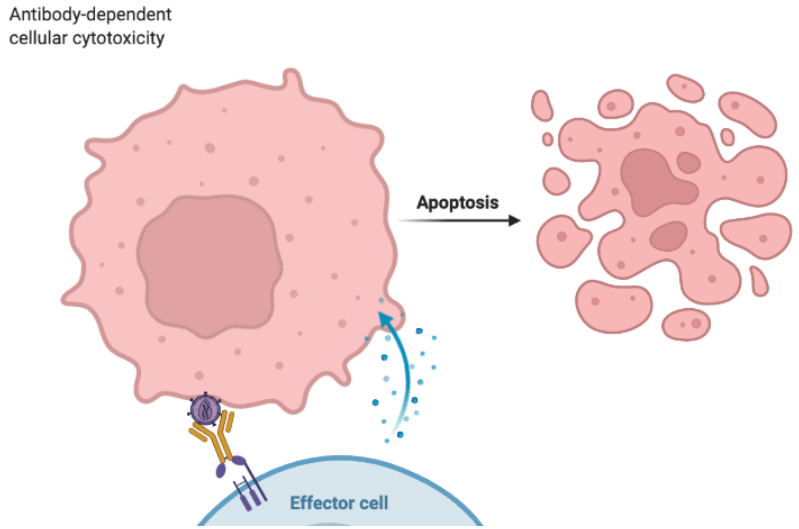
Caskey et al. NEJM 2016

How do bNAbs work?

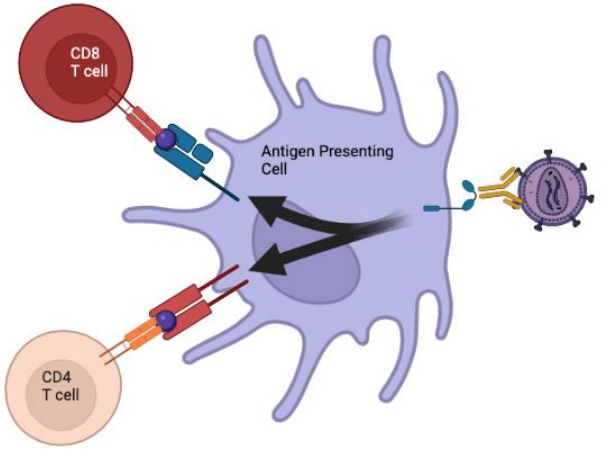
Disrupting virus-receptor interactions



Antibody-dependent cell-mediated cytotoxicity (ADCC)

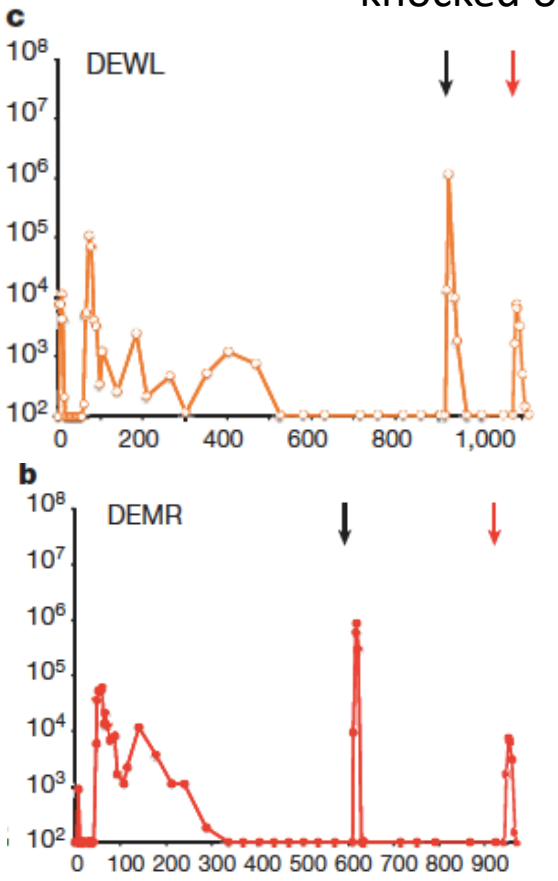


**Stimulating long-lasting HIV-specific CD8-mediated cellular immune responses (Vaccinal effect)*



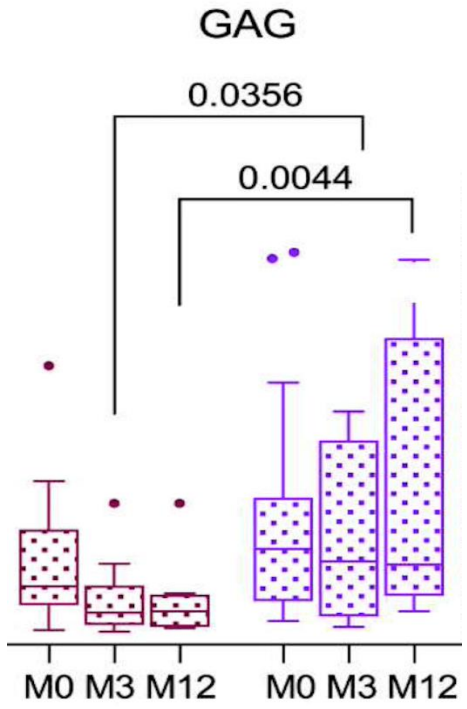
Evidence for a bNAB-related vaccinal effect

T cells knocked out



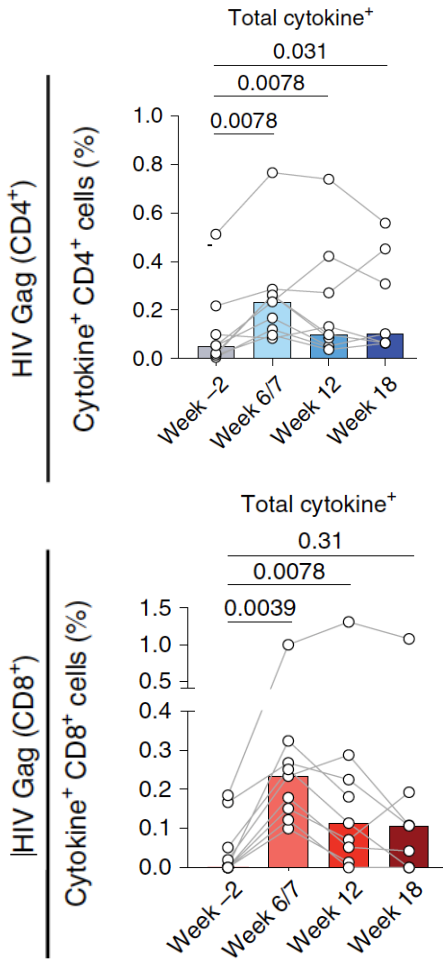
Nishimura; Nature

Post-bNAb control in macaques reversed by anti-CD8 Rx



Rosas-Umbert, Sogaard; CROI 2022

Gag-specific CD8s increase after 3BNC-117



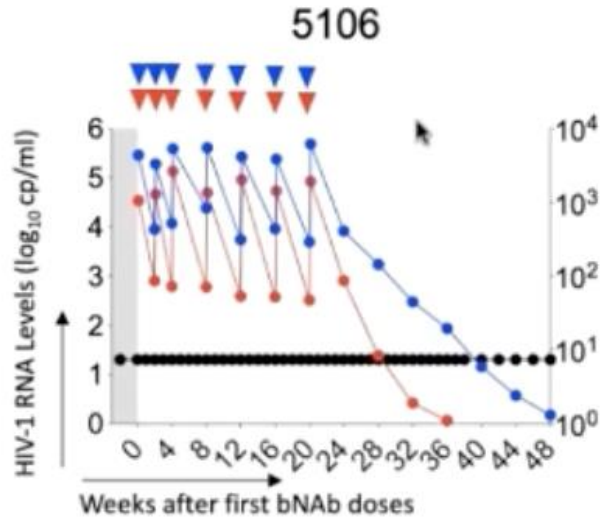
Niessl; Nat Med

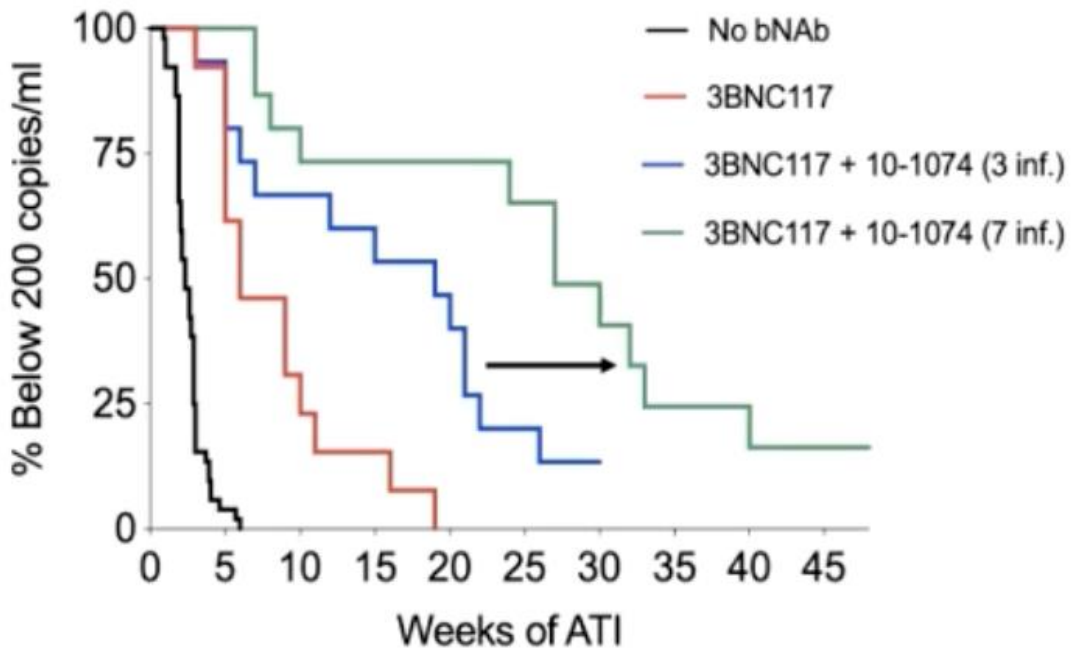
Increase in multiple cytokines after bNAbs

Combination of two bNAbs: maintains viral suppression in the absence of ART

Preliminary ongoing study

3BNC117+ 10-1074– infusions over 20 weeks in the absence of ART

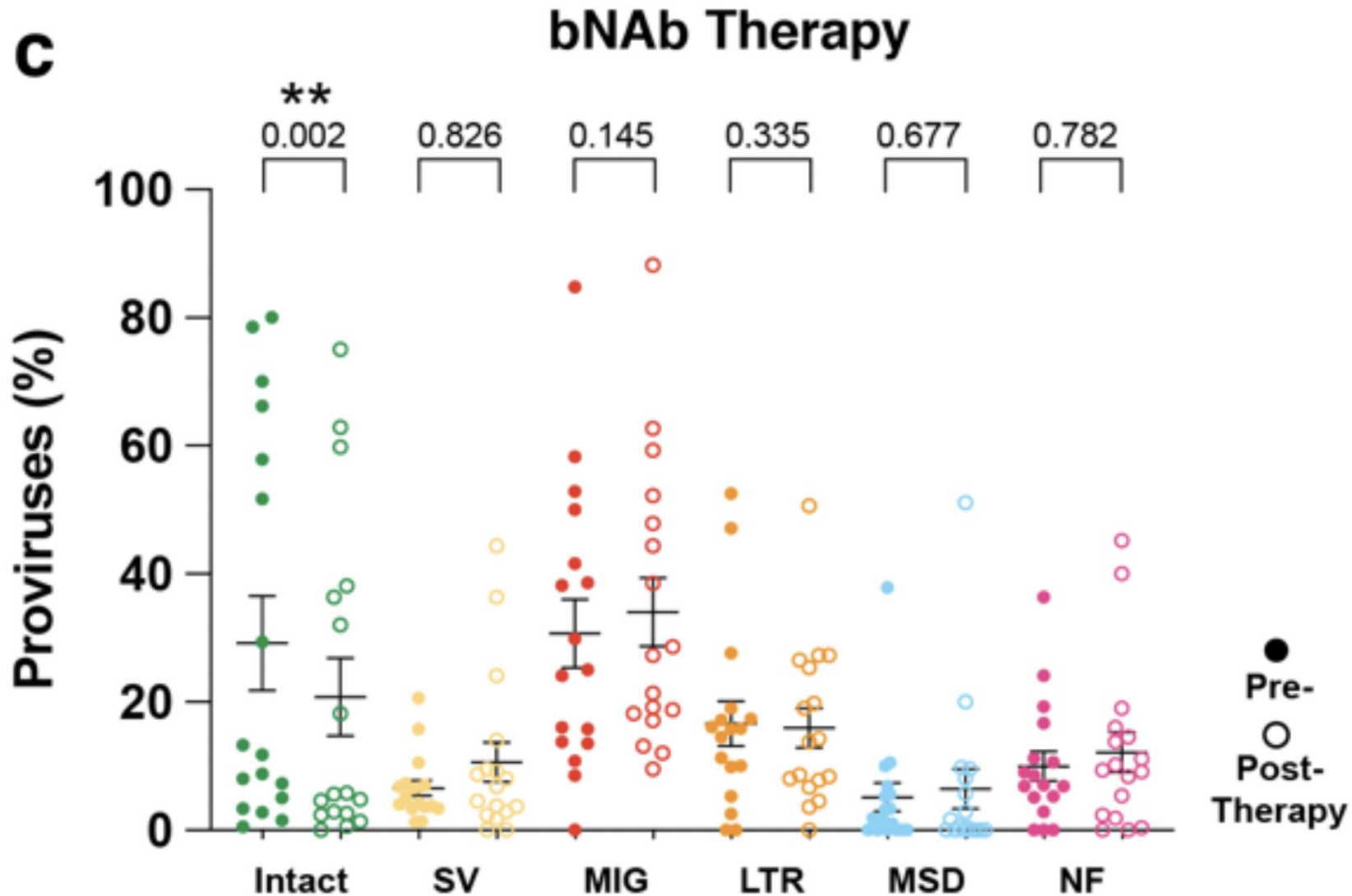




- ***~ 75% (13 out 17 participants) maintained viral suppression for > 20 wks post ATI***
  - 2 maintained suppression for at least 12 months
- Early rebounds associated with resistance to at least 1 of the bNAbs.

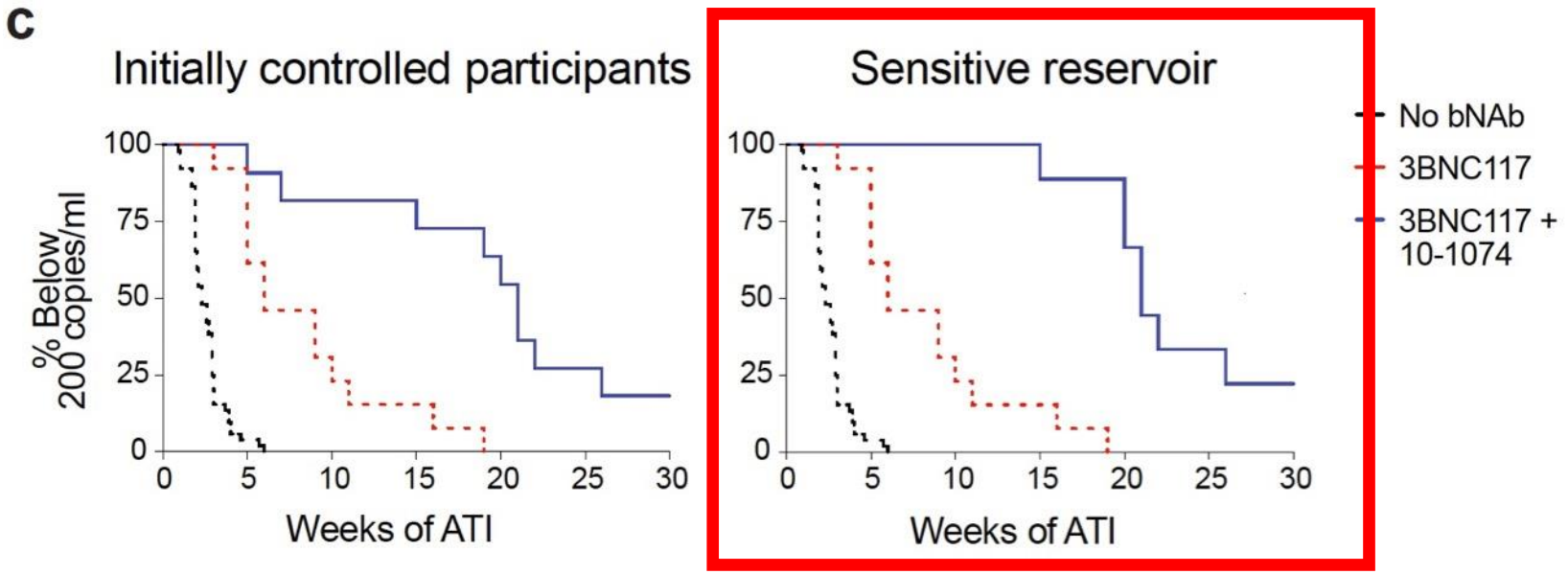
Scheid et al, Nature 2016
Mendoza et al, Nature 2018

Impact of repeated doses od bNAbs on measures of the intact viral reservoir using Q4PCR



Gaeblar Nature 2022

Dual bNAbs confer control……



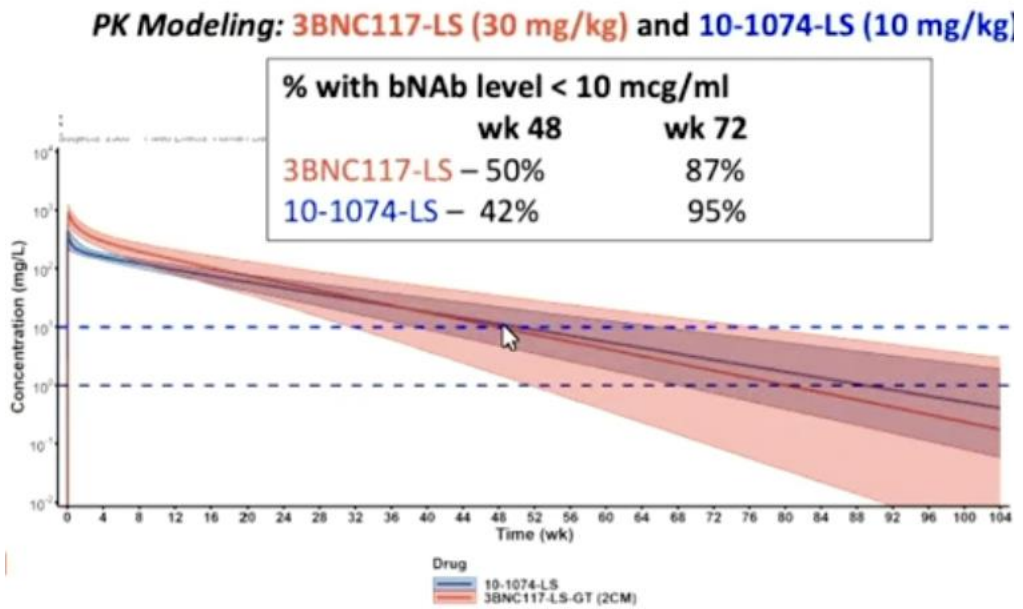
- Viral suppression for 5 to >30 weeks
- Median time to rebound 21 weeks vs 2.3 weeks for ART-only controls vs 6-10 weeks for single bNAb.
- Two never rebounded (? now one)
- Rebound in others due to resistance or as bNAb concentration dropped.

LS variants of bNAbs have long half-lives

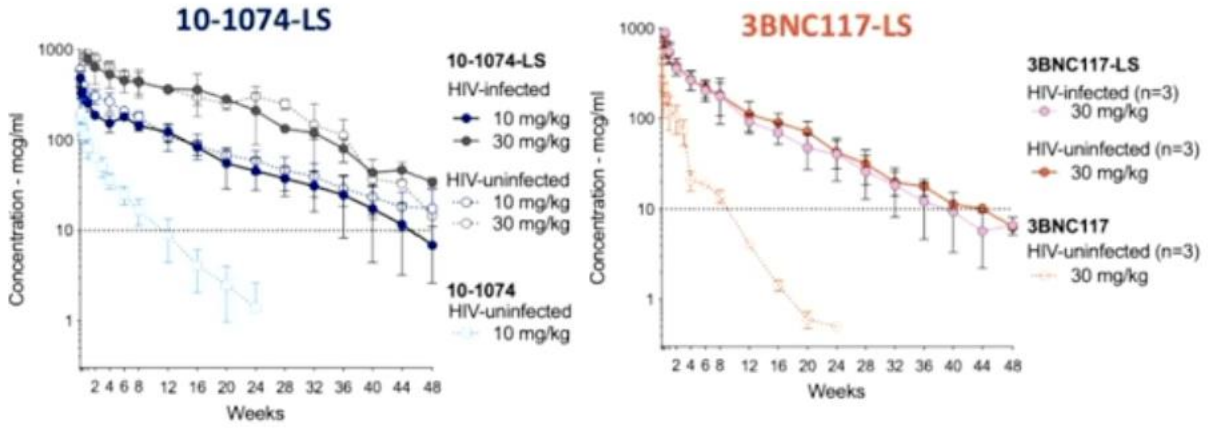
- LS variants are bNAbs with modified Fc portion, enhanced FcRn binding, increasing half lives >3-fold of parental antibodies

- 10-1074LS
  - $T_{1/2}$ = 80 days
  - C.f. non-LS variant $T_{1/2}$ = 24 days

- 3BNC117-LS
  - $T_{1/2}$ = 62 days
  - C.f. non-LS variant $T_{1/2}$ = 17.6 days



Pk Simulations by Qing Ma (Univ Buffalo) and Yanan Zheng (Gilead)



Caskey. CROI 2022

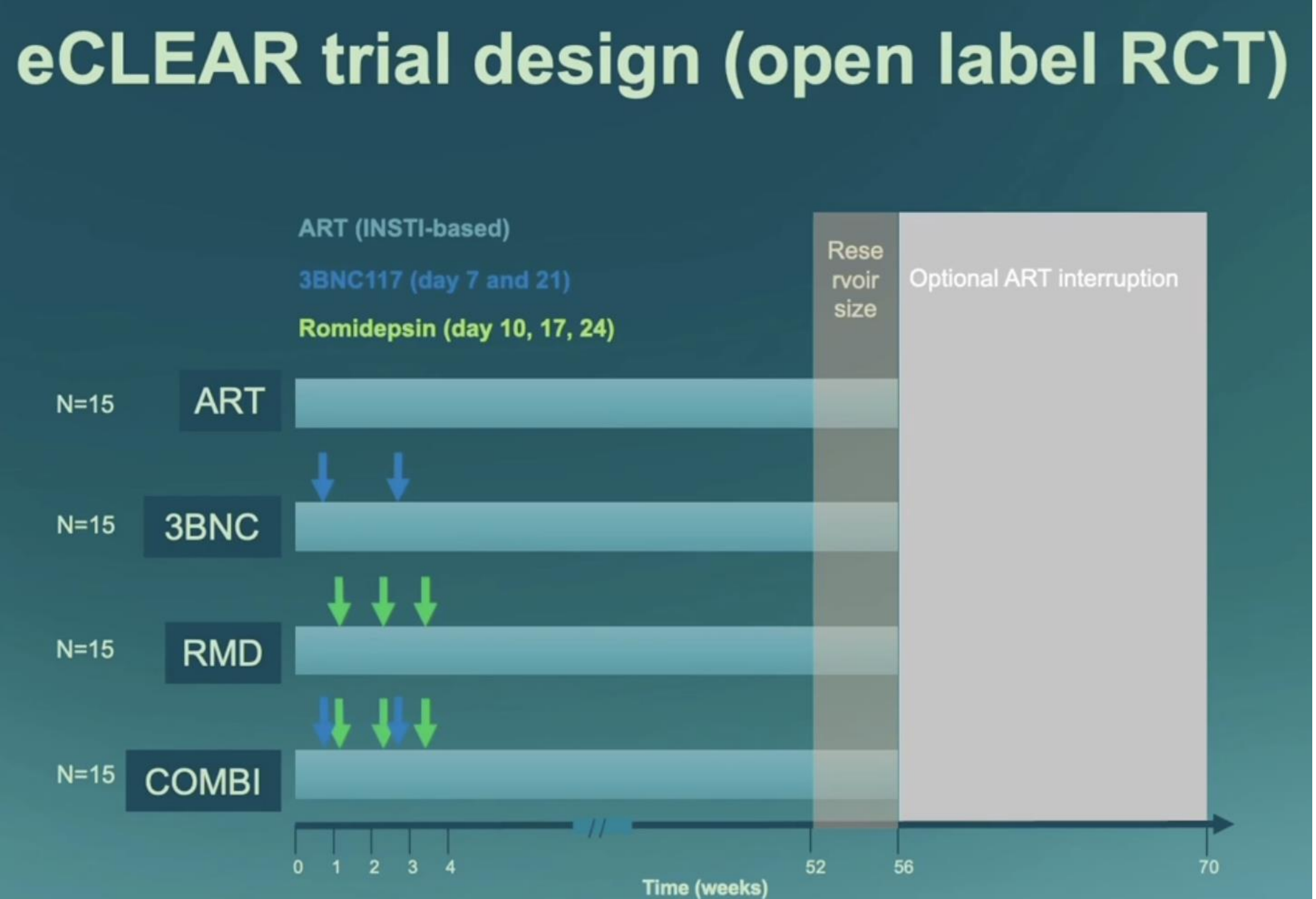
The RIO trial

- The first phase II randomised placebo-controlled trial of dual broadly neutralising antibodies in people treated early in HIV infection

Research question

- How long can one single dose of dual bNAb confer post viral control compared with placebo?

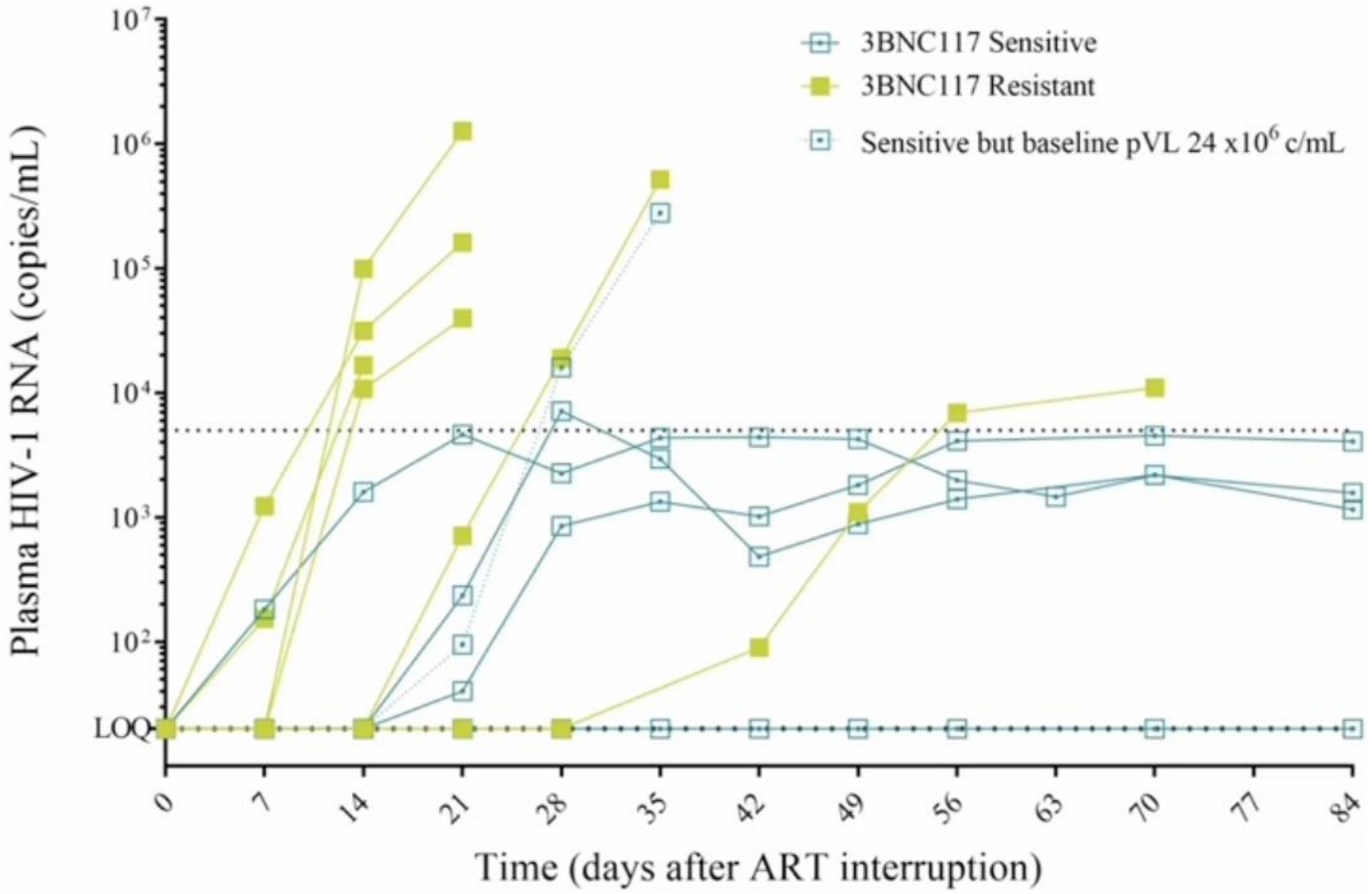
eCLEAR trial design (open label RCT)



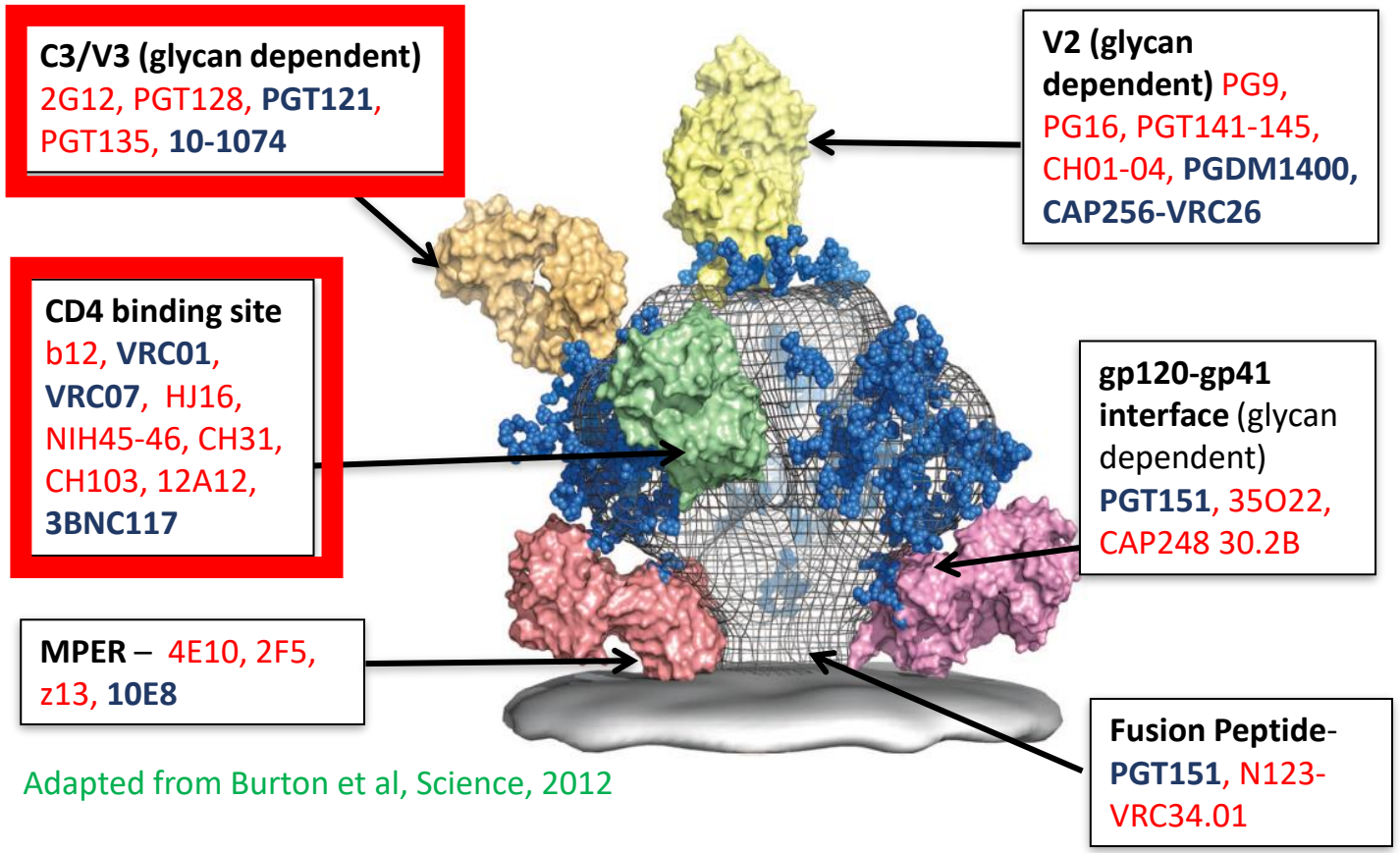
Søgaard et al
Nature Medicine
2022

eCLEAR study

- n=20
- ATI >400days after starting ART
- Viral rebound = 2 consecutive pVLs >5000c/ml
- 1 individual remained undetectable at 3.7 years after stopping ART



bNAb binding on HIV envelope glycoprotein

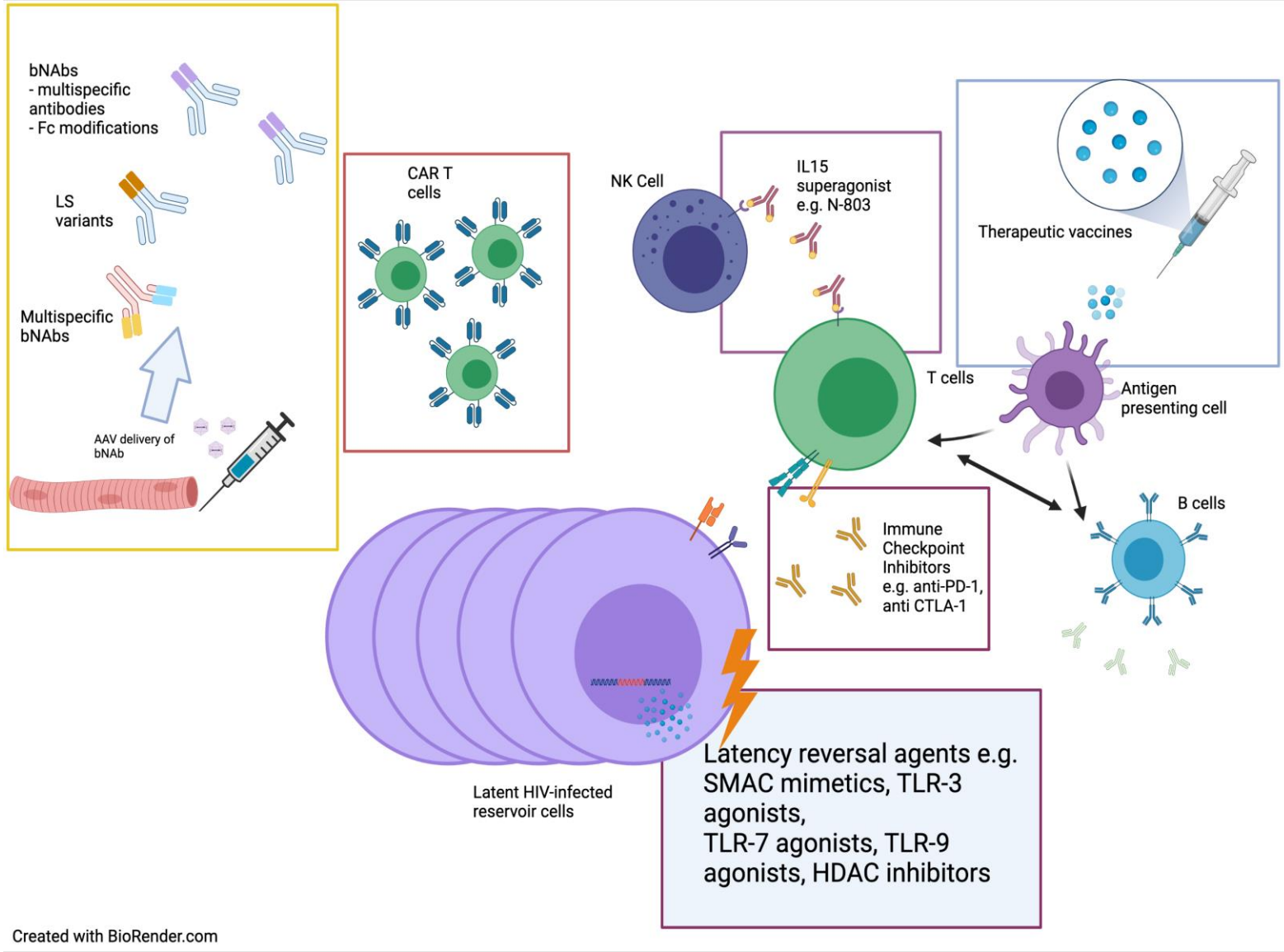


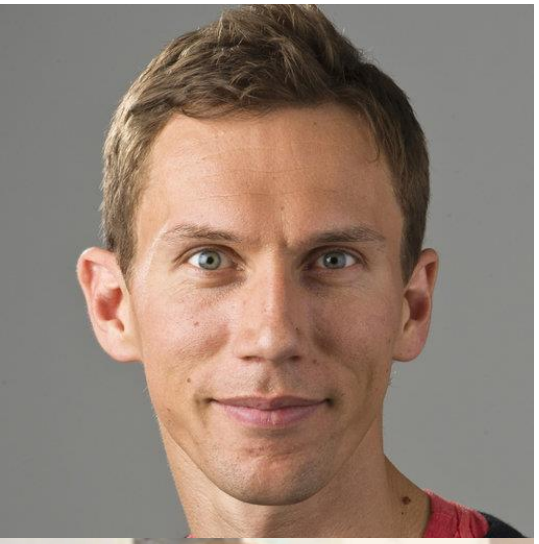
Adapted from Burton et al, Science, 2012

Combination immunotherapy: clinical trials planned/underway

Name	Intervention		Population	Status	ATI
ROADMAP (Sogaard/Caskey/Fatkenheuer)	3BNC117	Romidepsin	Chronic	CROI2020	yes
eCLEAR (Sogaard/Fidler)	3BNC117	Romidepsin	Early infection (viremic)	Late follow up	yes
A5386 (ACTG –Wilkin/Caskey/Jones)	VRC07-523LS 10-1074	N-803	Chronic	Planned 2021	yes
U01 – RU/Penn/Cornell (Caskey/Wilkin/Tebas)	3BNC117-LS 10-1074-LS	N-803	Chronic	Planned 2021	yes
BEAT HIV2 (Monaner/Tebas)	3BNC117 10-1074	Type I IFN	Chronic	Ongoing	yes
TITAN (Sogaard/Lewin)	3BNC117 10-1074	TLR9	Chronic	Ongoing	yes
amfAR/UCSF (Deeks)	VRC07-523LS 10-1074	DNA/MVA TLR9	Treated during acute infection	Ongoing	yes
A5374 (ACTG – Riddler/Gay/Mellors)	3BNC117-LS* 10-1074-LS*	ChAd/MVA TLR7	Treated during acute infection	Planned 2021	yes

- **Summary**
- New approaches to HIV treatment that involve augmentation of the immune responses show promise
- Probably will need to be given in combination
- Currently the only efficacy outcome is ATI

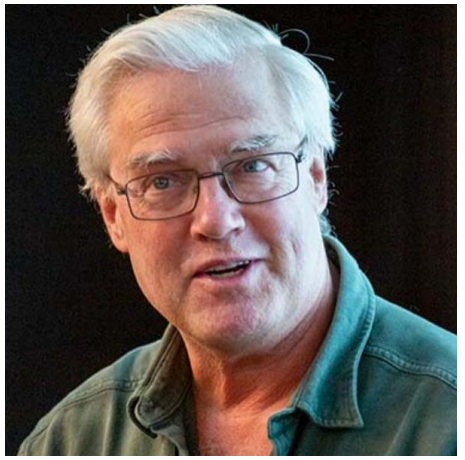


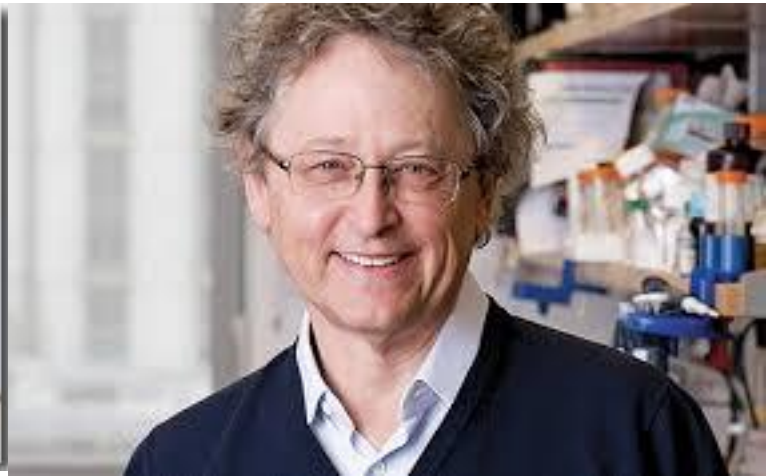


TO ALL OUR STUDY PARTICIPANTS

THANK YOU!

BILL & MELINDA GATES foundation





IMC-M113V-103

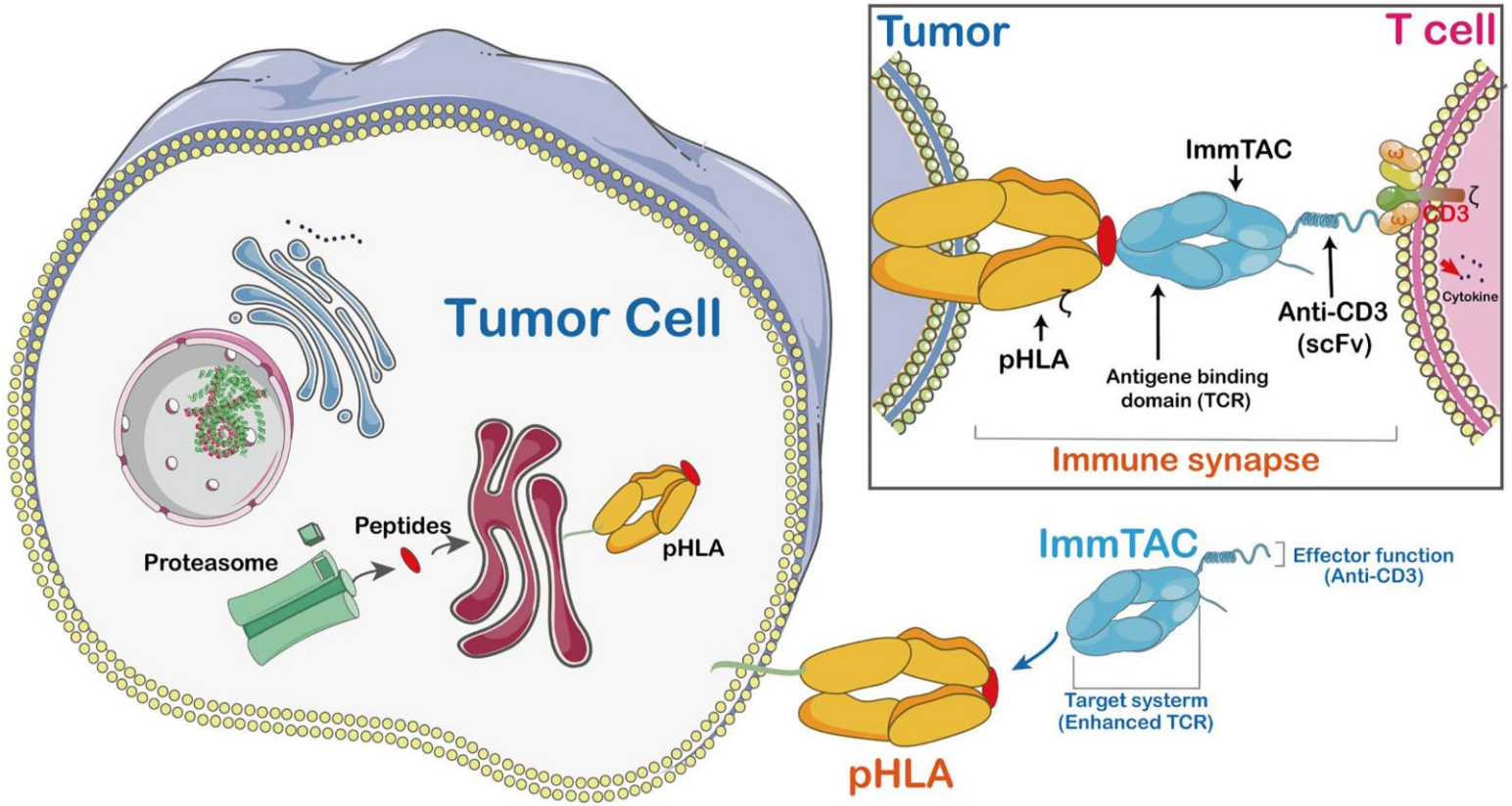
First in human study

Assessing the safety, tolerability and PK profile of IMC-M113V in a single and multiple dose regimens

Aims to identify safe, tolerable, and pharmacologically active dosing regimens of iMC-M113V

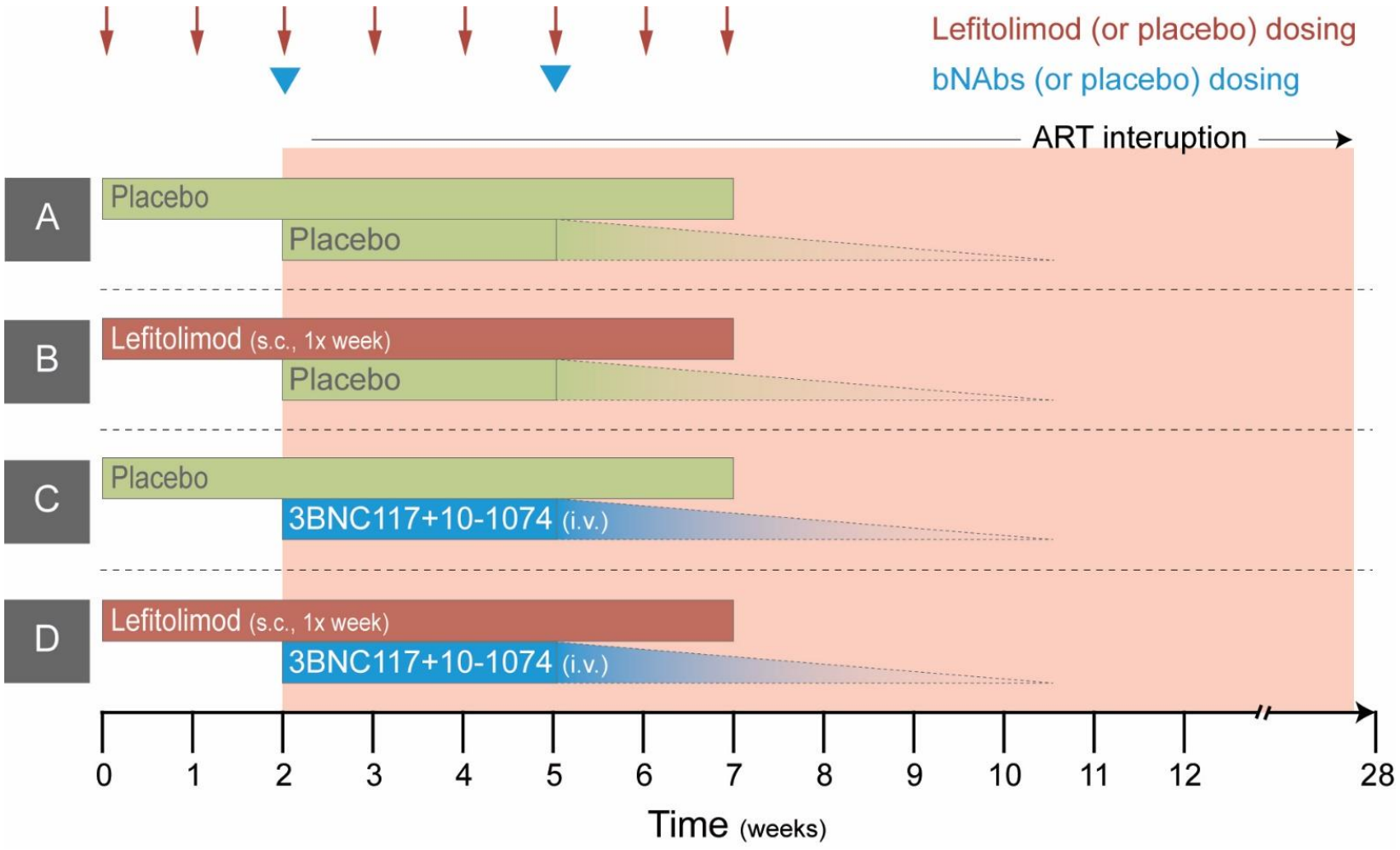
The Immunocore study (IMC-M113V-103)

- Phase 1/2 study of an immune-mobilizing monoclonal T cell receptor



Zhao et al. Frontiers 2021

Design: double-blind, placebo-controlled RCT



Combining a TLR9 agonist with broadly neutralizing antibodies for reservoir reduction and immunological control of HIV infection: An investigator-initiated randomized, placebo-controlled, phase IIa trial

TITAN