Broadly neutralizing antibodies to treat or cure HIV

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Imperial College London UK

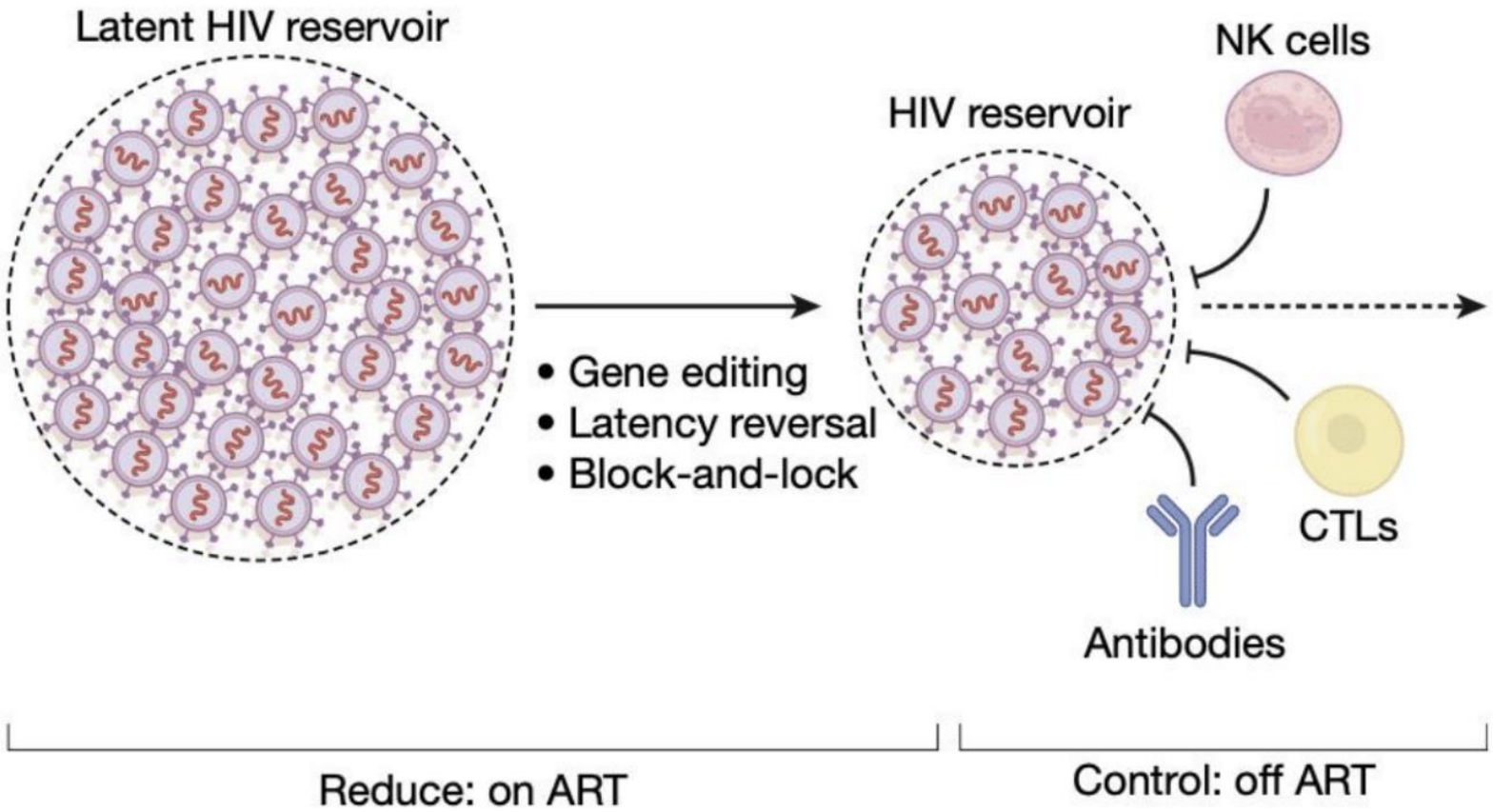
Summary of talk

- What is a broadly neutralizing antibody
- How do they work
- What we know from clinical trials using bNAbs to treat HIV+ people
- What studies are ongoing at the moment

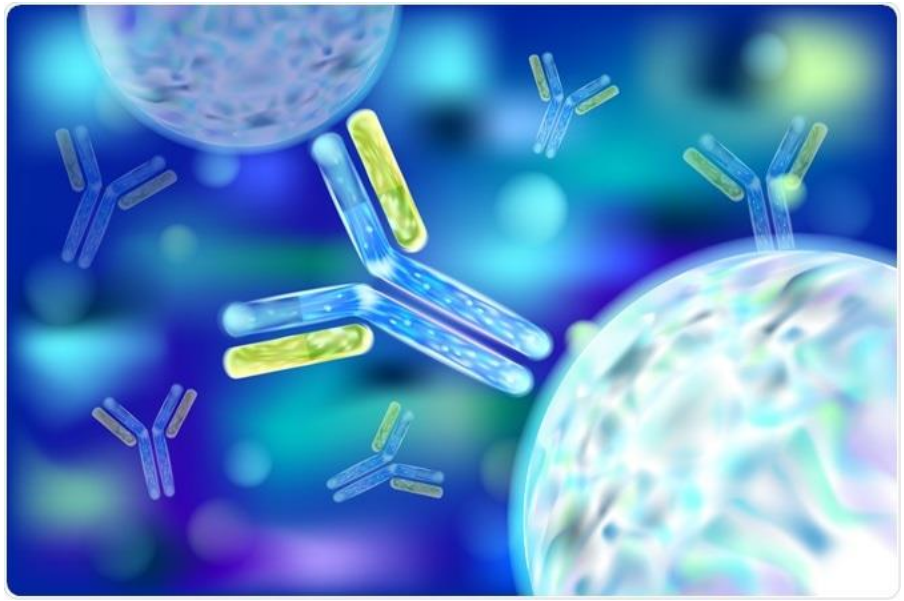
Antiretroviral therapy works great, and is getting better, so why do we need a cure?

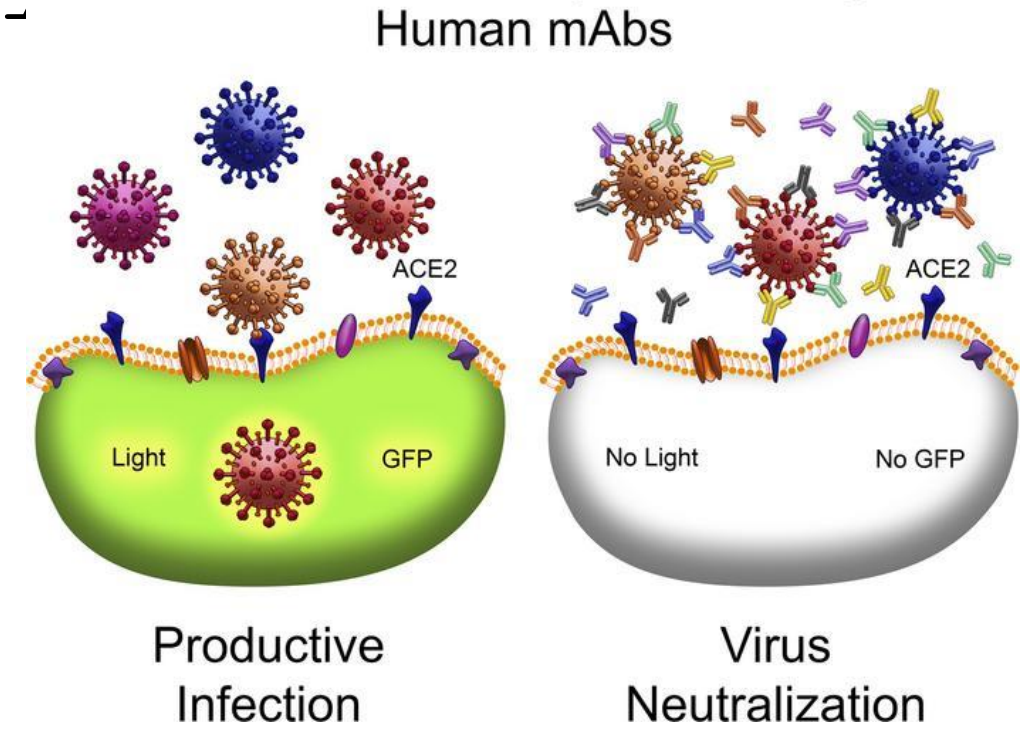
HIV Remission: Reduce and Control

All models of HIV remission (control, not cure) suggest you need a low reservoir and a sustained mechanism of immune control



What is an antibody



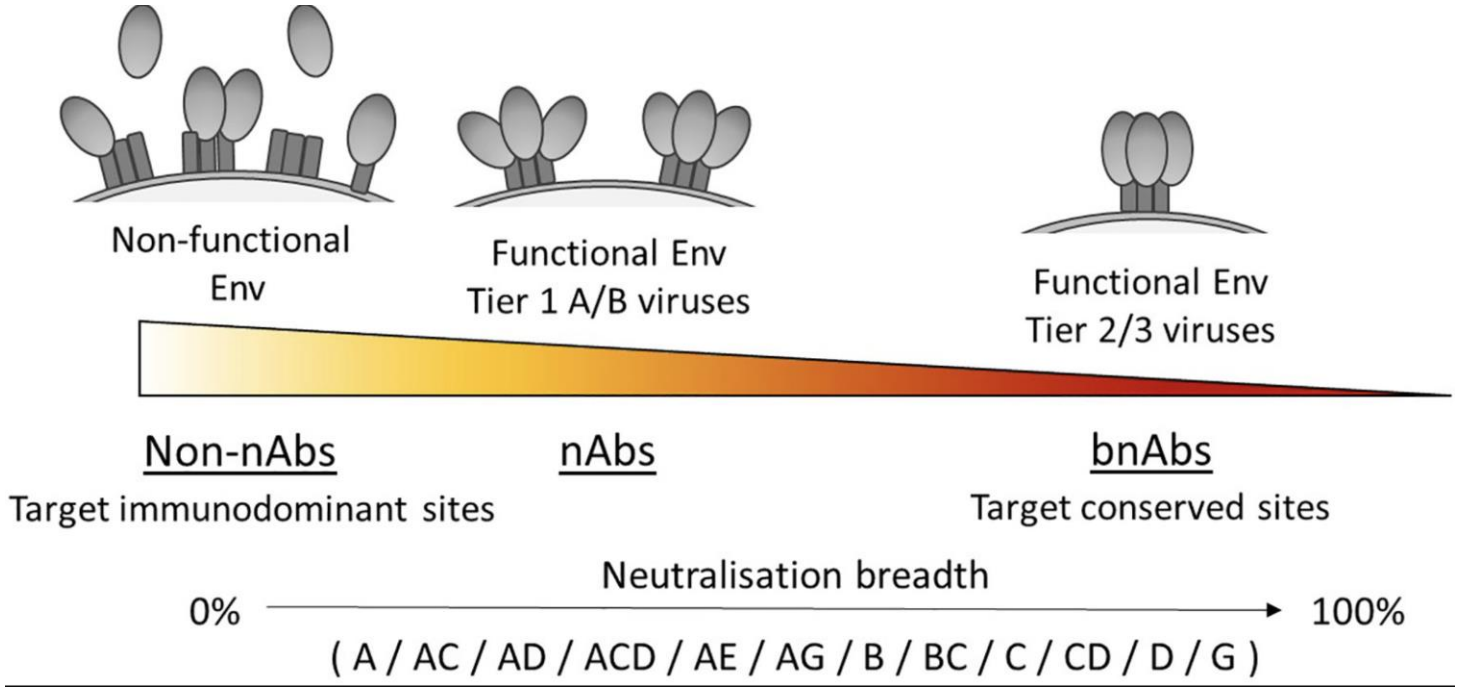


Antibodies are proteins made by immune cells called B-cells that recognize "foreign" proteins and remove them
They do this by attaching to the surface of viruses and bacteria and killing the infected cells

Broadly Neutralizing Antibodies are antibodies that in a test tube can block infection of a cell when exposed to that virus. In the case of HIV they can protect new cells from becoming infected with HIV, and also kill cells that express HIV proteins

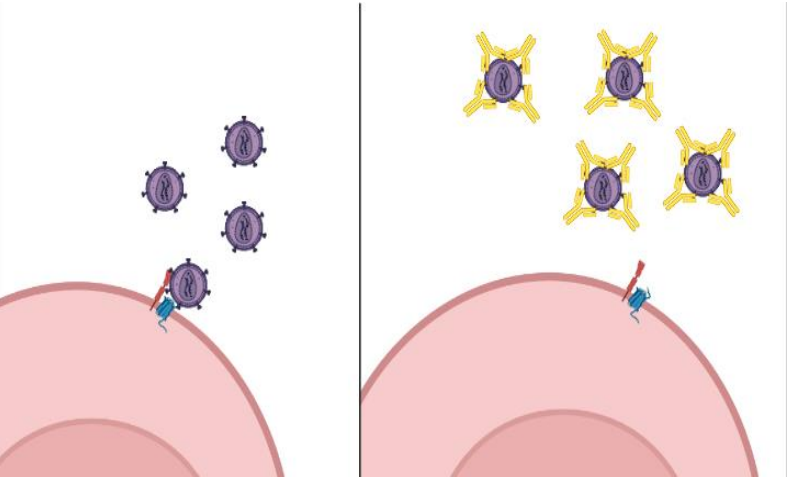
Broadly neutralizing antibodies (bNabs)

- Highly effective at in vitro neutralization against most circulating strains of HIV
- Neutralise a wide range of genetically diverse HIV-1 subtypes

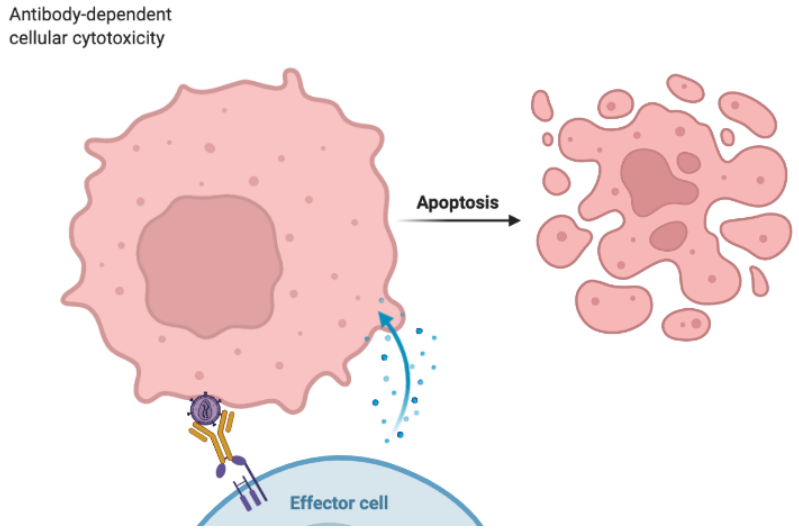


How do antibodies work?

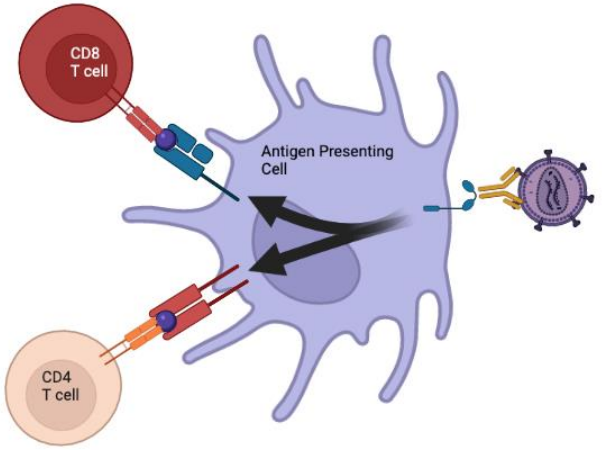
Disrupting virus-receptor interactions

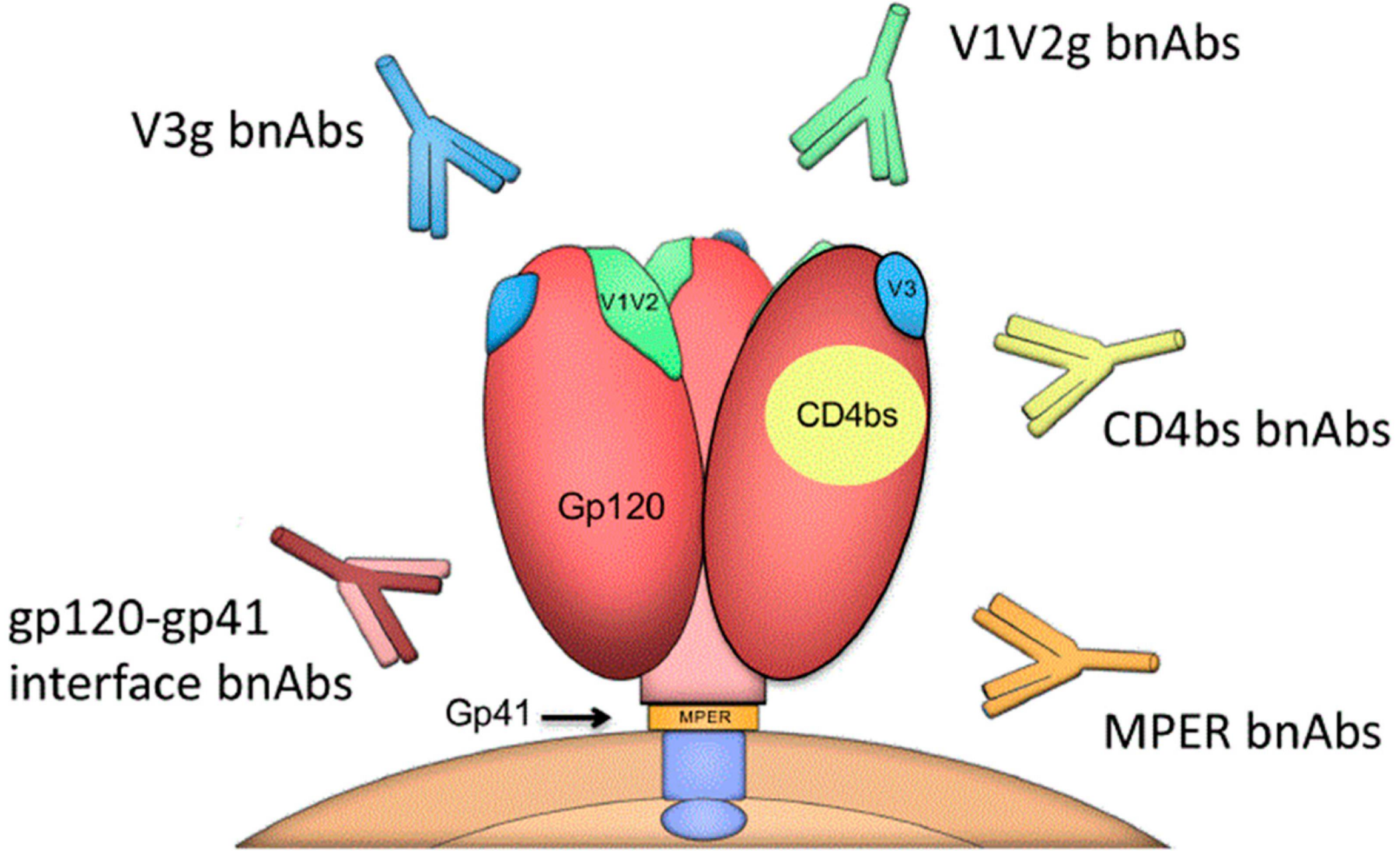


Antibody-dependent cell-mediated cytotoxicity (ADCC)

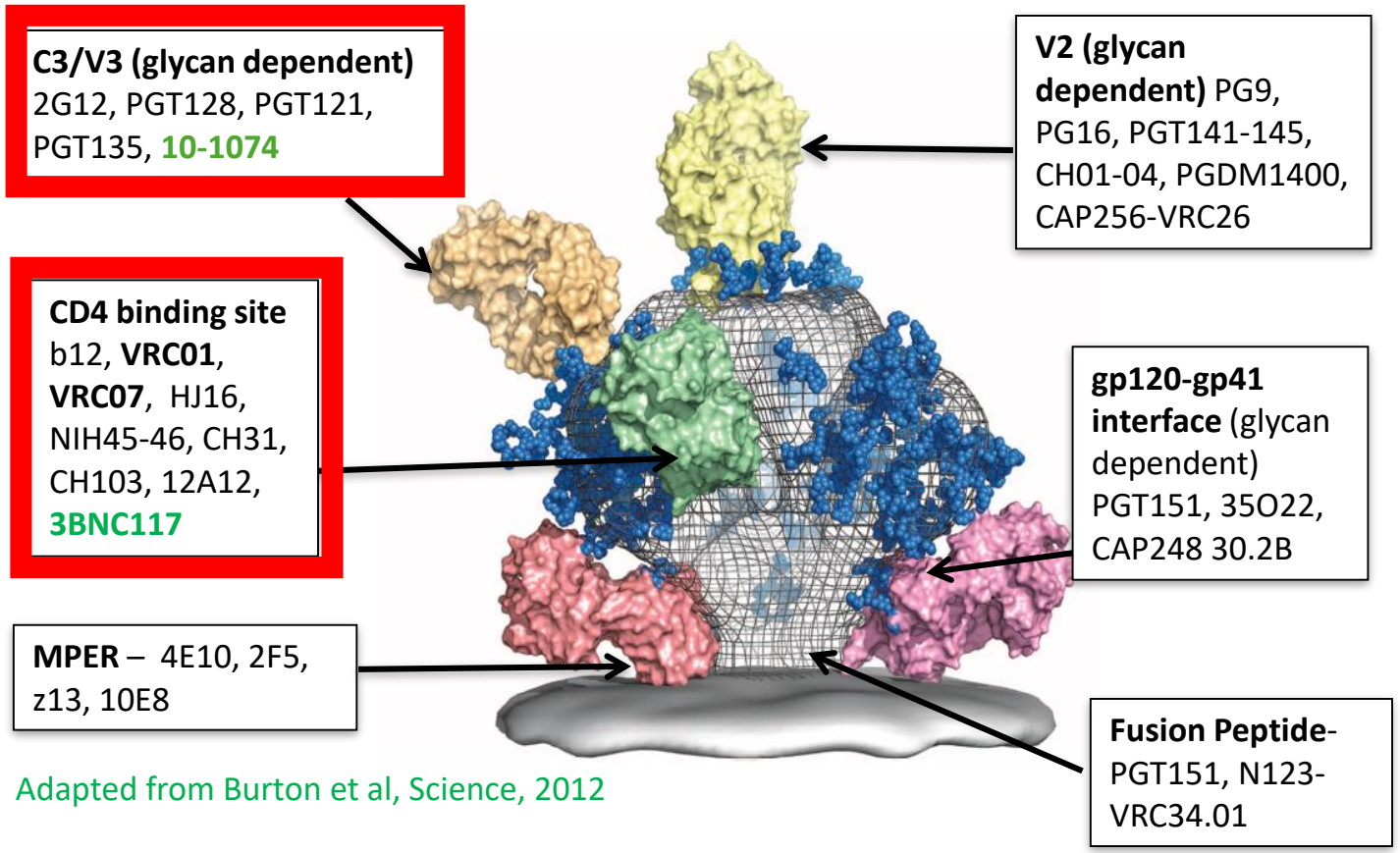


*Stimulating long-lasting HIV-specific CD8-mediated cellular immune responses (Vaccinal effect)



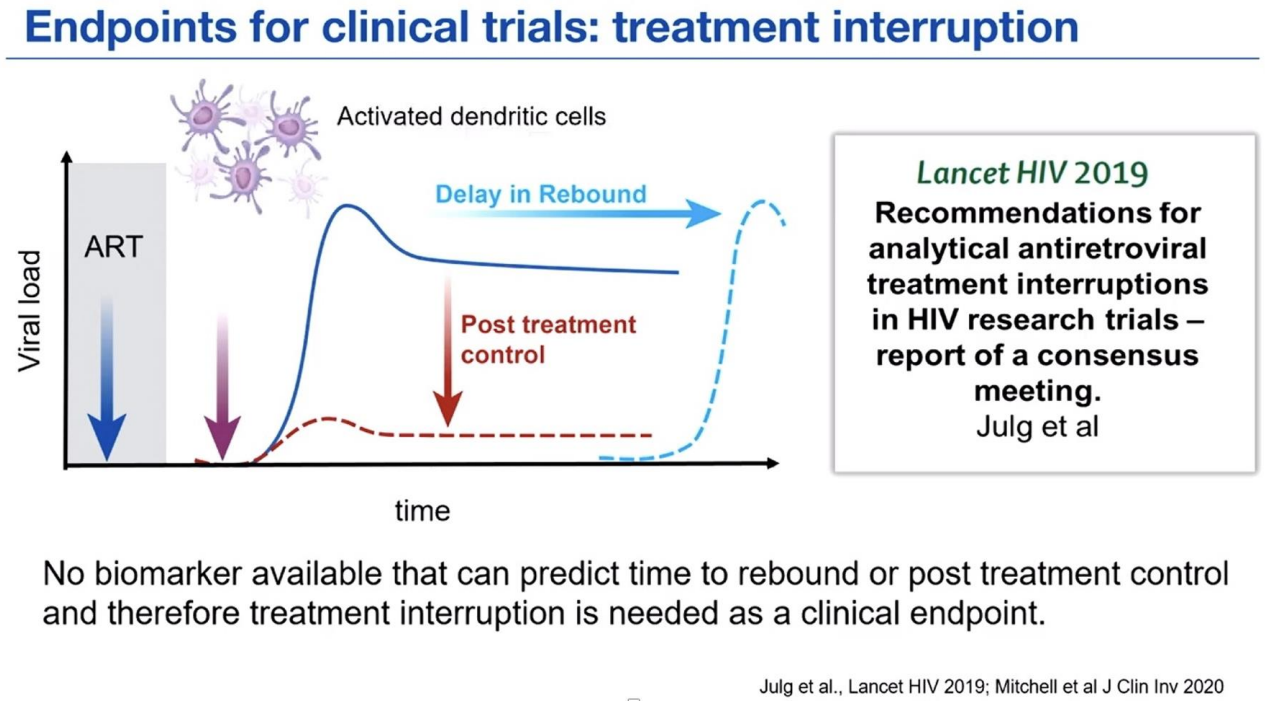

V3g bnAbs
V1V2g bnAbs
V1V2
V3
CD4bs
Gp120
CD4bs bnAbs
gp120-gp41
interface bnAbs
Gp41
MPER
MPER bnAbs

Antibody binding to the HIV envelope glycoprotein



Adapted from Burton et al, Science, 2012

How to design HIV "cure" trials



- Whilst there are a huge range of assays to measure the HIV reservoir, none accurately predict when virus will return (rebound)

- The only way to really test if a new treatment can control viral replication off ART is to stop ART and keep measuring HIV viral

Can ART on its own lead to post-treatment viral control?

OPEN ACCESS Freely available online

PLOS | PATHOGENS

Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

Asier Sáez-Cirión[1]*, Charline Bacchus[2], Laurent Hocqueloux[3], Véronique Avettand-Fenoel[4,5], Isabelle Girault[6], Camille Lecuroux[6], Valerie Potard[7,8], Pierre Versmisse[1], Adeline Melard[4], Thierry Prazuck[3], Benjamin Descours[2], Julien Guergnon[2], Jean-Paul Viard[5,9], Faroudy Boufassa[10], Olivier Lambotte[6,11], Cécile Goujard[10,11], Laurence Meyer[10,12], Dominique Costagliola[7,8,13], Alain Venet[6], Gianfranco Pancino[1], Brigitte Autran[2], Christine Rouzioux[4,5]*, the ANRS VISCONTI Study Group[¶]

1 Institut Pasteur, Unité de Régulation des Infections Rétrovirales, Paris, France, 2 Université Pierre et Marie Curie, INSERM UMR-S 945 Immunité et Infection, Hôpital Pitié-Salpétrière, Paris, France, 3 Centre Hospitalier Régional d'Orléans, Service des Maladies Infectieuses et Tropicales, Orléans, France, 4 AP-HP, CHU Necker-Enfants Malades, Laboratoire de Virologie, Paris, France, 5 EA 3620, Université Paris-Descartes, Sorbonne Paris Cité, Paris, France, 6 INSERM U1012, Université Paris-Sud 11, Le Kremlin Bicêtre, France, 7 UPMC Univ Paris 06, UMR_S 943, Paris, France, 8 INSERM, U943, Paris, France, 9 AP-HP, Hôtel-Dieu, Paris, France, 10 INSERM U1018, Université Paris-Sud 11, Le Kremlin Bicêtre, France, 11 AP-HP, Hôpital de Bicêtre, Service de Médecine Interne, Le Kremlin Bicêtre, France, 12 AP-HP, Hôpital de Bicêtre, Département d'épidémiologie, Le Kremlin Bicêtre, France, 13 AP-HP, Groupe hospitalier Pitié-Salpétrière, Service de Maladies Infectieuses et Tropicales, Paris, France

The Journal of Infectious Diseases

MAJOR ARTICLE

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

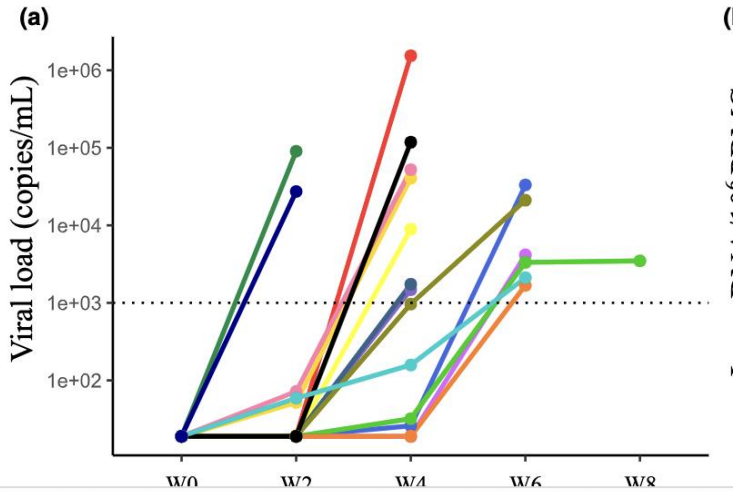
The Control of HIV After Antiretroviral Medication Pause (CHAMP) Study: Posttreatment Controllers Identified From 14 Clinical Studies

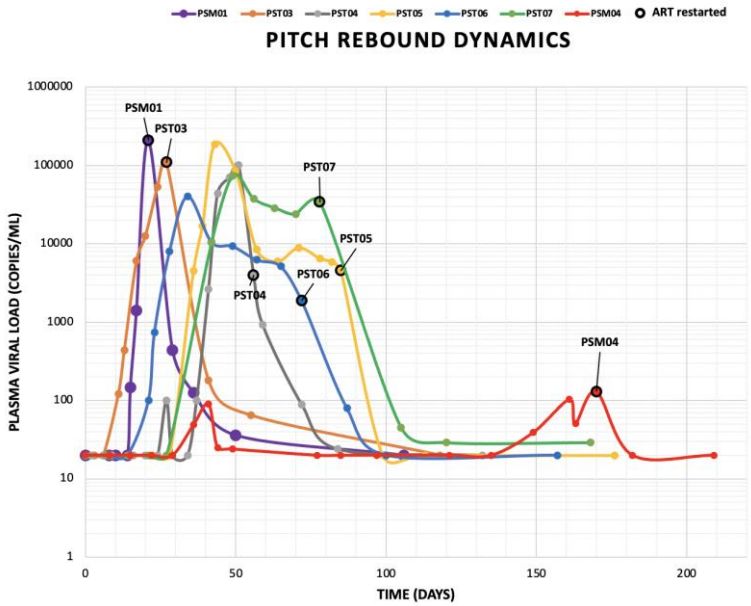
Golnaz Namazi,[1,a] Jesse M. Fajnzylber,[1,a] Evgenia Aga,[2] Ronald J. Bosch,[2] Edward P. Acosta,[3] Radwa Sharaf,[1] Wendy Hartogensis,[4] Jeffrey M. Jacobson,[5] Elizabeth Connick,[6] Paul Volberding,[4] Daniel Skiest,[7] David Margolis,[8] Michael C. Sneller,[9] Susan J. Little,[10] Sara Gianella,[10] Davey M. Smith,[10] Daniel R. Kuritzkes,[1] Roy M. Gulick,[11] John W. Mellors,[12] Vikram Mehraj,[13] Rajesh T. Gandhi,[14] Ronald Mitsuyasu,[15] Robert T. Schooley,[10] Keith Henry,[16] Pablo Tebas,[17] Steven G. Deeks,[4] Tae-Wook Chun,[9] Ann C. Collier,[18] Jean-Pierre Routy,[13] Frederick M. Hecht,[4] Bruce D. Walker,[19] and Jonathan Z. Li[1]

Post treatment controllers were more frequently identified in those treated during early versus chronic infection (13% vs 4%, *P* < .001)

ISALA n = 14PITCH n = 7

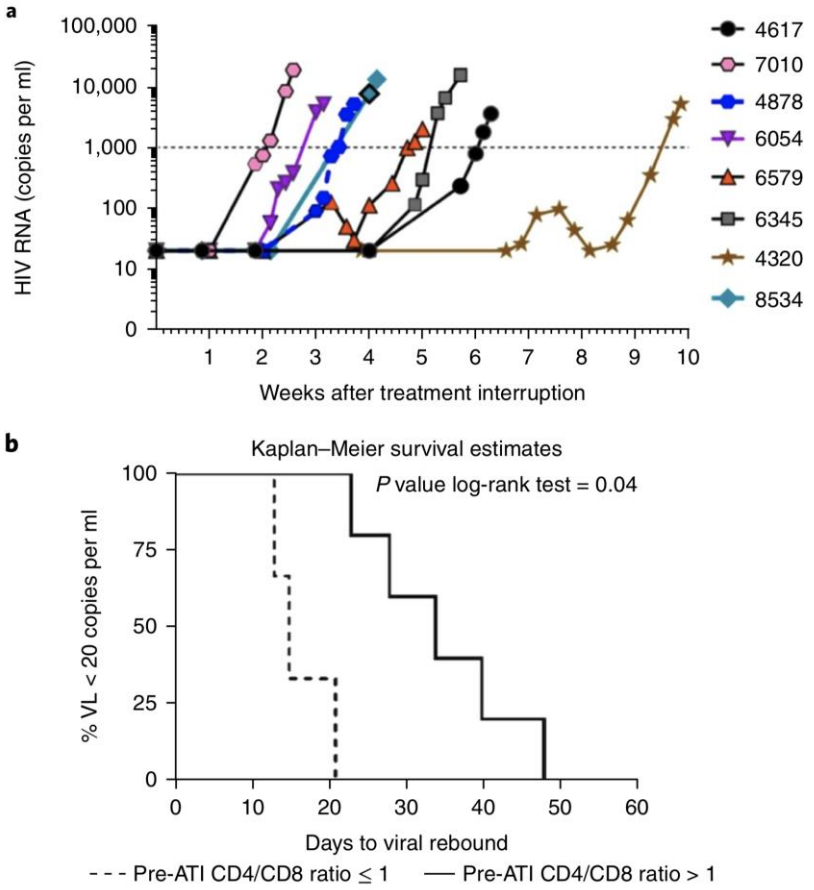
Pannus et al JIAS 2020





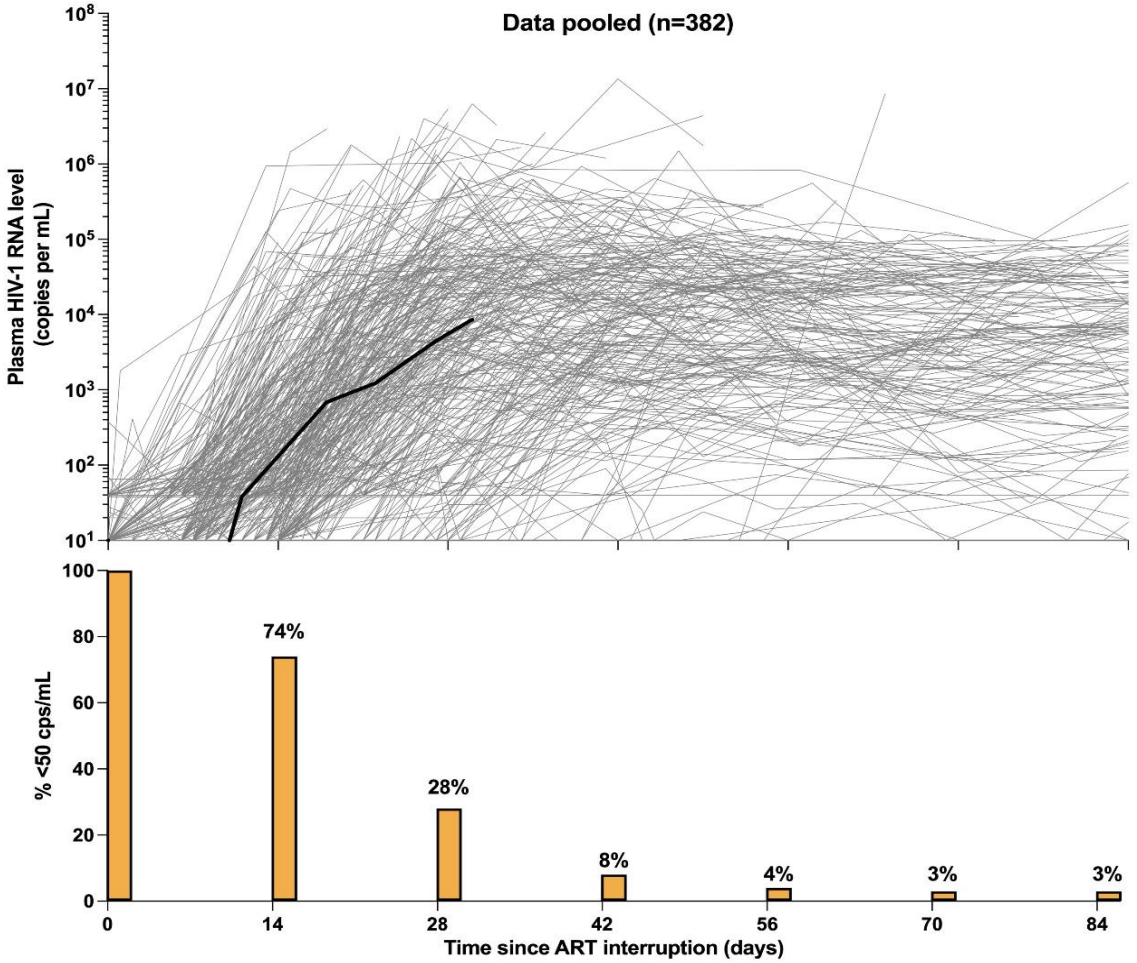
RV411 n = 8

Colby et al Nature Med 2018



Frequency of control during 84 days of ATI

Dr Jesper Gun



Meta-analysis of 24 trials where ART is stopped as part of a study with regular VL r

For the majority of people stopping ART is accompanied by rapid

4% controlled virus off ART from day 56

What are the concerns and motivations of people living with HIV around treatment interruption studies?

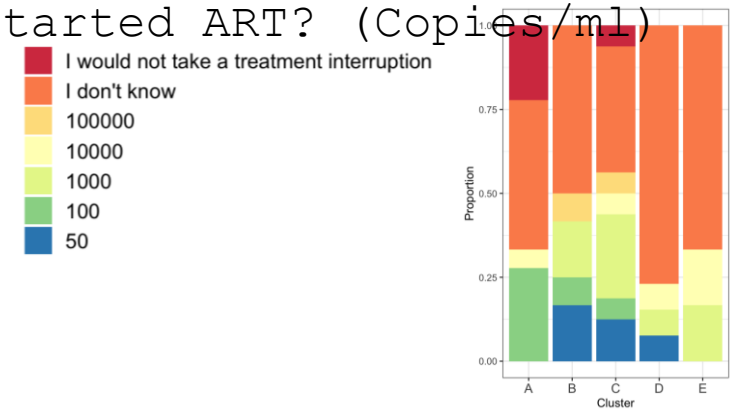
Attitudes towards participation in HIV cure trials which include a treatment interruption amongst participants in an observational study

Ming Jie Lee[1,2,3], Simon Collins[4], Piyumika Godakandaarachchi[3], Mariusz Racz[3], Alice Sharp[3], Sarah Fidler[1,2], Julie Fox[3]
1.Department of Infectious Disease, Imperial College London, UK,2.Imperial College Healthcare NHS Trust, UK, 3.Harrison Wing, Department of HIV, Guy's and St Thomas Hospital NHS FT, UK, 4.HIV i-Base, UK

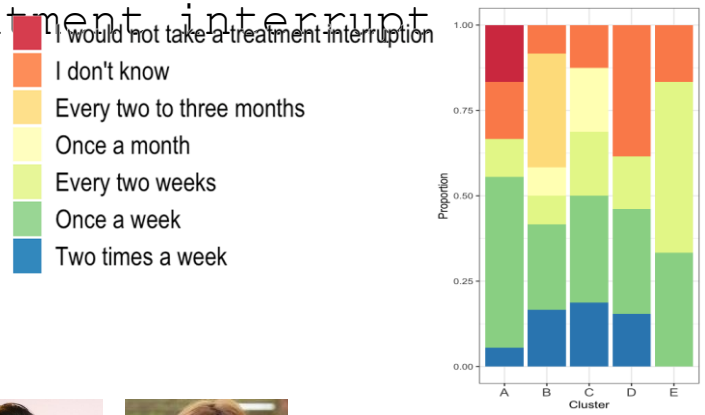
Poster no.

- 75 survey participants, 29 (39%) were interested in joining TI studies. The majority were white, cis-male, and men who have sex with men. Primarily motivated (81.5%) by an **altruistic desire to help scientific research**
- Predominant concern was around **risks of onward HIV transmission** (89.3% very or moderately concerned).
- Concern was not related to magnitude of viral rebound
- Frequency of VL and CD4 monitoring: most participants preferred weekly (35.4%) or fortnightly (16.9%) viral load monitoring during an ATI.

How high would you want to let the viral load rebound before you restarted ART? (Copies/ml)



How often would you want your viral load monitored during a treatment interrupt



Is there evidence that bNAbs act as antiviral agents and block viral replication

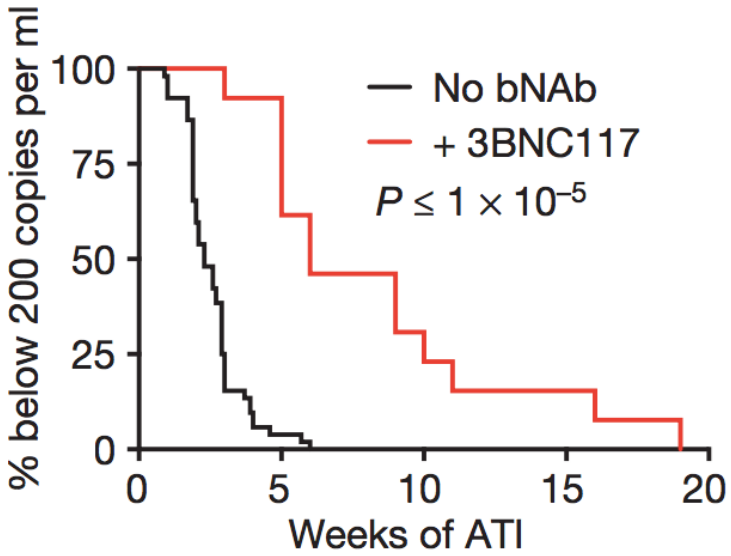
- To test this studies select bNAbs and then interrupt ART
- IF the bNAbs can control viral replication off ART then this suggests they are able to block virus activation

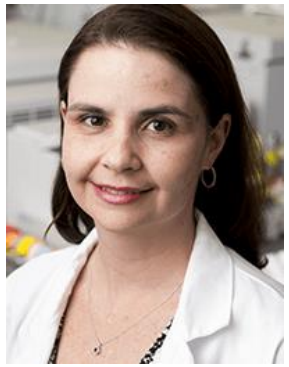
LETTER

doi:10.1038/nature18929

HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption

Johannes F. Scheid[1,2*], Joshua A. Horwitz[1*], Yotam Bar-On[1], Edward F. Kreider[3], Ching-Lan Lu[1], Julio C. C. Lorenzi[1], Anna Feldmann[4], Malte Braunschweig[1], Lilian Nogueira[1], Thiago Oliveira[1], Irina Shimeliovich[1], Roshni Patel[1], Leah Burke[5], Yehuda Z. Cohen[1], Sonya Hadrigan[1], Allison Settler[1], Maggi Witmer-Pack[1], Anthony P. West Jr[6], Boris Juelg[7], Tibor Keler[8], Thomas Hawthorne[8], Barry Zingman[9], Roy M. Gulick[5], Nico Pfeifer[4], Gerald H. Learn[3], Michael S. Seaman[10], Pamela J. Bjorkman[6], Florian Klein[1,11,12], Sarah J. Schlesinger[1], Bruce D. Walker[7,13], Beatrice H. Hahn[3], Michel C. Nussenzweig[1,14] & Marina Caskey[1]





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RESEARCH ARTICLE | HIV

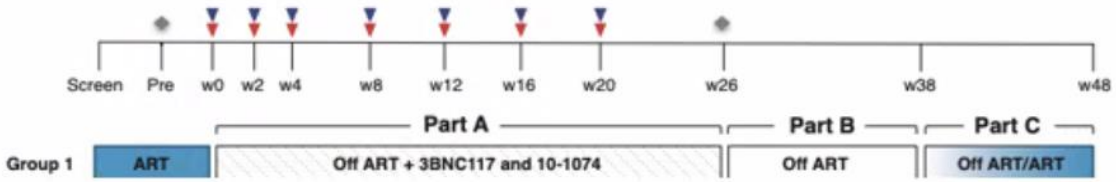
Broadly neutralizing antibody treatment maintained HIV suppression in children with favorable reservoir characteristics in Botswana

ROGER L. SHAPIRO, GBOLAHAN AJIBOLA, KENNETH MASWABI, MICHAEL HUGHES, BRYAN S. NELSON, AISCHA NIESAR, MOLLY PRETORIUS HOLME, KATHLEEN M. POWIS, MAUREEN SAKOI, [...], AND MATHIAS LICHTERFELD +22 authors Authors Info & Affiliations

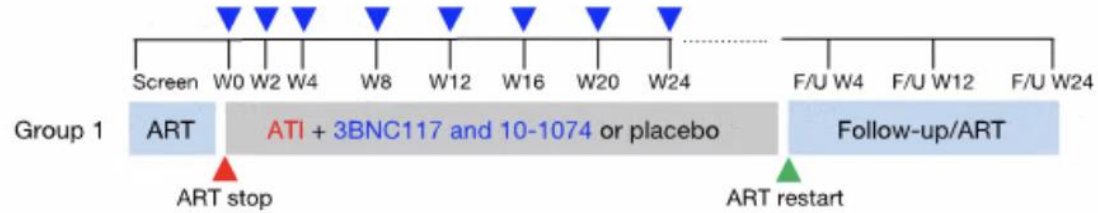
SCIENCE TRANSLATIONAL MEDICINE • 5 Jul 2023 • Vol 15, Issue 703 • DOI: 10.1126/scitranslmed.adh0004

VRC01LS and 10-1074
11/25 (44%) children maintained HIV-1 RNA below 400 copies/ml through 24 weeks of bNAb-only treatment;

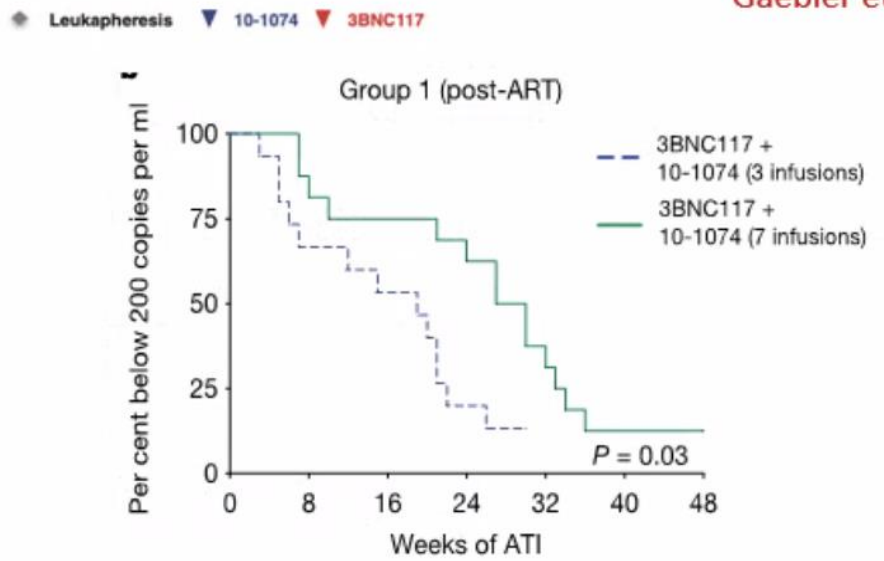
Repeated doses of two bNAbs can maintain suppression of sensitive viruses in the absence of ART

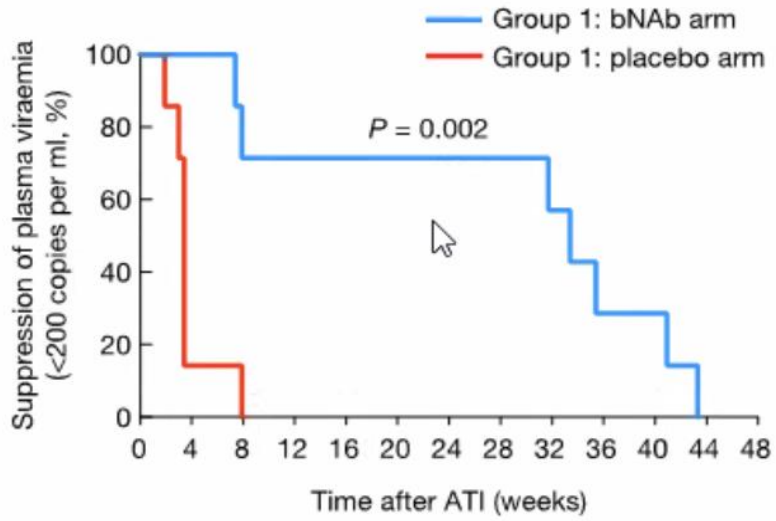


Gaebler et al., 2022



Sneller et al., 2022



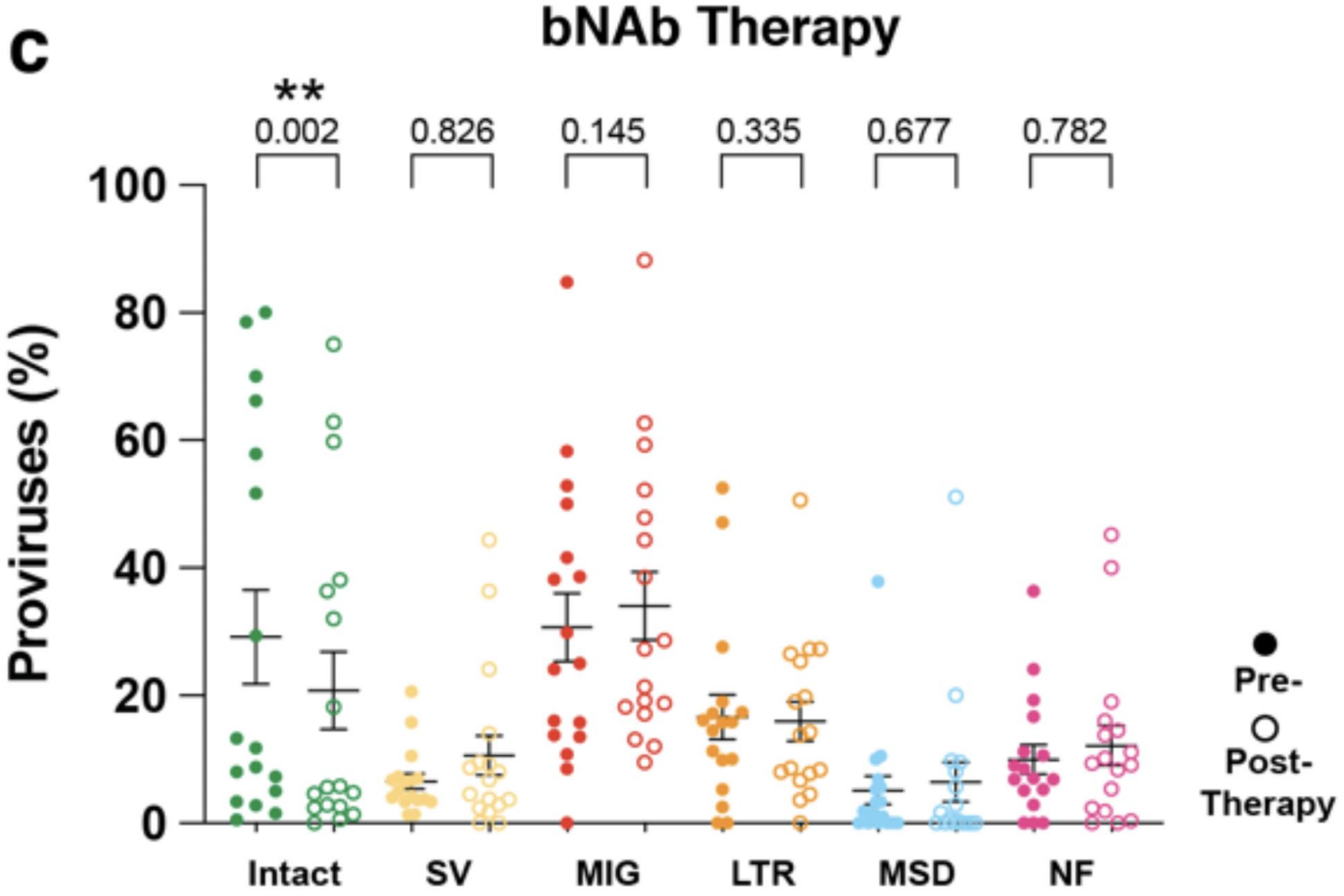


- Participants not screened for sensitivity
  - **13/17 (76%)** ppts maintained VL < 200 cp/ml through the dosing period of 20 weeks.

- **Participants initiated on ART during acute/early HIV**
- Participants not screened for sensitivity
  - 5/7 ppts maintained VL < 40 cp/ml for > 28wks

Do bNAbs affect the HIV reservoir?

Repeated doses (7) of 2 bNAbs impact the size of the intact HIV re
Gaeblar et al Nature 2022

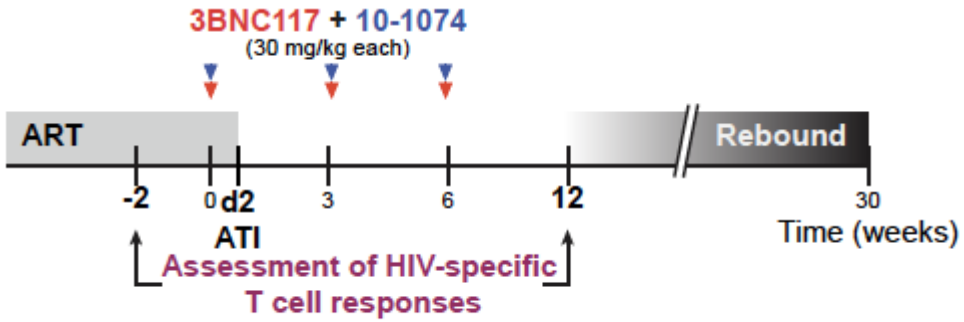


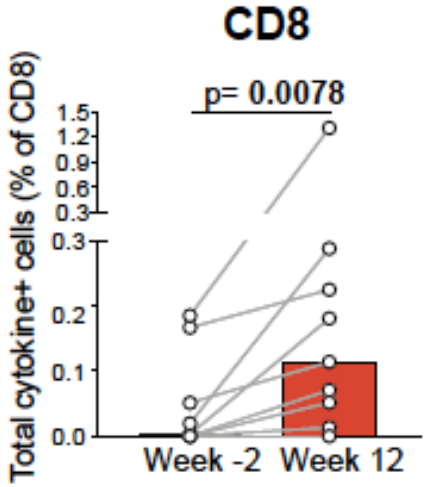
Do bNAbs induce new HIV-specific immune responses?

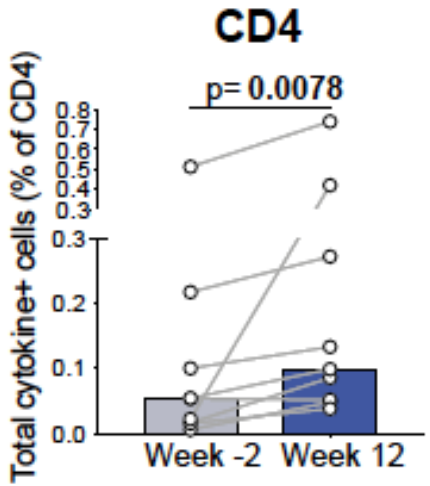
Is there evidence that bNAbs induce T-ce

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

Evolution of Gag-specific T cell responses during suppressed viremia



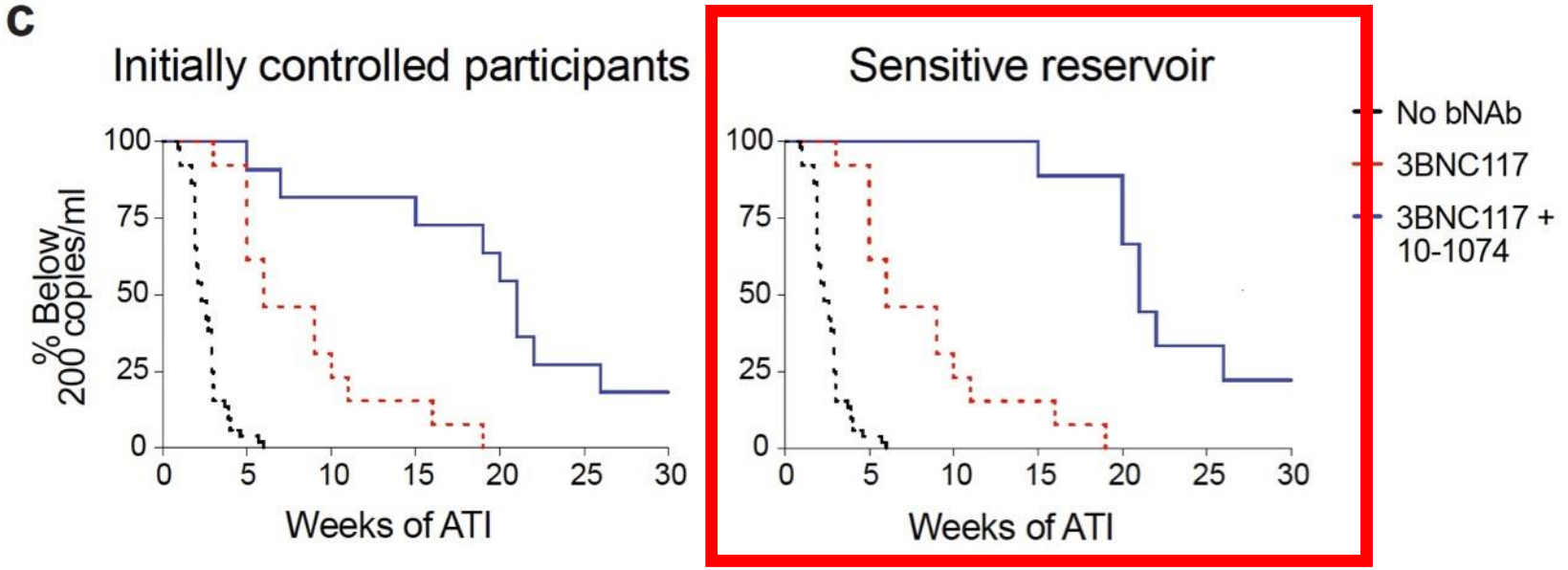




Niessl et al, *Nature Med.*, 2020

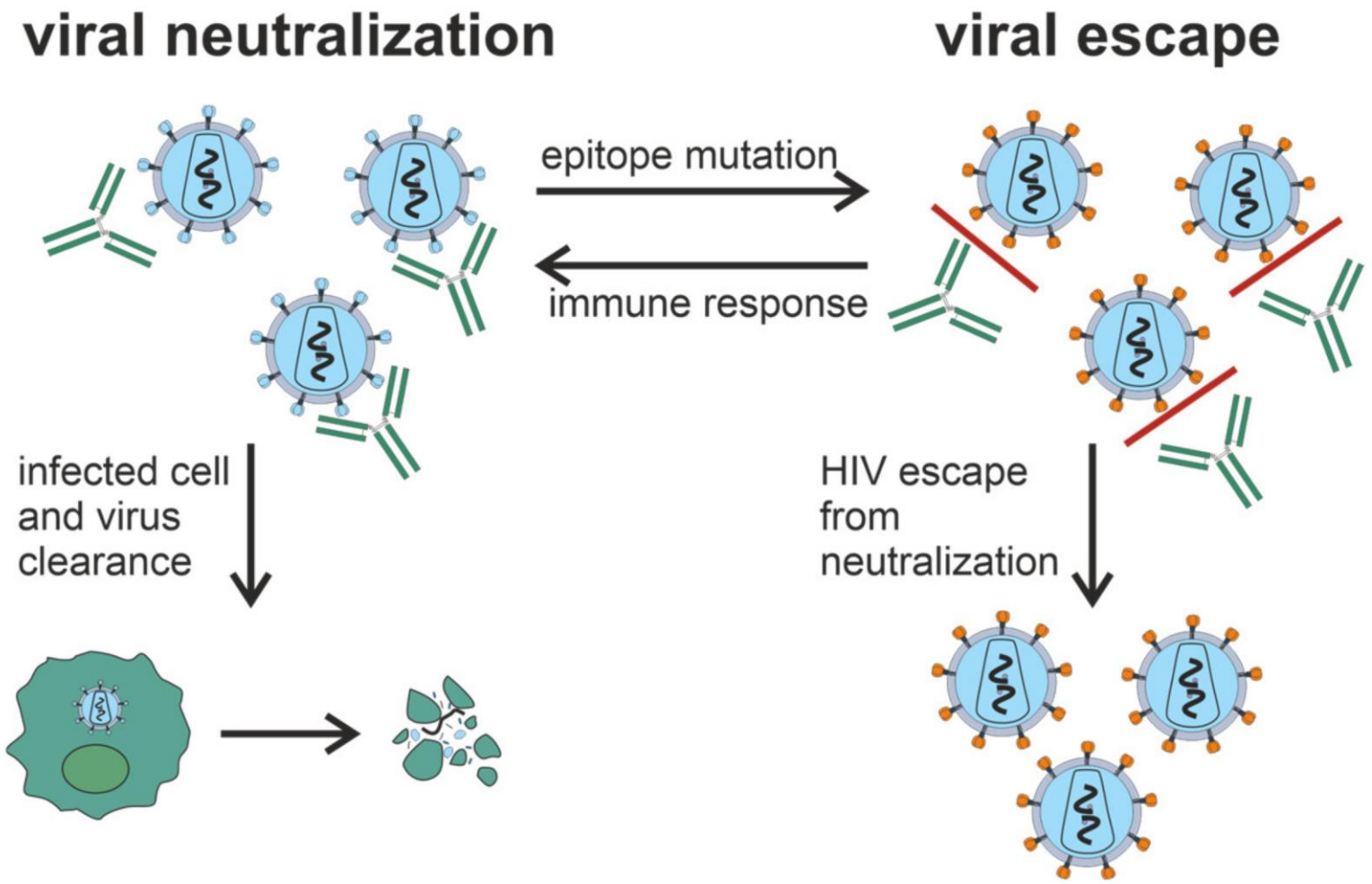
- bnAbs also enhance the clearance of HIV infected cells in vivo through engagement of Fcγ receptors (Lu et al, *Science*, 2016)

bNAbs are most effective at controlling virus off ART if they bind to correct epitopes on the virus envelope

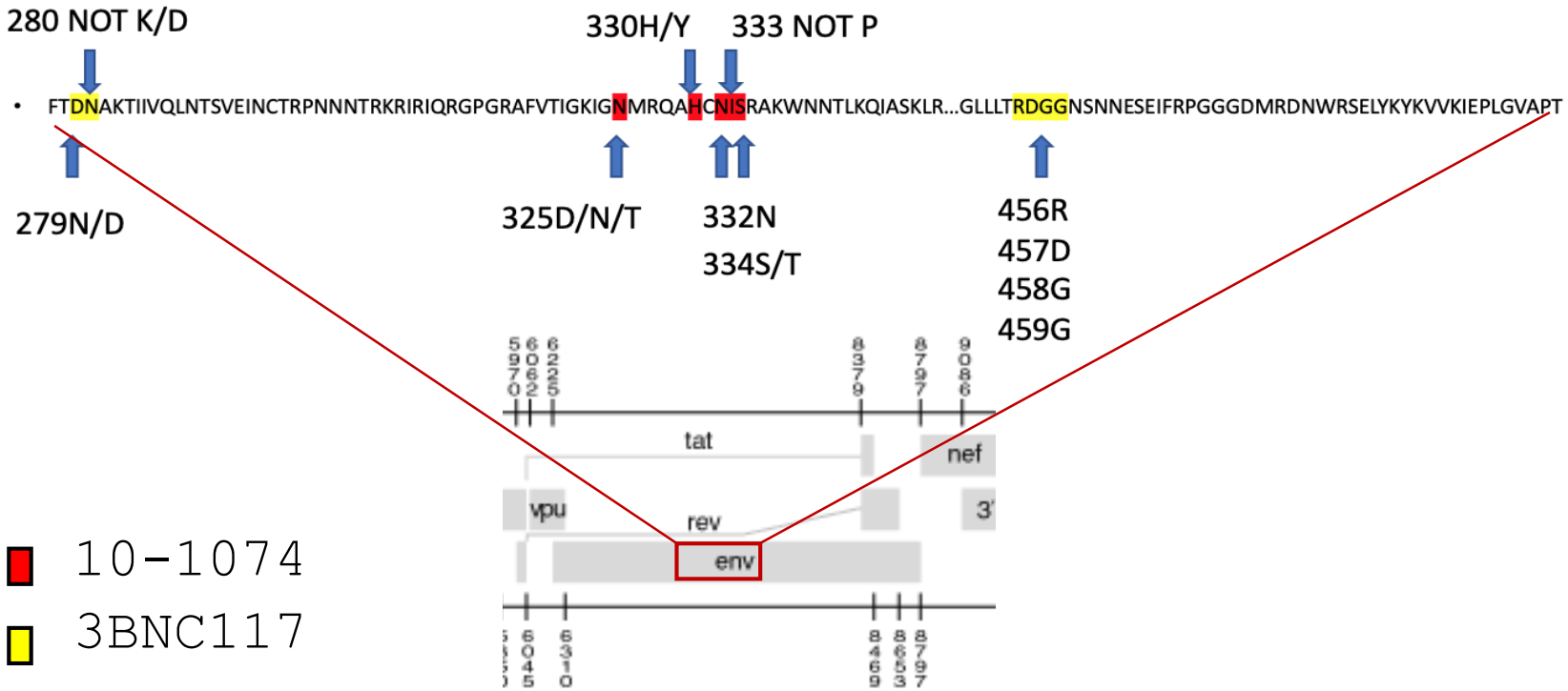


- Viral suppression for 5 to >30 weeks
- Median time to rebound 21 weeks vs 2.3 weeks for ART-only controls vs 6-10 weeks for single bNAb.
- Two never rebounded (? now one)
- Rebound in others due to resistance or as bNAb concentration dropped.

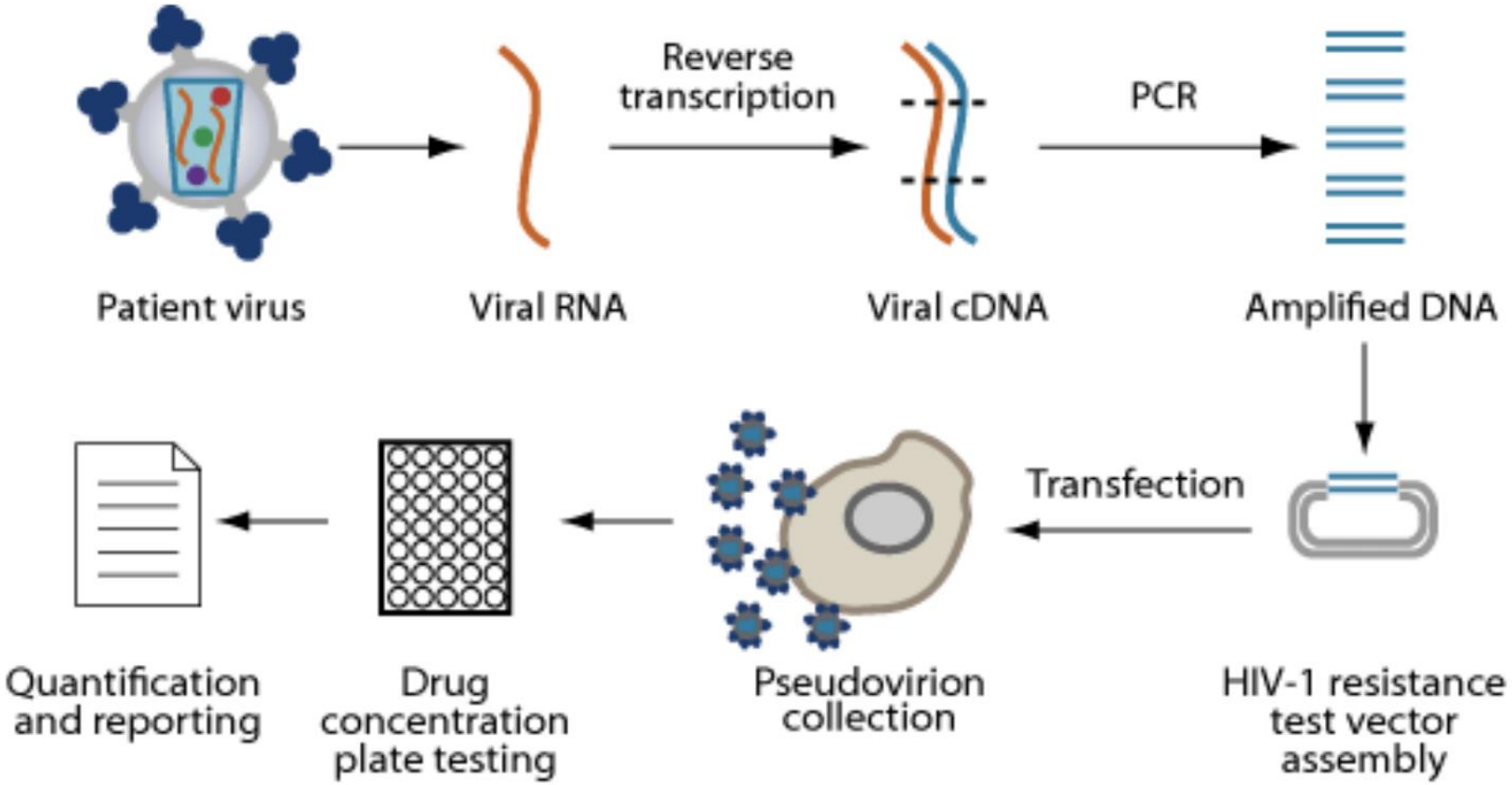
How do we pick the right bNAb?



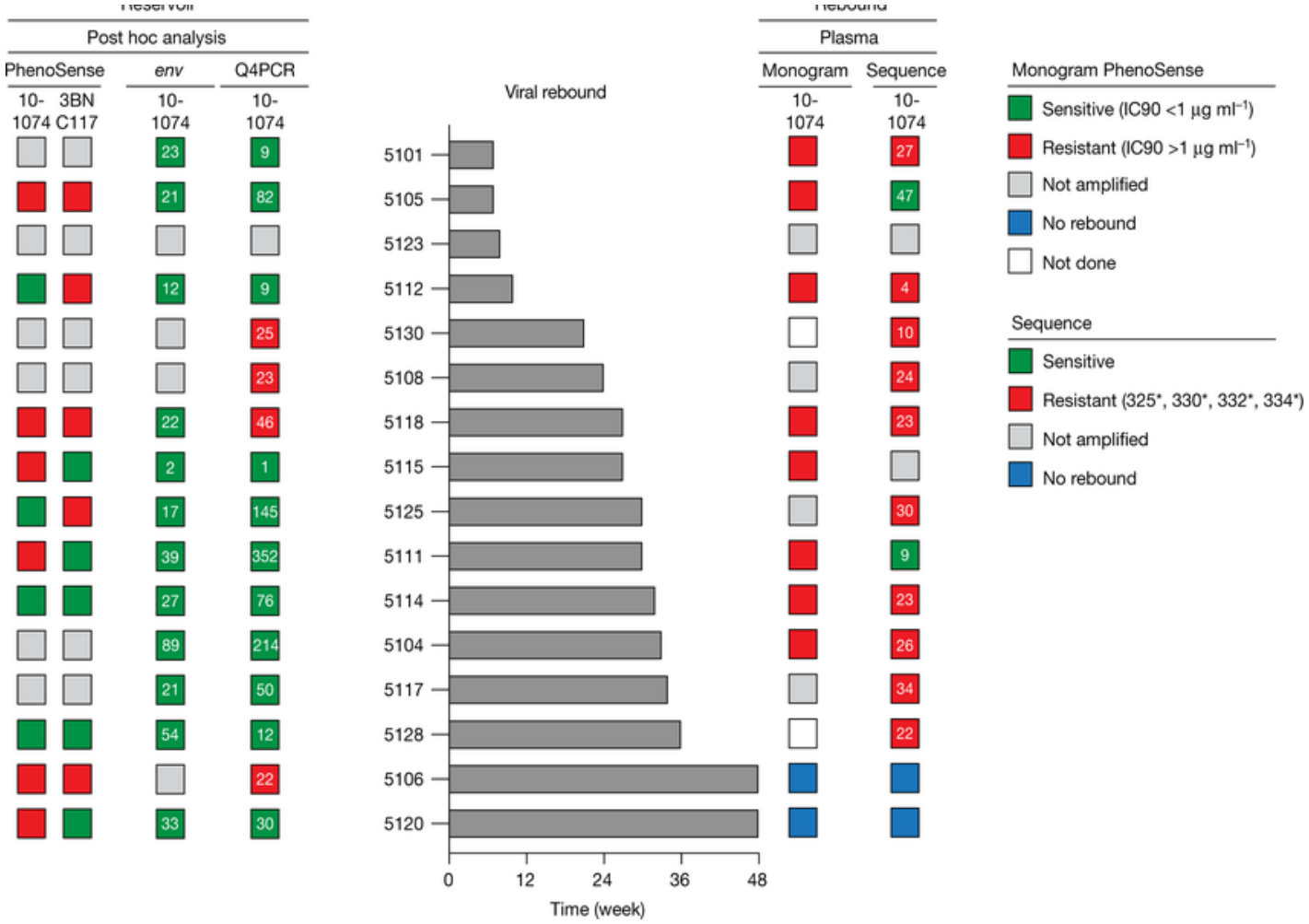
Measure antibody sensitivity using envelope genotype



Sensitivity to bNabs using Phenotype assays



Comparing genotype with phenotype with viral rebound

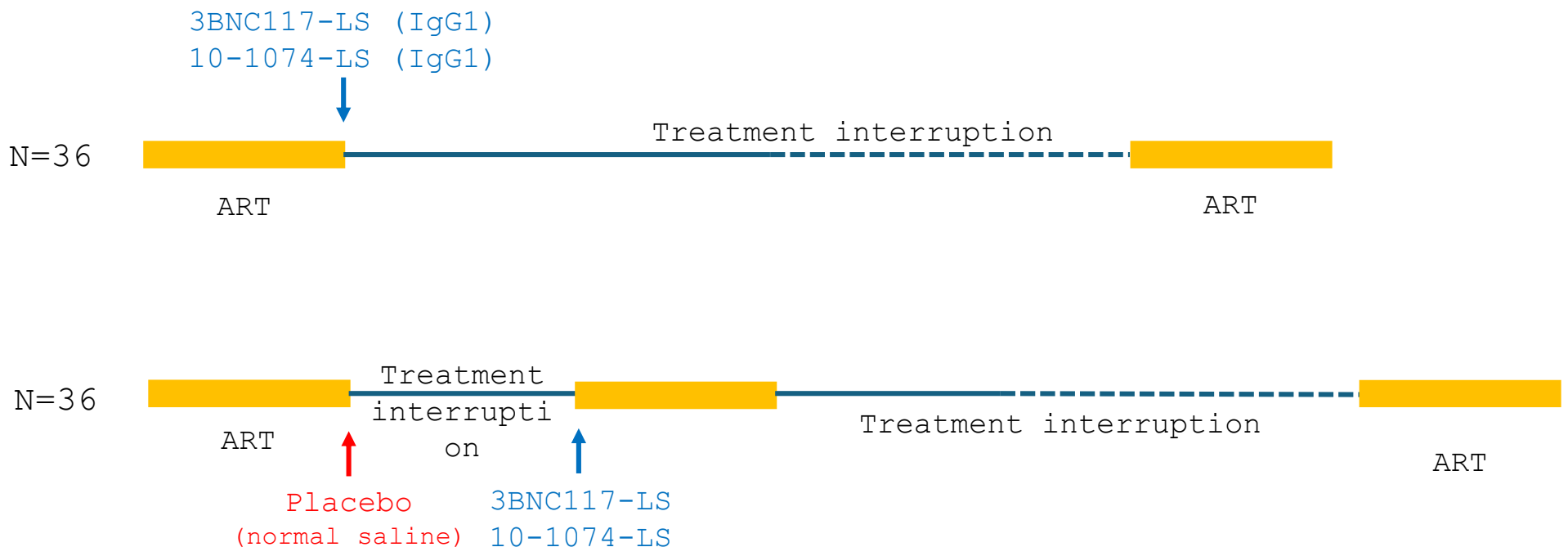


- Time to viral rebound compares predictive performance of the two different assays
- Both are imperfect
- Time consuming
- Expensive
- Not suitable for "roll out"

- The first double blinded randomised placebo controlled trial of 2 long-acting HIV-specific broadly neutralising antibodies (bNAbs) vs placebo in treated early HIV Infection on viral control off ART

RIO study design

PRIMARY ENDPOINT
% of participants with HIV viral load <50 copies RNA/ml
20 weeks after stopping ART



Eigibility:
Treated at the time of acute or early infection
HIV envelope sequences show no evidence of resistance on genotype

RIO so far…

N = 65/72 dosed

48 Total unblinded to date

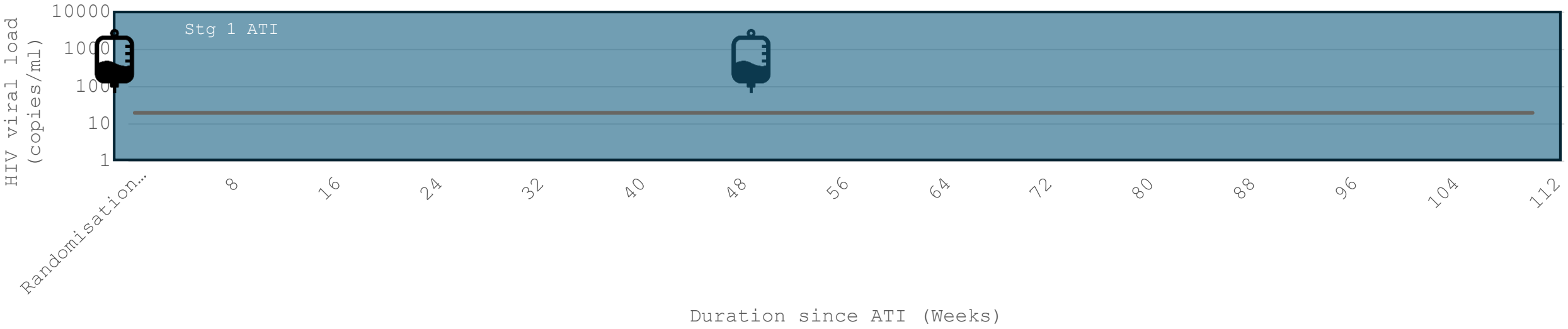
16 remain blinded not reached VL rebound (range 22- 110 weeks)

28 gut biopsy sub study

22 VL < 20 off ART to week 20

12 VL < 20 off ART for > 48 weeks

5 VL < 20 off ART for > 72 weeks

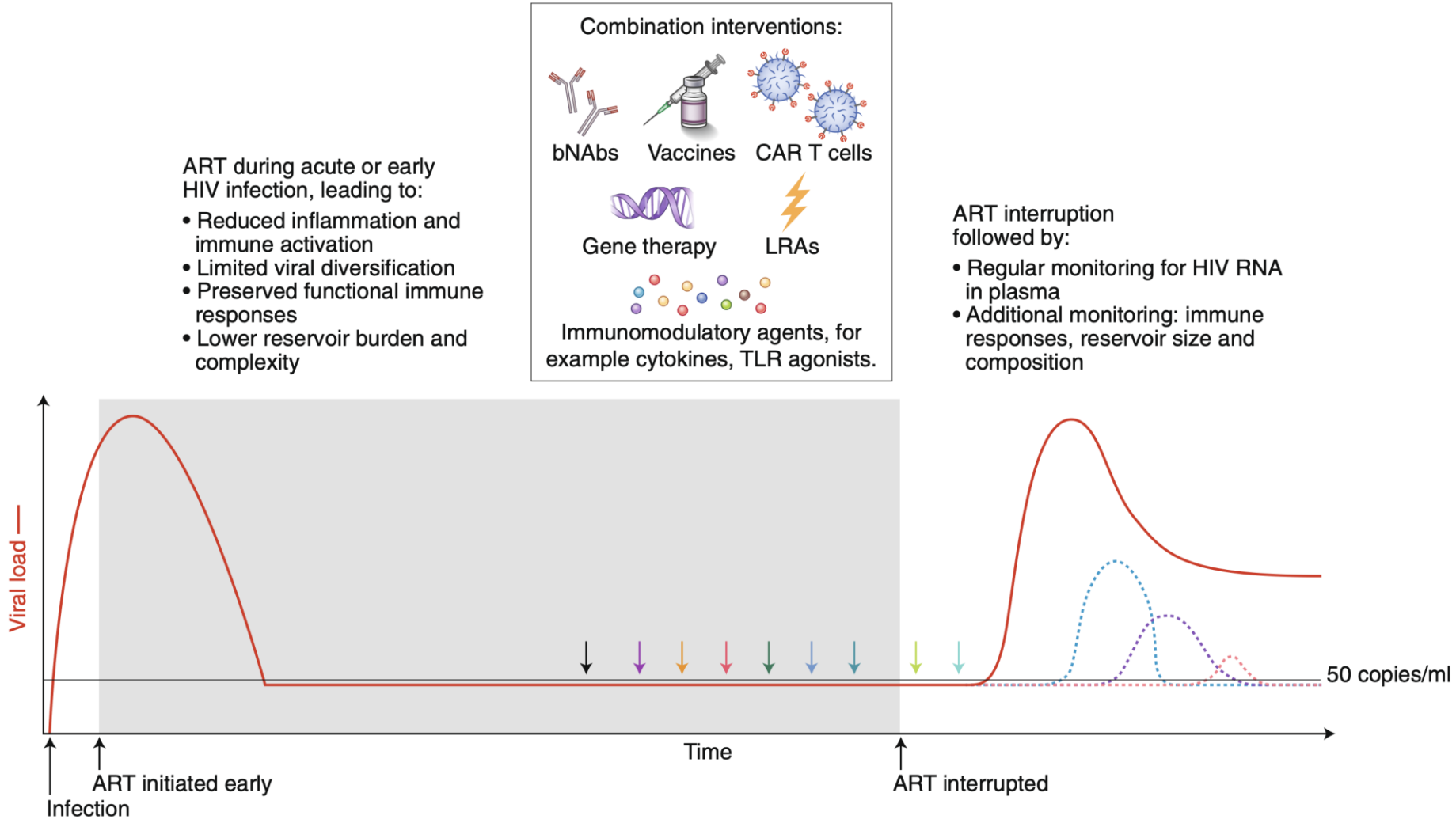


HIV treatment studies using bNAbs

Name of study	Trial design	Study outcome	bNAbs	Trial status
RIO UK-Europe	RCT bNAbs vs placebo treated PHI	Time to VL rebound after ATI week 20	3BNC-117-LS + 10-1074-LS	90% recruited still open
RHIVIERA-02 France	RCT bNAbs vs placebo at acute infection diagnosis	Time to VL rebound after ATI 24 weeks	3BNC-117-LS+ 10-1074-LS	Open to recruitment
MCA-1034 USA	RCT bNAbs vs placebo	Safety PK and reservoir after 3 doses	3BNC-117-LS +10-1074-LS	Open to recruitment
ACTG 5416 PAUSE SSA	Phase I RCT bNAbs vs placebo SSA	Time to VL rebound after ATI	3BNC-117-LSJ + 10-1074-LSJ	Open to recruitment
ACTG 5417 SSA ACACIA	RCT bNAb vs placebo at ART initiation	Time to VL rebound	3BNC-117-LS + 10-1074-LS	Open to recruitment
ACTG 5388	RCT bNAb vs	Time to VL >	VRC07-523LS +	Open to

Combination approaches towards cure

Combination immune based therapies

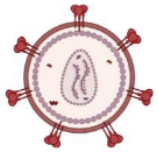


Rationale: Immunotherapy in NHPs

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], Abishek Chandrashekar[1], Katherine Molloy[1], Galit Alter[2], Jeffrey M. Gerold[3], Alison L. Hill[3], Mark G. Lewis[4], Maria G. Pau[5], Hanneke Schuitemaker[5], Joseph Hesselgesser[6], Romas Geleziunas[6], Jerome H. Kim[7]†, Merlin L. Robb[7], Nelson L. Michael[7] & Dan H. Barouch[1,2]



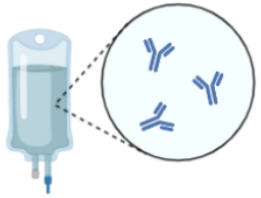
Conserved element vaccine

Vaccine adjuvant

nature

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

Erica N. Borducchi[1,6], Jinyan Liu[1,6], Joseph P. Nkolola[1,6], Anthony M. Cadena[1,6], Wen-Han Yu[2], Stephanie Fischinger[2], Thomas Broge[2], Peter Abbink[1], Noe B. Mercado[1], Abishek Chandrashekar[1], David Jetton[1], Lauren Peter[1], Katherine McMahan[1], Edward T. Moseley[1], Elena Bekerman[3], Joseph Hesselgesser[3], Wenjun Li[4], Mark G. Lewis[5], Galit Alter[2], Romas Geleziunas[3] & Dan H. Barouch[1,2]*



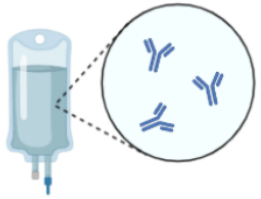
bNAbs

TLR Agonist

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]



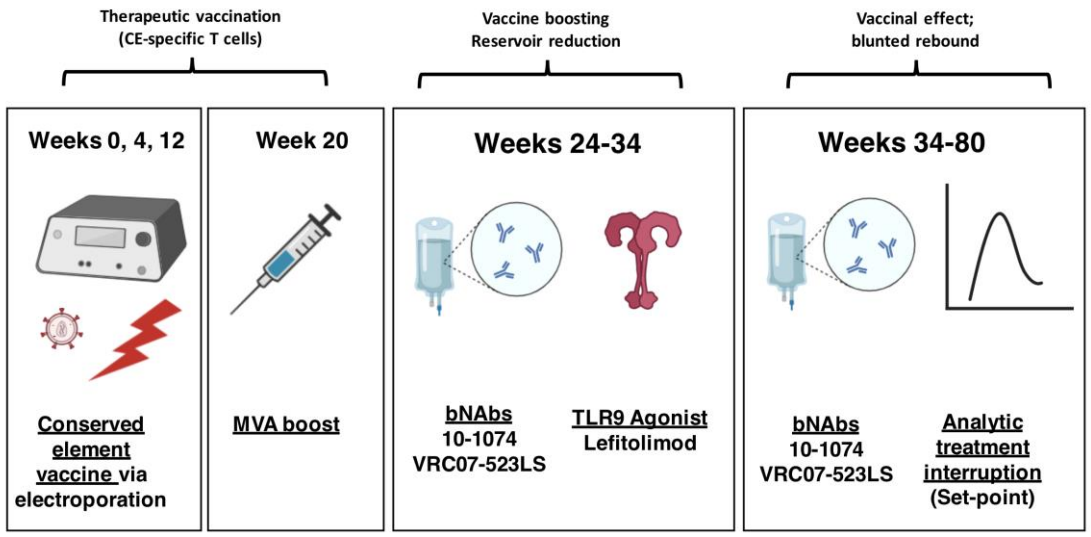
bNAbs

HIV viremia

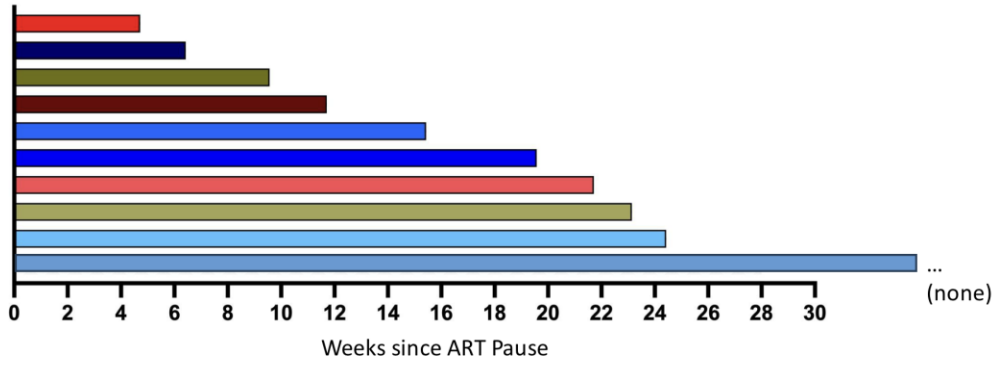
AMFAR study UCSF 7/10 controlled VL 1,000 cpm 1 no rebound to 36 weeks

- Combinatorial therapy with a therapeutic conserved element DNA/MVA vaccine strategy, a TLR9 agonist and broadly neutralizing antibodies

Clinical Trial Schematic



Time to Rebound (Weeks)



Rebound occurred at a mean of 15 weeks after ART interruption

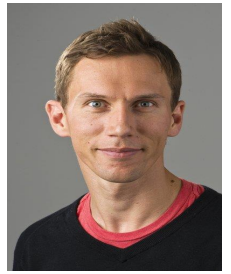
eCLEAR

nature medicine

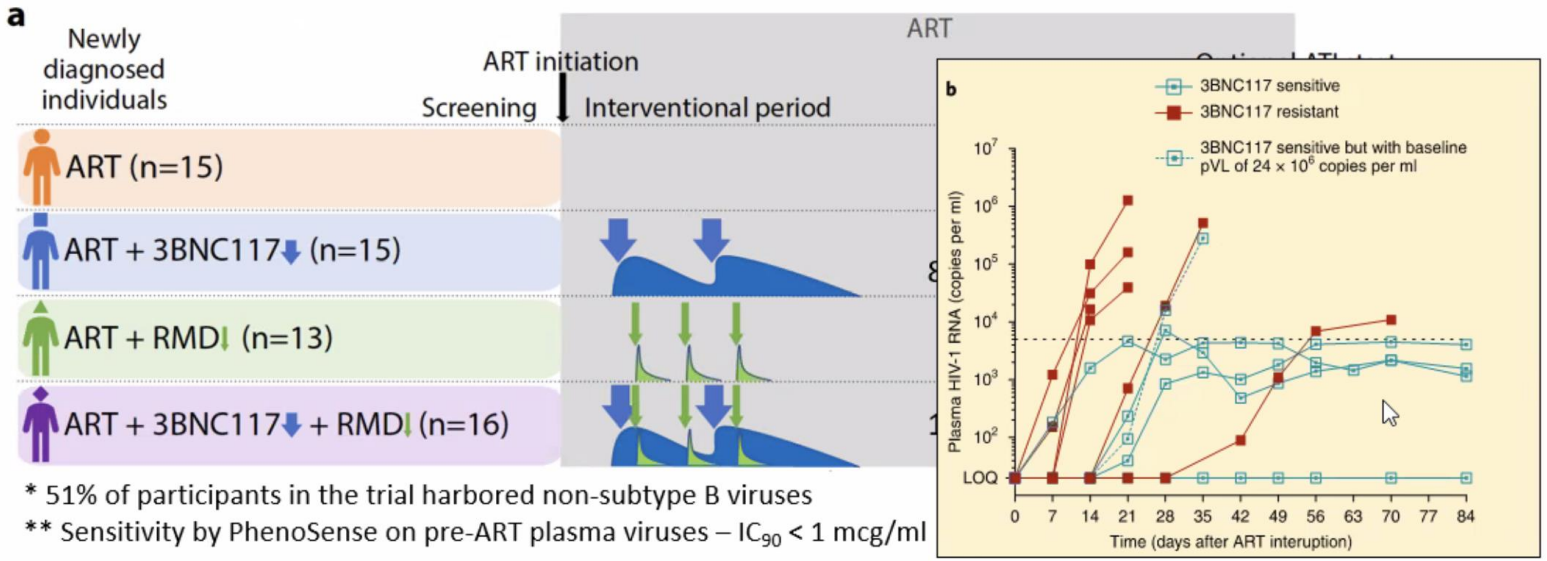
Article

https://doi.org/10.1038/s41591-022-02023-7

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



eCLEAR Study: 3BNC117 +/- Romidepsin at ART Initiation



- **Decrease in median intact proviruses (3dPCR) in all groups**
  - Largest decreases among interventional groups, **but no significant diff. between groups**

- **Enhanced HIV gag-specific CD8 T cell responses** among participants harboring 3BNC117 sensitive pre-ART viruses pre-ART viruses

- **Delayed time to viral rebound** after ATI among participants harboring 3BNC117 sensitive pre-ART viruses

Gunst et al, Nat Med 2022
Rosás-Umbert et al, Nat Comm 2022

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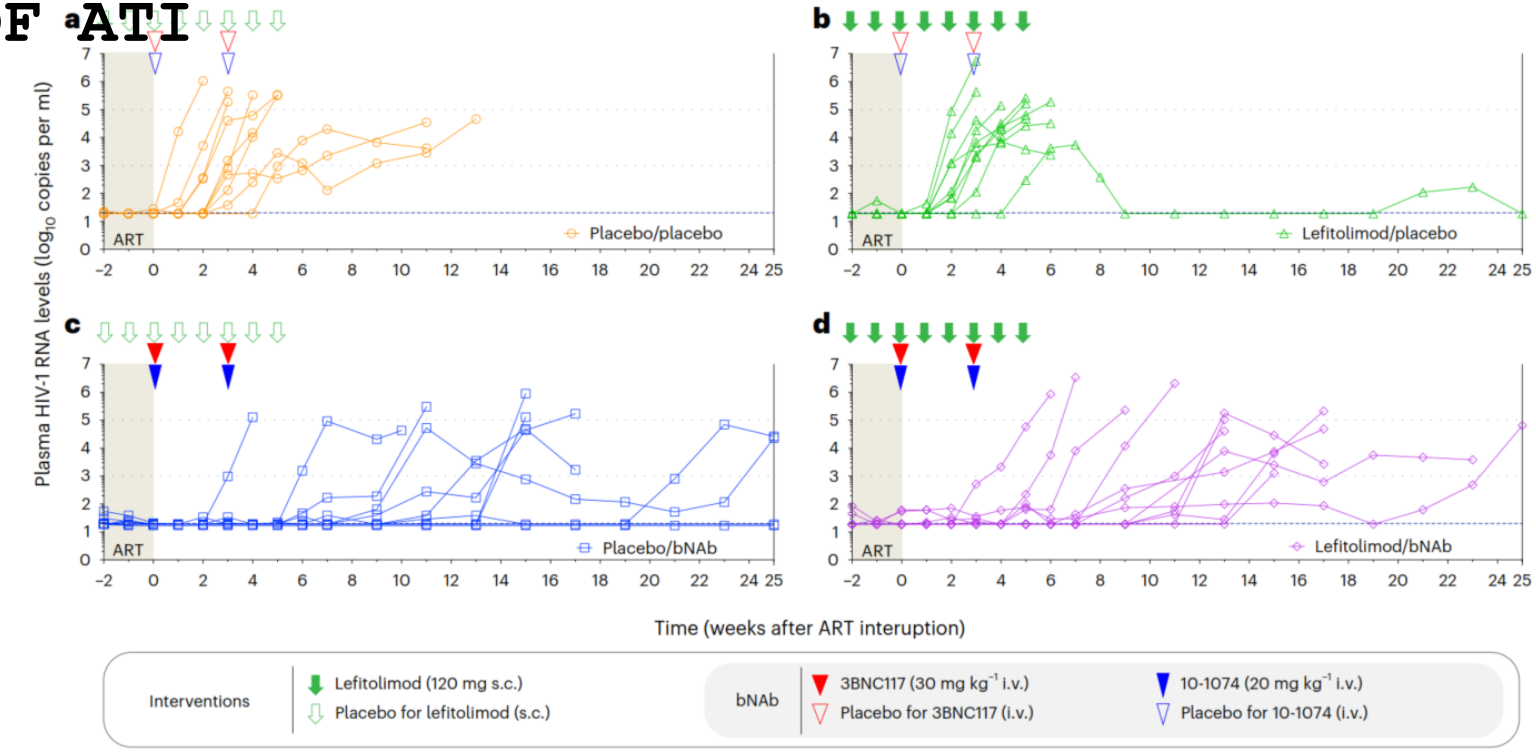
Article | Open access | Published: 11 September 2023

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

PRIMARY ENDPOINT: TIME TO LOSS OF VIROLOGIC CONTROL AFTER 25-WEEKS OF ATI



Defined as 4 weeks with sustained plasma HIV-1 RNA ≥1,000 copies/mL or 2x >100,000 copies/mL.

HIV treatment studies using combination immune approaches bNAbs + vaccine + immune activators

Name of study	Trial design	Study outcome	bNAbs	Trial status
ACTG 5374	RCT vaccine + TLR7 + bNAbs vs placebo 2:1	Safety viral rebound after ATI	Mosiac T-cell Vaccine, TLR-7 agonist 3BNC-117-LS + 10-1074-LS	Open April 2024
AbVAX	RCT vaccine+ bNAb + ATI	Safety, immunogenicity and time to VL rebound	3BNC-117-LS + 10-1074-LS + Mosaic T-cell vaccine _+ TIIV	Due to open end 2024
eCLEAR	RCT bNAb +/- Romidespin + ART at ART initiation	Safety and time to VL rebound	3BNC-117 + Romidepsin	Completed bNAb delayed TTVR No effect Romidepsin
TiTAN	RCT bNAb +/- TLR9 agonist	Safety and time to VL rebound	3BNC-117 + 10-1074+ TLR-9 Agonist	Completed bNAbs delayed TTVR no effect of TLR9 Ag
AMFAR study	Single arm n = 10 Vaccine + MVA boost + bNAbs + TLR9Agonist	Safety and Time to VL rebound	Vaccine 10-1074 + VRC07-523LS + TLR9 Ag	Some delay in viral rebound amongst 30% of participants
Lenacapavir + bNAbs	RCT to dose of bNAb	Safety and viral suppression week 24	3BNC-117 + 10-1074 + Lenacapavir	9/10 maintained VL < 50 for 24 weeks
BEAT-2	Single arm	Safety and time to viral	Peg IFNg + 3BNC-117 +	Complete 40% PTC

bNAbs with long-acting ART

ORAL ABSTRACT: OA-12

Wednesday, February 22, 2023

LENACAPAVIR WITH bNAbs GS-5423 AND GS-2872 DOSED EVERY 6 MONTHS IN PEOPLE WITH HIV

Joseph J. Eron

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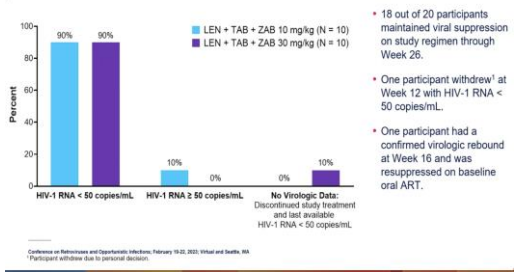
Virologic Efficacy Outcomes at Week 26 by FDA Snapshot Algorithm

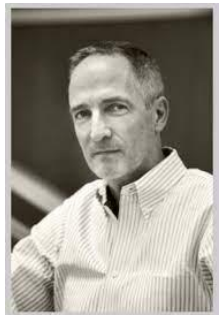


- 18 out of 20 participants maintained viral suppression on study regimen through Week 26.
- One participant withdrew[1] at Week 12 with HIV-1 RNA < 50 copies/mL.
- One participant had a confirmed virologic rebound at Week 16 and was resuppressed on baseline oral ART.

[1] Participant withdrew due to personal decision.

CROI

Presentation #2258



About CROI Abstracts Presenters CROI Conference on Retroviruses and Opportunistic Infections Attendees Scholarships Program

Safety and Efficacy of VRC07-523LS Plus Long-Acting Cabotegravir in the Phase II ACTG A5357 Trial

Professor Babafemi Taiwo

long-acting cabotegravir injections every four weeks and 40 mg/kg infusions of VRC07-523LS every eight weeks. N = 60

93% maintained viral suppression, defined as 200 copies or less at 48 weeks

5 failed and 1 developed INI resistance

Lenacapavir Plus bNAbs for People with HIV and Susceptibility to Either Teropavimab or Zinlirvimab

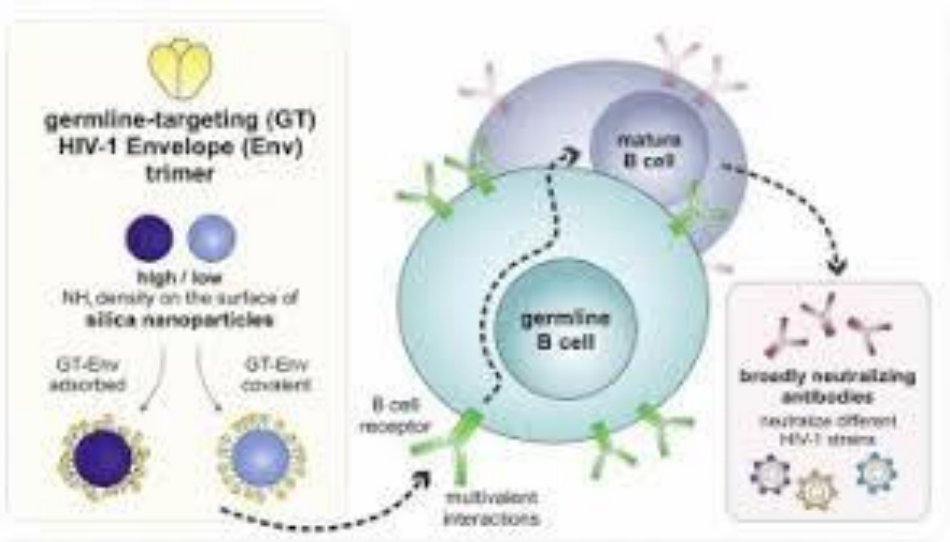
Joseph J Eron,[1] Paul P Cook,[2] Megha L Mehrotra,[3] Hailin Huang,[3] Marina Caskey,[4] Gordon E Crofoot,[5] Edwin DeJesus,[6] Linda Gorgos,[7] Laurie A VanderVeen,[3] Olayemi O Osiyemi,[8] Cynthia Brinson,[9] Sean E Collins[3]

Viral Suppression at Week 26

	LEN + TAB + ZAB 10 mg/kg (n=4)[a]	LEN + TAB + ZAB 30 mg/kg (n=6)	Total (N=10)
HIV-1 RNA ≥50 copies/mL, **n** (%; [95% CI])	**2** (50; [7, 93])	**0** (0; [0, 46])	**2** (20; [3, 56])
HIV-1 RNA <50 copies/mL, **n** (%; [95% CI])	**2** (50; [7, 93])	**6** (100; [54, 100])	**8** (80; [44, 98])

- Eight out of 10 participants remained virologically suppressed with HIV-1 RNA <50 copies/mL 6 months after dosing
- All participants in the higher dose group (n=6; ZAB 30 mg/kg) remained suppressed at Week 26

Future direction: generate bNAbs using a vaccine



› Cell Rep Med. 2023 Apr 18;4(4):101003. doi: 10.1016/j.xcrm.2023.101003. Epub 2023 Apr 11.

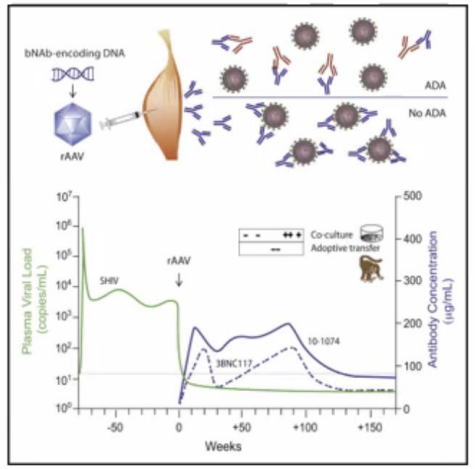
Germline-targeting HIV-1 Env vaccination induces VRC01-class antibodies with rare insertions

Tom G Caniels [1], Max Medina-Ramírez [1], Jinsong Zhang [2], Anita Sarkar [3], Sonu Kumar [3], Alex LaBranche [2], Ronald Derking [1], Joel D Allen [4], Jonne L Snitselaar [1], Joan Capella-Pujol [1], Iván Del Moral Sánchez [1], Anila Yasr[illegible]n [1], Tom P L Bijl [1], Sravani Venkatayogi [6], Joshua S Ma[illegible]huancang Jiang [5], Wen-Hsin Lee [3], Maarten Pater [1], J[illegible]emen [1], Steven W de Taeye [1], Kimmo Rantalainen [3], Celia LaBranche [6], Kevin O Saunders [6], David Montefiori [7], Gabriel Ozorowski [3], Andrew B Ward [3], Max Crispin [4], John P Moore [5], Per Johan Klasse [5], Barton F Haynes [8], Ian A Wilson [9], Kevin Wiehe [8], Laurent Verkoczy [10], Rogier W Sanders [11]

Department of Medical Microbiology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; Amsterdam Institute for Infection and Immunity, Infectious Diseases, Amsterdam, the Netherlands.

Alternatives

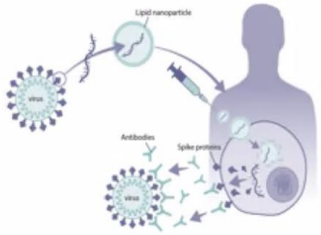
Vector Technology for Delivery



The Miami Monkey

VRC 603

A Phase I Dose-Escalation Study of the Safety of **AAV8-VRC07** (VRC-HIVAAV070-00-GT) Recombinant AAV Vector Expressing VRC07 HIV-1 Neutralizing Antibody in Antiretroviral -Treated, HIV-1 Infected Adults With Controlled Viremia.



mRNA technology

Summary

➢ *Effects on viremia*

- In viremic participants, 3BNC117+10-1074 (and LS variants) lead to transient decline in viremia (Bar-On *et al*, Nat Med 2018).
- **Viral suppression is maintained** with repeated dosing during ART interruption **in participants harboring sensitive proviruses** (Mendoza *et al*, Nat Med 2018, Gaebler *et al,* Nature 2022, *Sneller et al*, Nature 2022*)*.

➢ *Effects on immune responses*

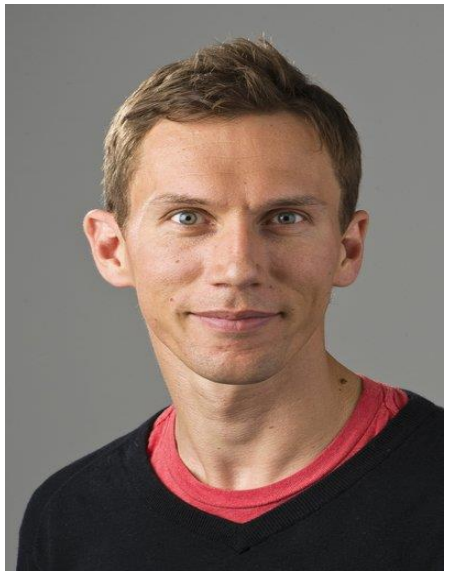
- 3BNC117 enhanced humoral immune responses in HIV-infected individuals (Schoofs *et al*, Science 2015).
- **HIV-1 specific T cell responses are enhanced during bNAb therapy** after ART discontinuation (Niessl *et al*, Nat Med 2020) and following bNAb administration at ART initiation (Gunst *et al*, Nat Med 2022, Rosás-Umbert *et al*, Nat Comm 2022).

➢ *Effects on the reservoir*

- **Immunotherapy with 3BNC117 and 10-1074** (over 6 months) is associated with **changes in the size of the intact proviral reservoir** without measurable effects on the defective reservoir (Gaebler *et al*, Nature *in* 2022).

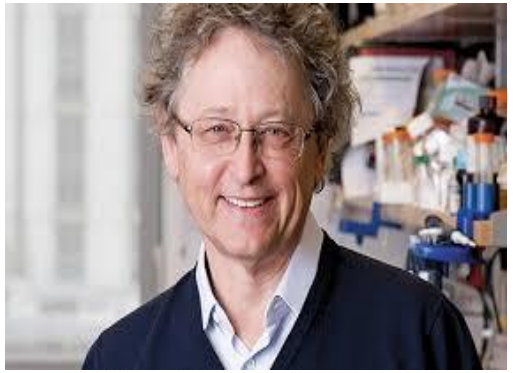
Community summary of antibody studies

- Broadly neutralizing antibodies (bNAbs) can block virus and seem to stimulate the immune system to help control virus off ART
- Different bNAbs only work against some strains of virus so we will probably need to use them in combination and check first which antibodies work best for each persons virus
- bNAbs are safe and one injection can last 6-12 months
- Evaluating bNAbs as if they are simple antiviral agents is ignoring their immu modulatory effects

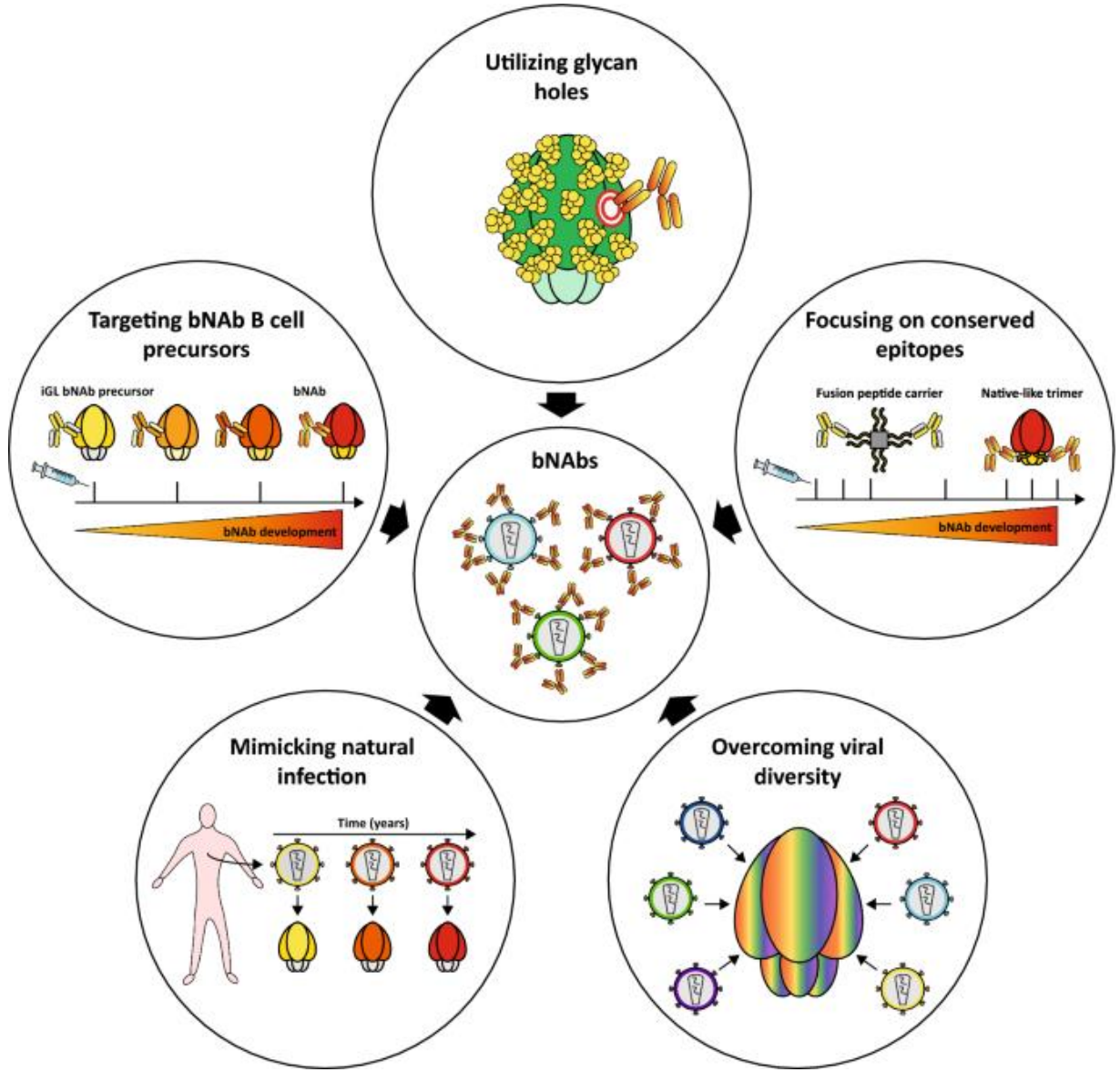






THANK YOU!


Utilizing glycan holes
Focusing on conserved epitopes
Fusion peptide carrier
Native-like trimer
bNAb development
Overcoming viral diversity
Mimicking natural infection
Time (years)
Targeting bNAb B cell precursors
iGL bNAb precursor
bNAb
bNAb development
bNAbs