Advances in HIV Cure Clinical Trials – Signals of ART free virological control

ASHM 2025

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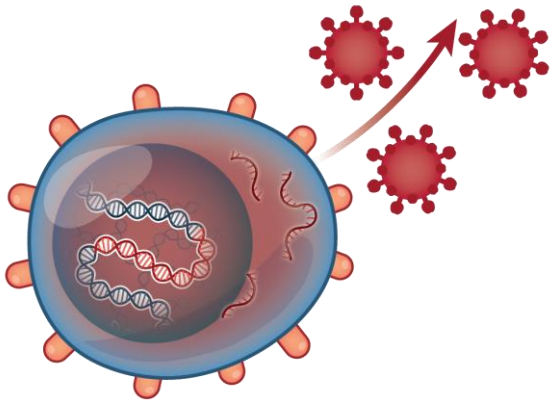
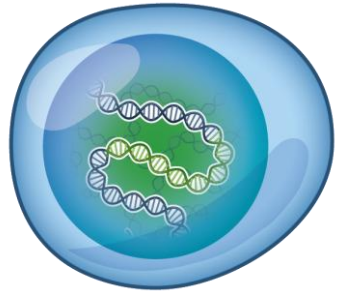
Overview

- Viral reservoirs
- Strategies for cure
- People with malignancy cured of HIV
- Examples of immune therapies
  - Anti-HIV broadly neutralising antibodies
  - Anti PD-1 antibodies

‘Reservoir’ of latently infected cells is established early in infection and is dynamic over time





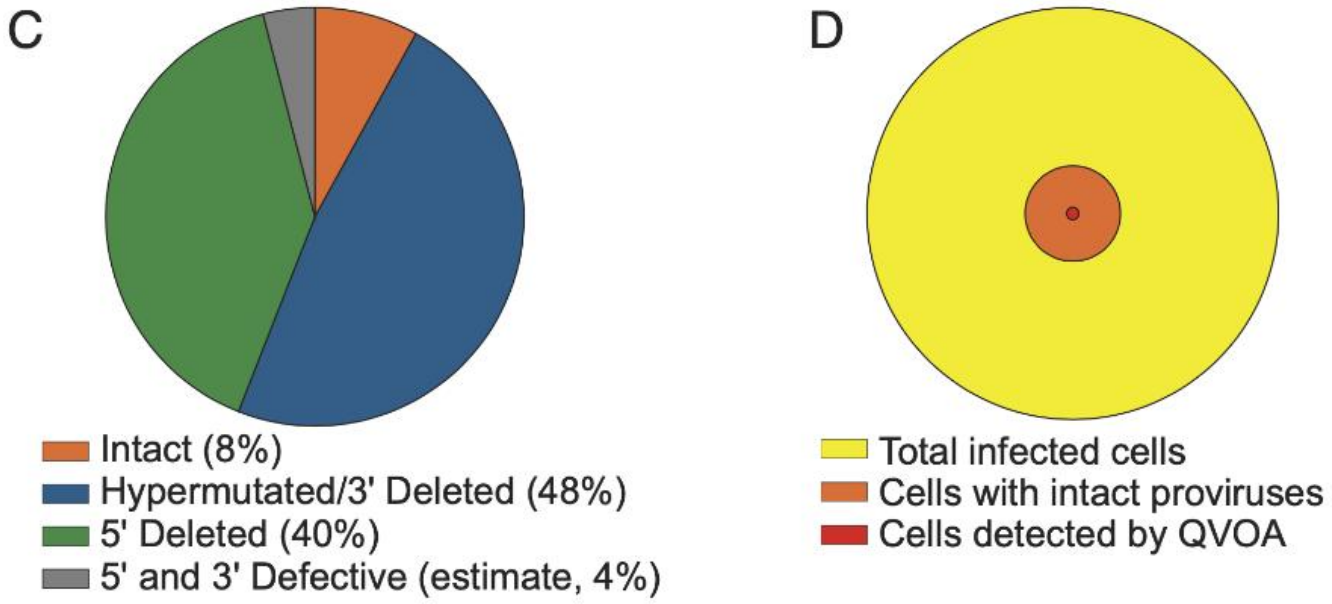
Productive infection
DNA positive
RNA positive
HIV protein positive
DEATH

Latent infection
DNA positive
RNA negative
HIV protein negative
SURVIVAL

Slide adapted from Sharon Lewin and Michael Roche

HIV Provirus that can lead to productive infection is rare

- Detection rates
  - QVOA (intact and inducible) detects ~ 1 per million resting* CD4+ T cells
  - IPDA (intact) detects ~ 38 per million resting* CD4+ T cells with intact provirus

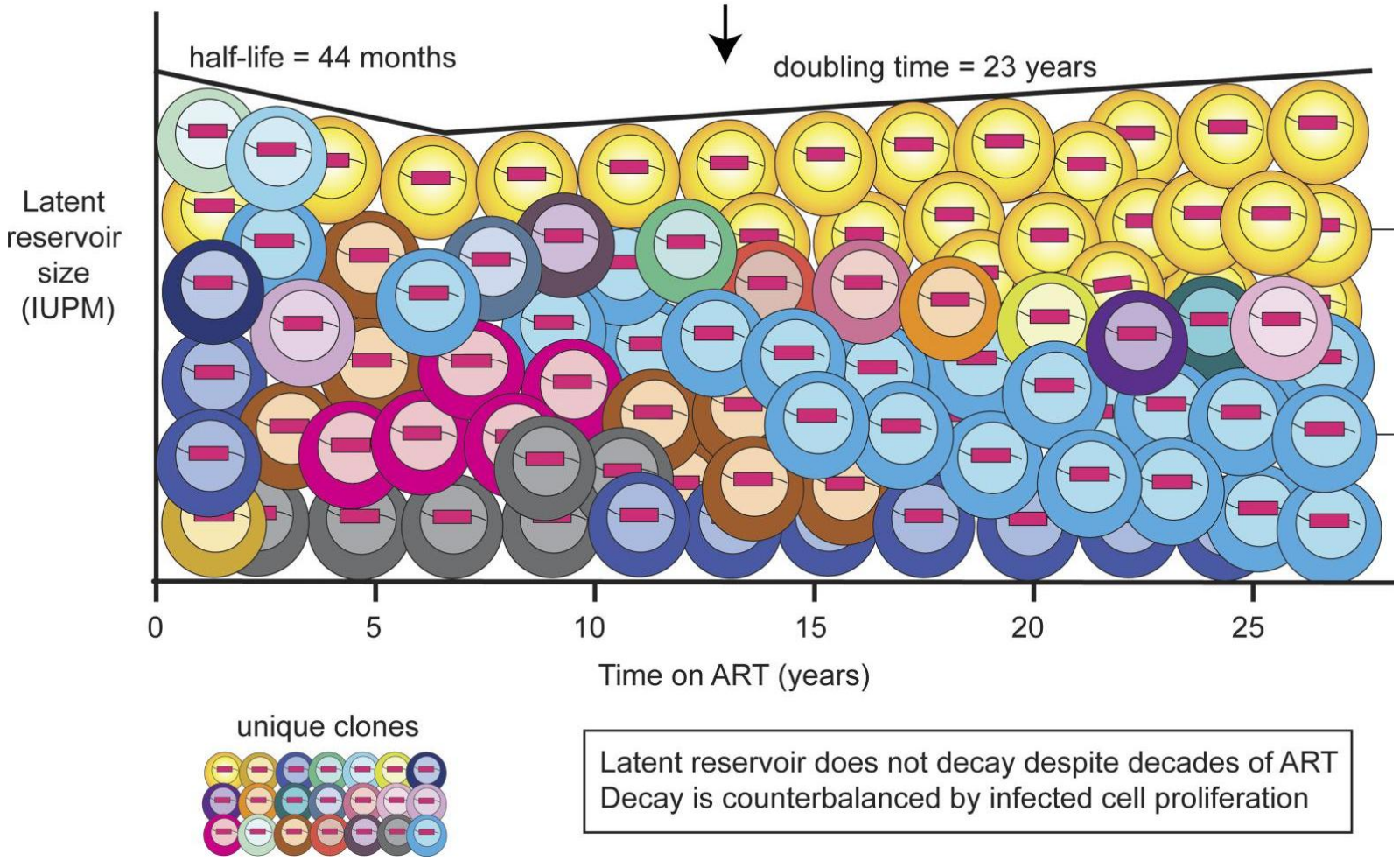


Simonetti, PNAS, 2020

* Resting are quiescent non-proliferating T-cells that are the major reservoir for latent HIV infection

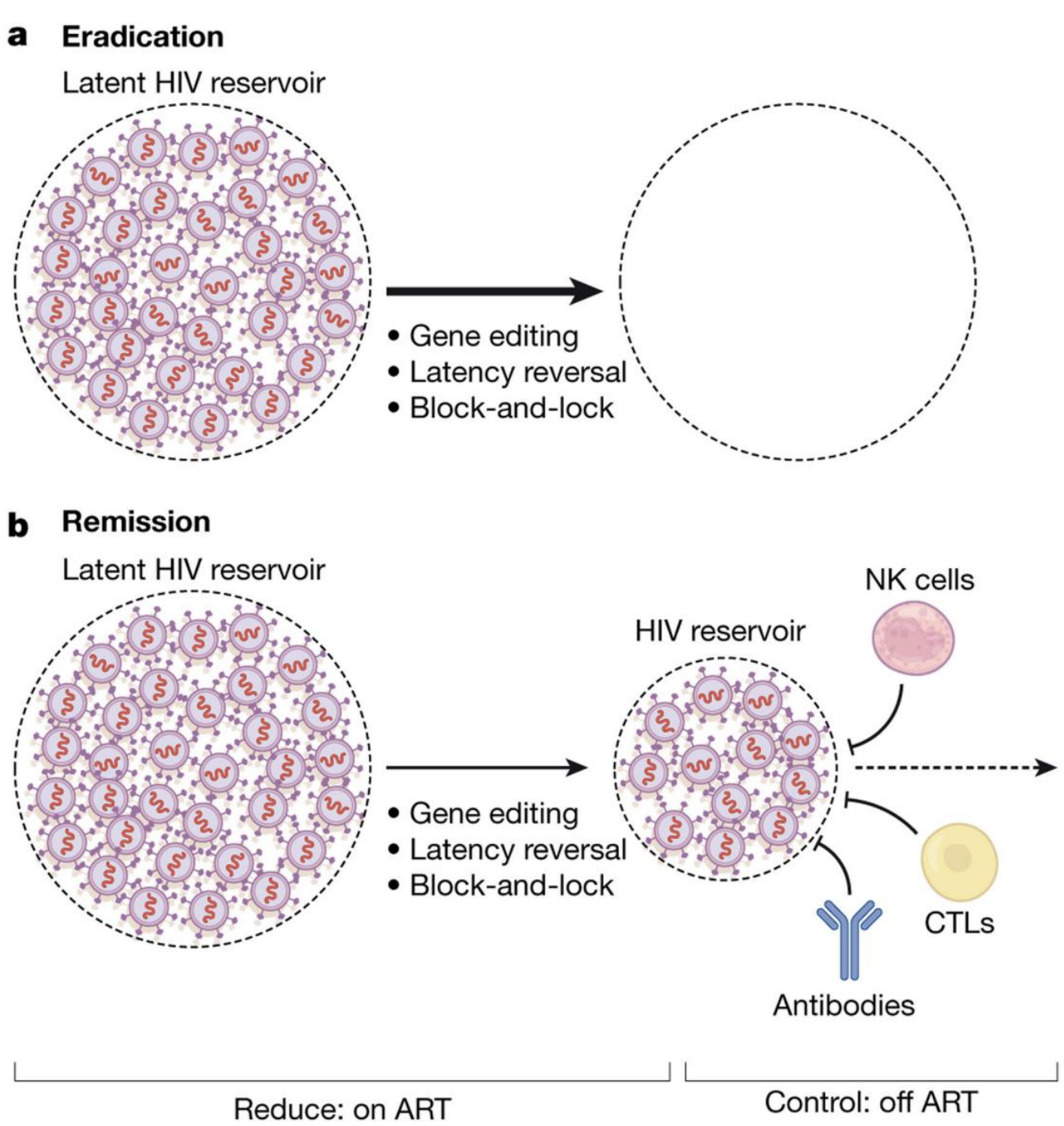
Frequency of replication competent HIV provirus is maintained over time

- N=42 people on median 22 years ART
- qVOA and IPDA assays



McMyn, JCI, 2023

Strategies for cure



Ndung'u Nature 2019

People cured of HIV

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"name" Sex, Age at Tx	Malignancy	Conditioning	Whole body irradiation	Graft v Host	Reservoir assessment Delta 32 status	ART stop, Time off ART
Berlin, Timothy Ray Brown Male,41	AML	intense	yes	mild	HIV RNA -ve HIV DNA -ve in PBMCs, GIT Homozygous Delta 32	2007 13 yrs, RIP
London, Adam Castillejo Male, 38	HL	Less intense	no	mild	HIV RNA -ve HIV DNA -ve PMBCs, CSF, GIT, LTR +ve LN, IPDA –ve Homozygous Delta 32	2017 8 yrs
Dusseldorf, Marc Franke Male, 49	AML	intense	?	?	HIV RNA -ve HIV DNA -ve in PBMCs, GIT, LN. QVOA –ve + DNAscope in some LN, GIT Homozygous Delta 32	2018 7 yrs
New York, Female "middle aged" haplo-cord Tx	AML	intense	yes	no	HIV RNA -ve HIV DNA -ve in PBMCs, BM Transient +ve LTR Homozygous Delta 32 (cord blood) and wild type	2021 4 yrs
City of Hope, Paul Edmonds Male, 63	AML	Less intense	?	mild	HIV RNA -ve No HIV Homozygous Delta 32	2021 4 yrs
Geneva Male	Biphenotypic Sarcoma	Intense	Yes	Chronic	HIV RNA -ve HIV DNA -ve in PBMCs, GIT. Defective DNA in PBMCs, BM **Wild type**	2021 4 yrs
Berlin II Male, 52	AML	Less intense	?	Mild	HIV RNA -ve HIV DNA -ve in PBMCs, GIT. QVOA –ve **Heterozygous Delta 32**	2018 7 yrs
Marseille Female, 50s	AML	Intense	Yes	Mild	HIV RNA -ve HIV DNA -ve in PBMCs Homozygous Delta 32	2023 2 yrs

Signals of ART free virological control bNAbs and anti-PD-1

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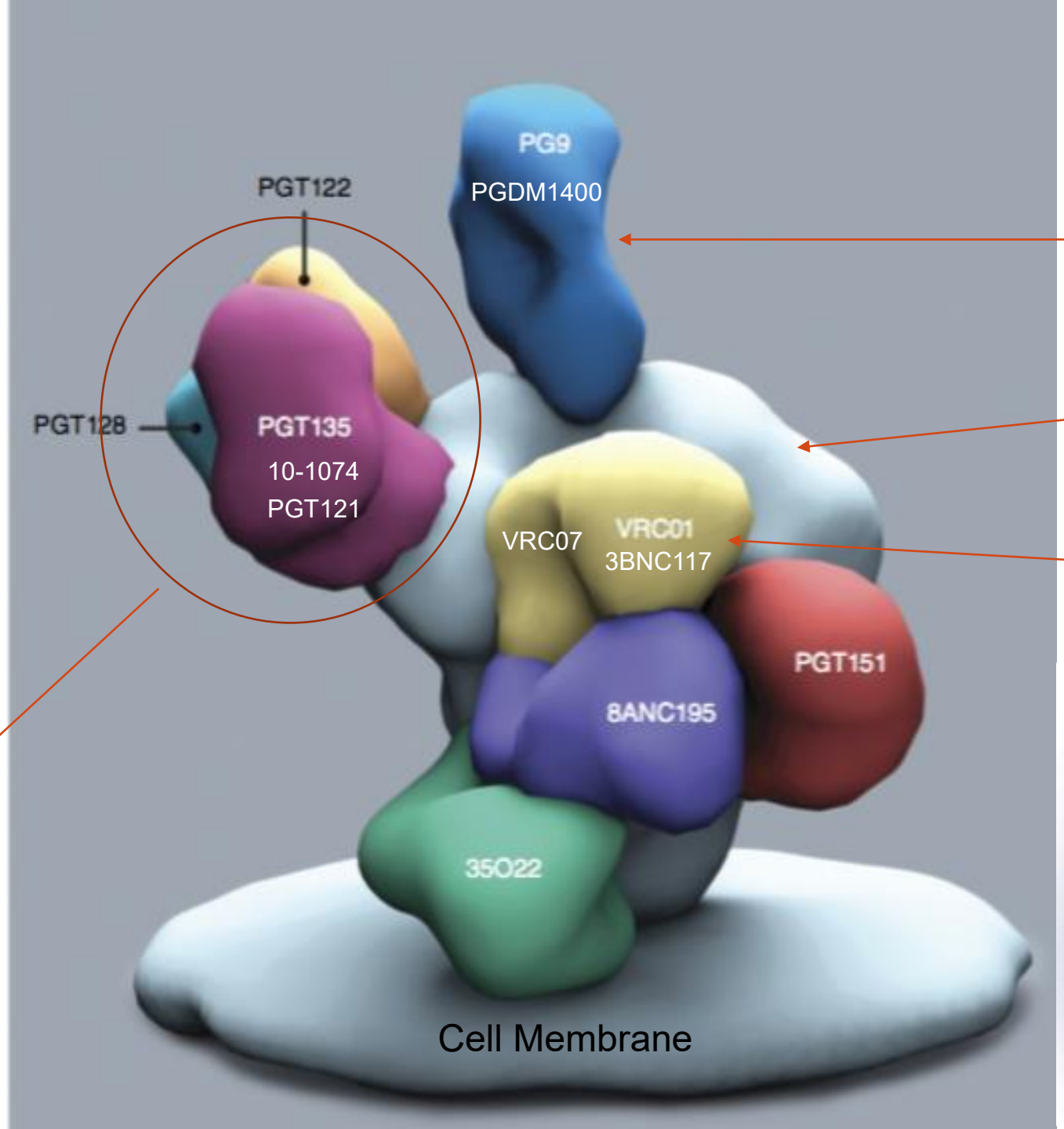
Broadly Neutralizing Abs bound to the HIV Envelope trimer

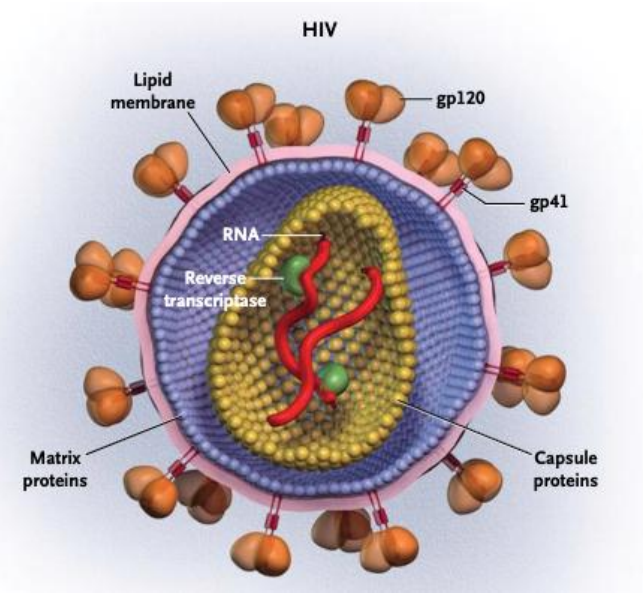


V1/V2 Apex

HIV Envelope Trimer

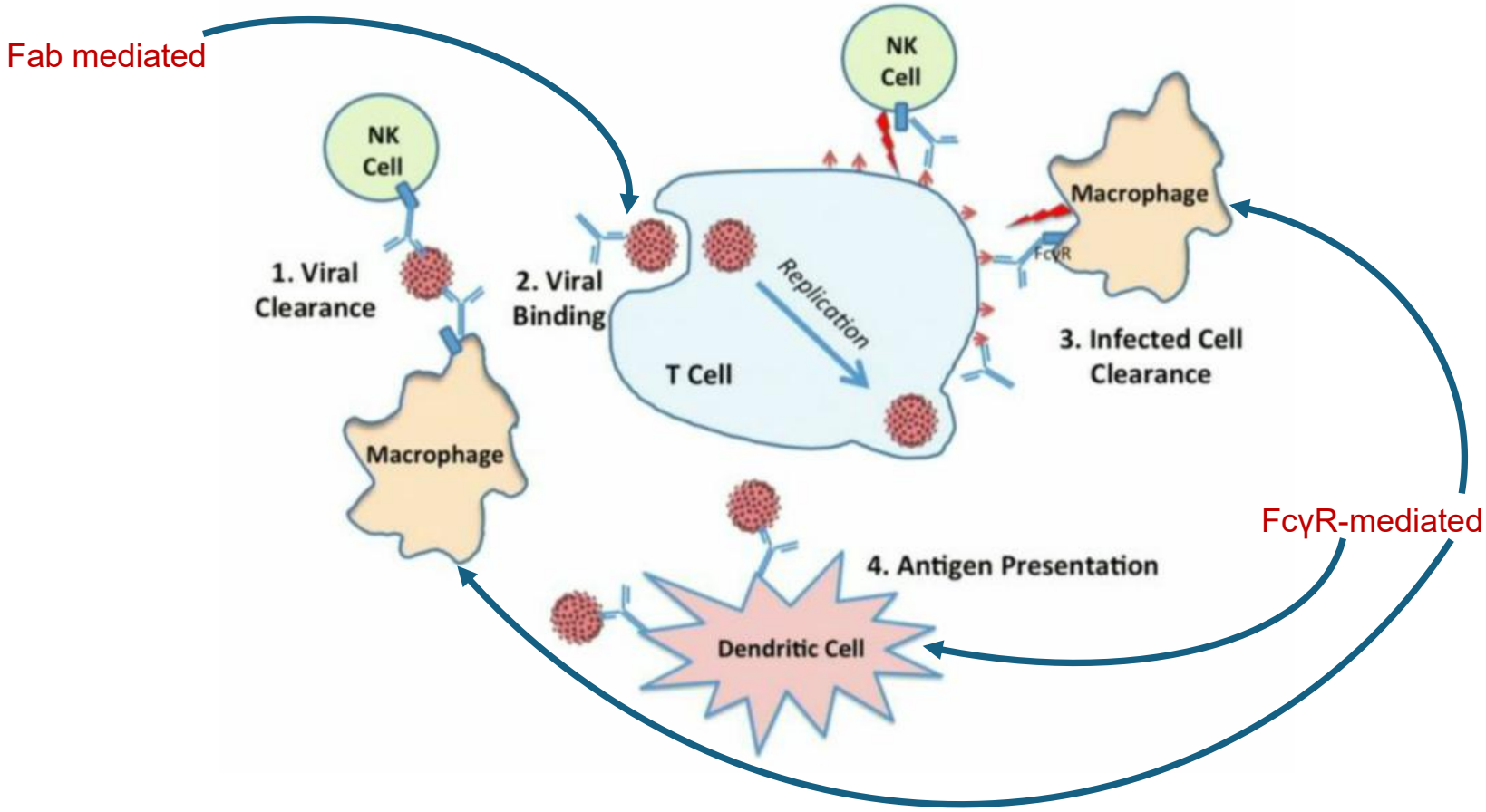
CD4 binding site

High Mannose Patch / V3 loop / N332 Glycan Supersite



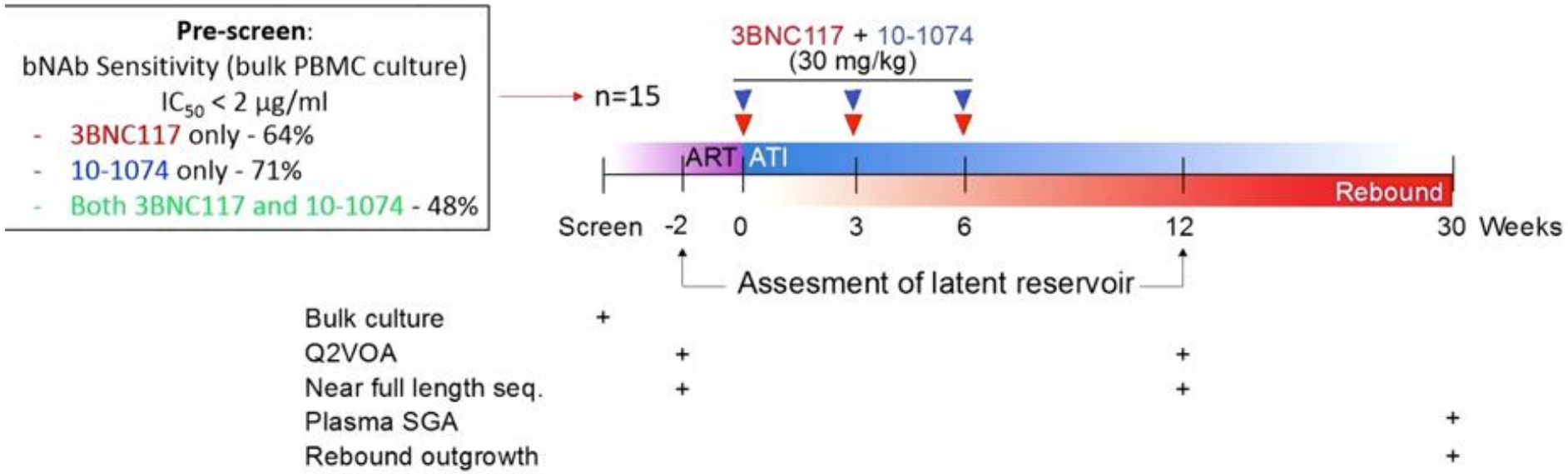
Adapted from Burton Nat Immunol 2015

Broadly Neutralizing Antibodies (bNAbs) - How do bNAbs work?



Adapted from Nussenzweig CROI 2017

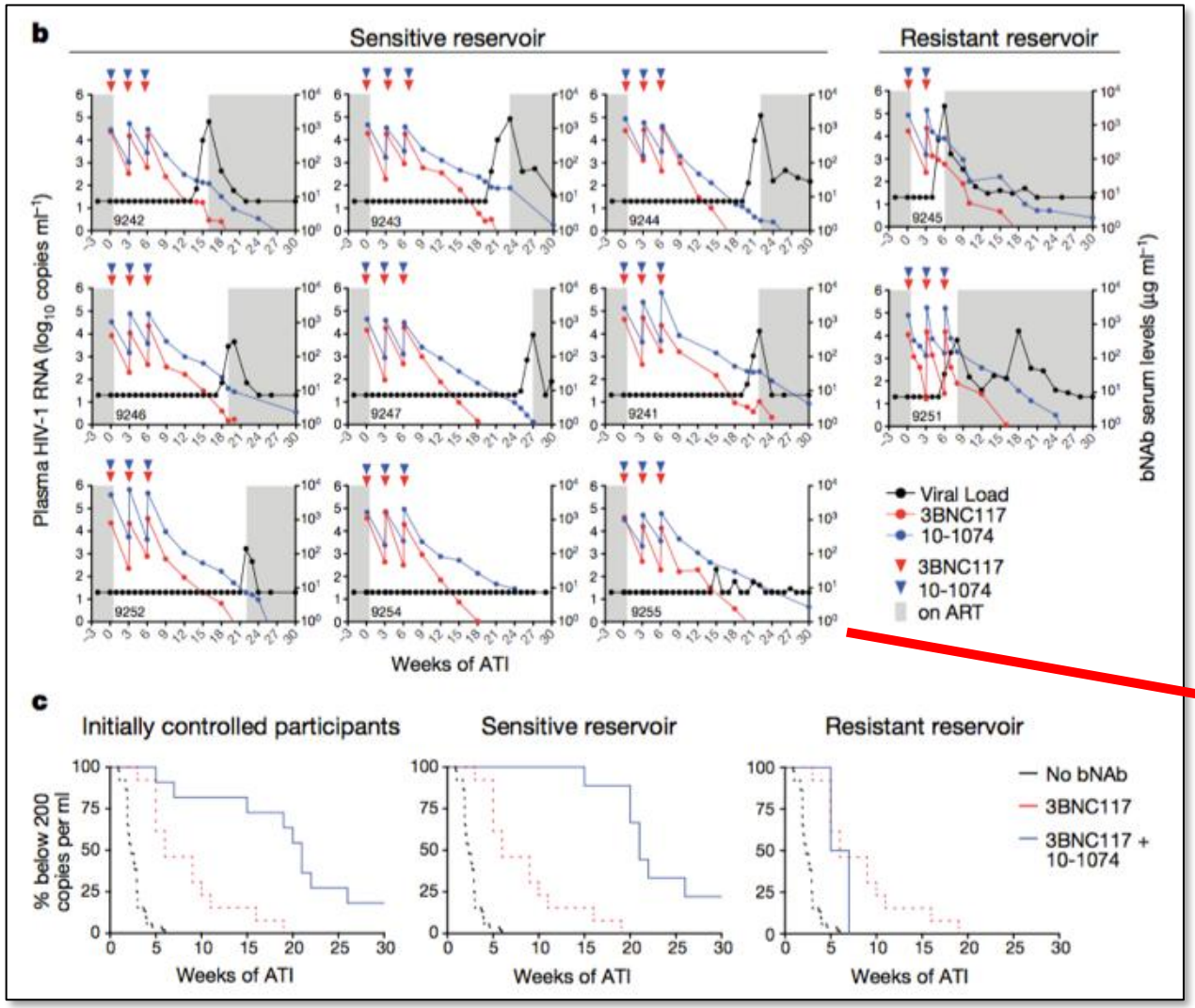
Combine bNAbs (3BNC117 and 10-1074) and interrupt ART



Study Population:

- On ART > 24 months, with HIV-1 VL < 50 copies/ml x 18 months and < 20 copies/ml at screen
- Current CD4 count > 500 cells/ul
- CD4 count nadir > 200/ul

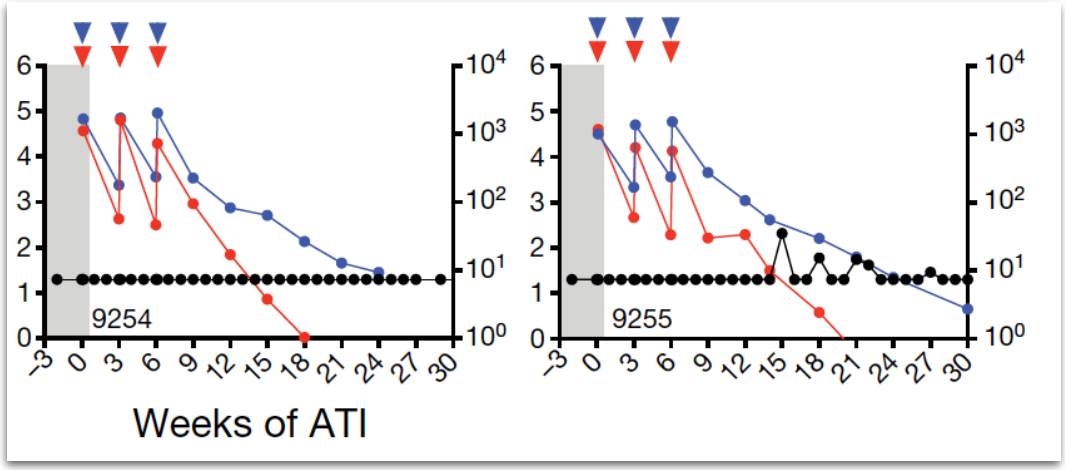
Mendoza, Nature, 2018



n=15

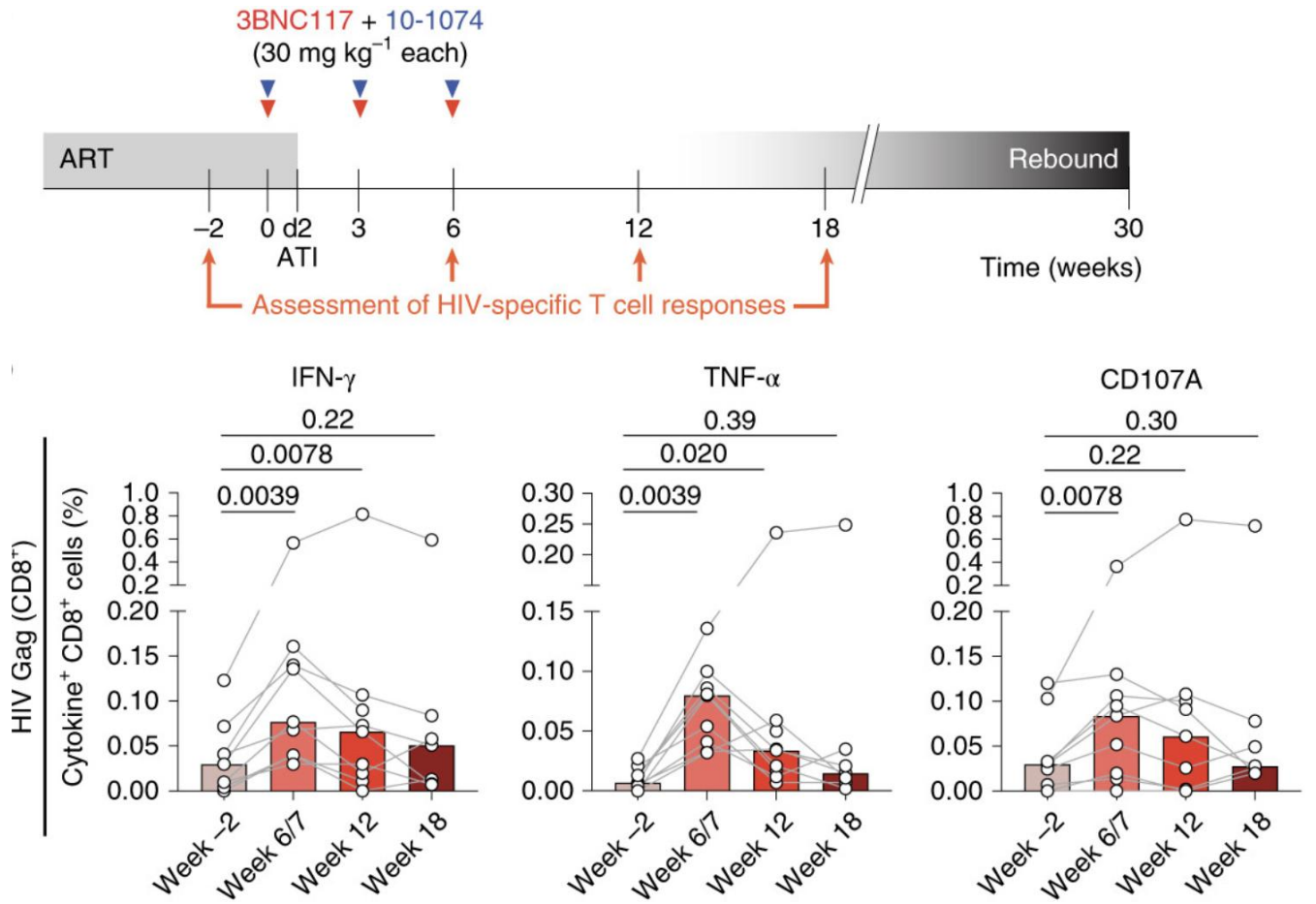
4 excluded from efficacy analysis as viral loads > 20 c/mL two weeks before or at time of the first bNAb infusion

Median time to rebound 21 weeks if sensitive virus and rebounded (n=7)



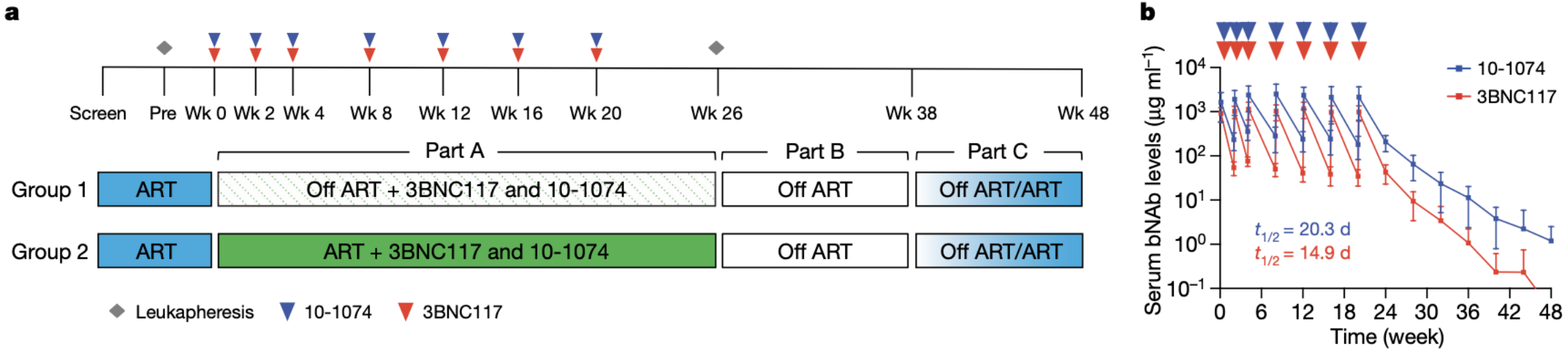
Mendoza, Nature, 2018

Increased HIV-specific immune responses in those receiving bNAbs even when virally suppressed



Niessl Nature Med 2020

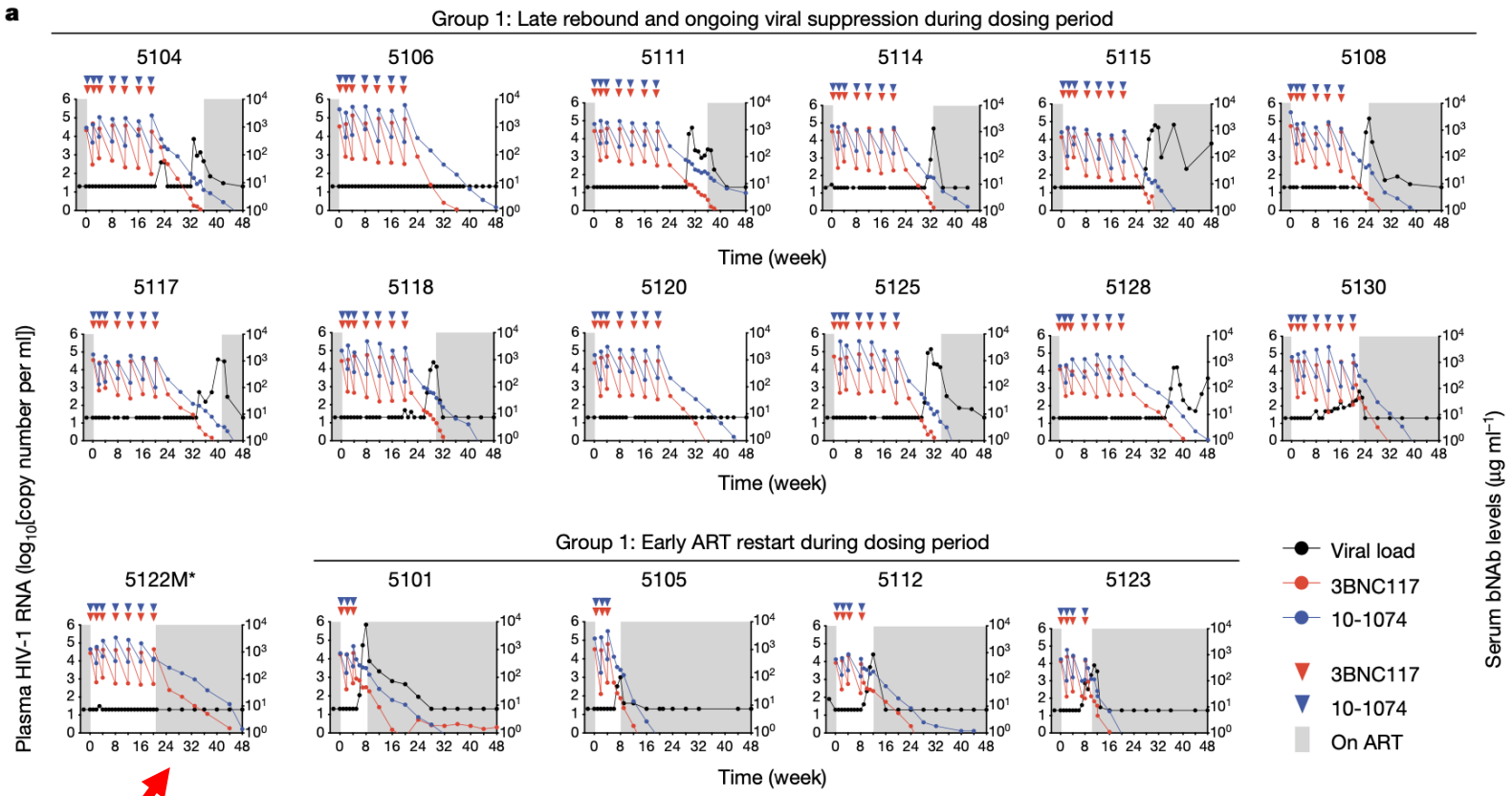
Same bNAbs, more infusions – could it control viral replication impact reservoir size



Gaebler, Nature. 2022

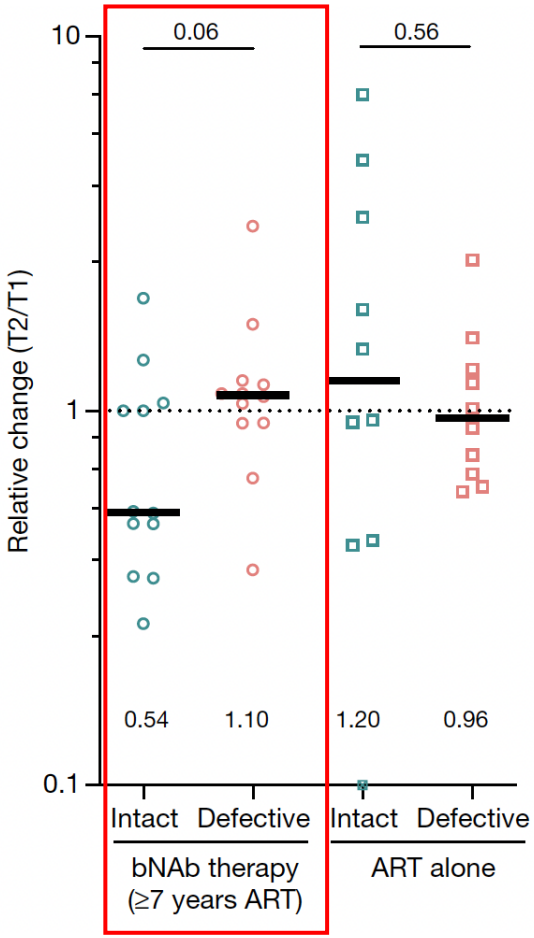
2 of 12 controlled viral replication post bNAb clearance

13 of 17 controlled post BNAb infusions



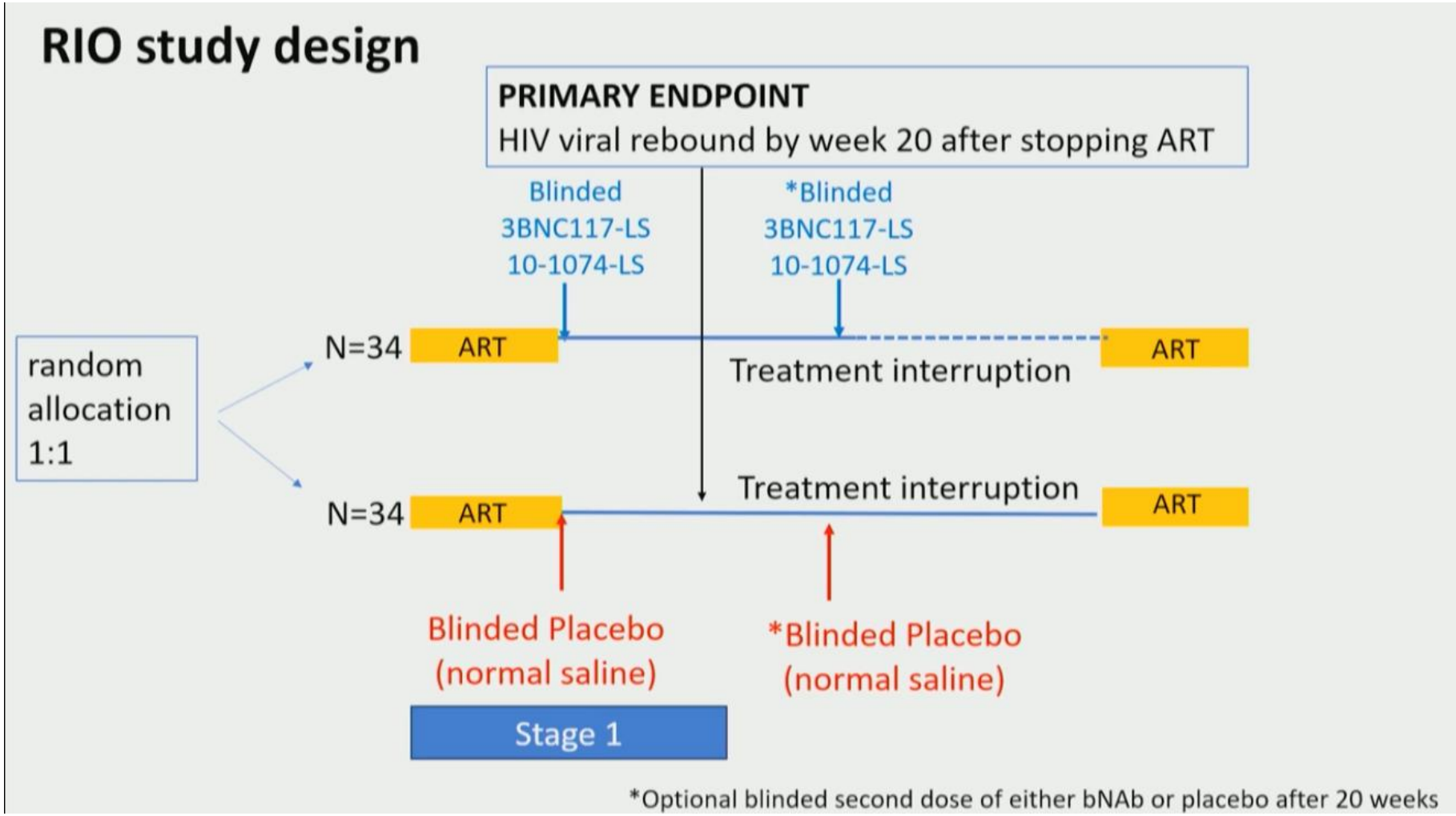
Restarted for COVID-19

46% reduction in the intact reservoir over 6 months



Gaebler, Nature. 2022

RIO Trial – RCT of 2 LS-bNAbs in People Treated in Early HIV



RIO Trial

- Eligibility
  - Started ART in primary HIV infection, OR nadir CD4 > 500
  - Suppressed on ART for at least 12 month prior to enrolment
  - Enrolment CD4 > 500 or CD4:8 >1
  - Willing to access PrEP and appropriate protection to prevent transmission
- Exclusions:
  - co-infections or co-morbidities
  - Predicted resistance to 10-1074 by envelope DNA sequencing
- Primary Endpoint – viral rebound 20 weeks after starting ART

Viral rebound patterns in those receiving bNAbs

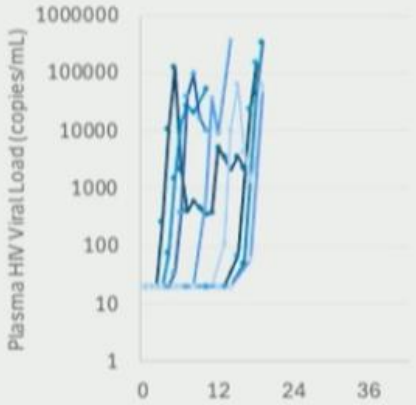
- ‘Vast majority’ received a second dose of bNAbs at week 20
- If received 2 doses then median time to rebound was 62 weeks
- Estimated half life 73 days 10-1074-LS, 65 days 3BNC117-LS

No HIV transmissions

No one restarted ART due to CD4 drop

No SAEs related to bNAbs

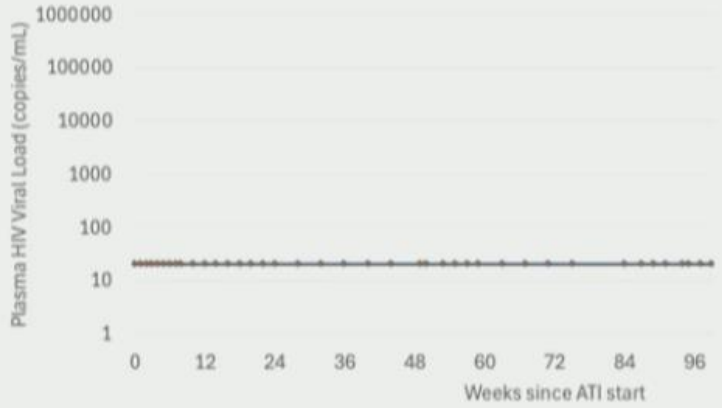
1. rapid rebound
8/34 (23.5%) rebounded within 20 weeks



4/8 had envelope sequences predicting 10-1074 resistance at rebound

2. delayed rebound
14/29 (48%) rebounded by week 72

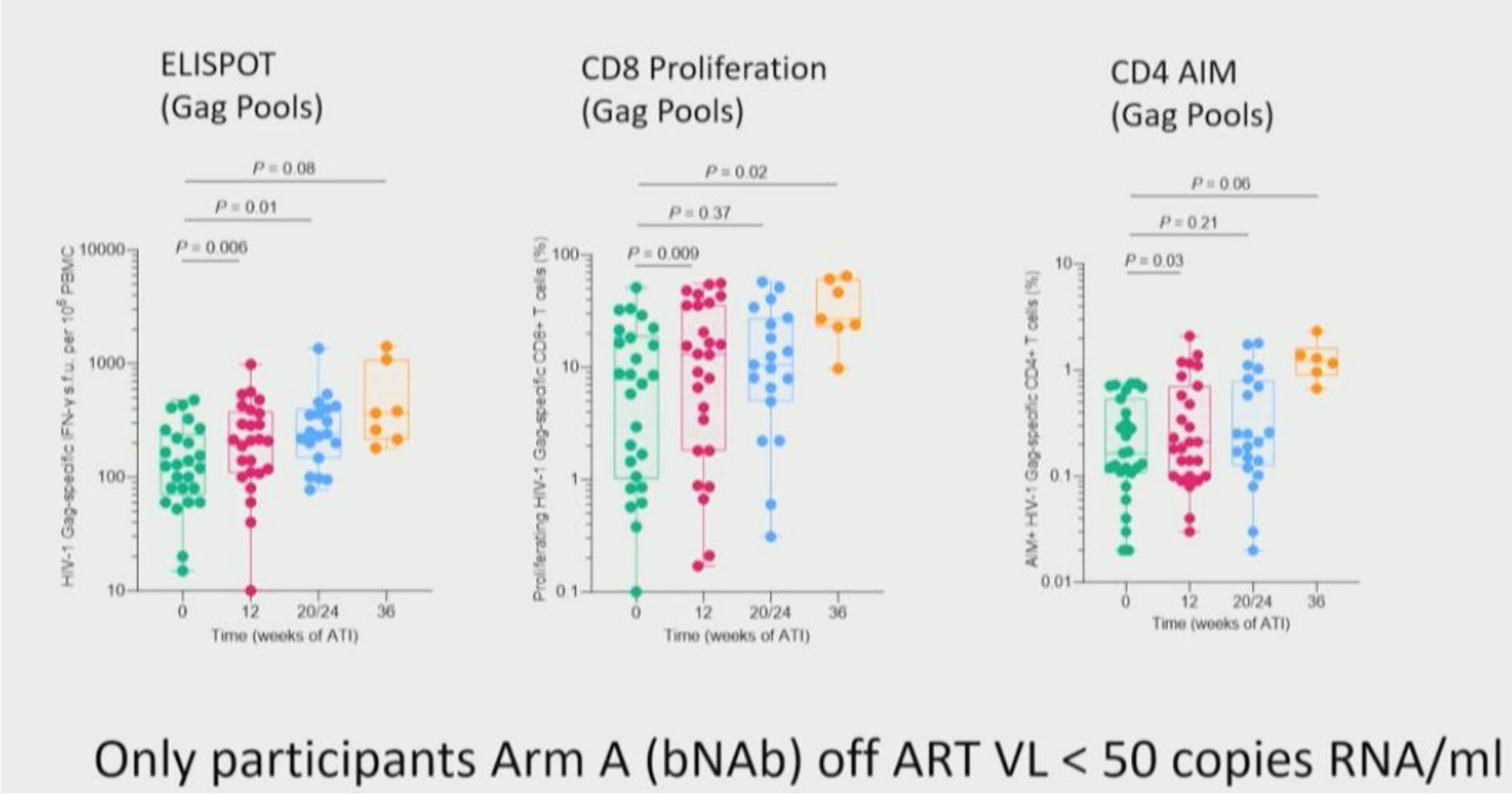
3. viral control
7/29 (24.1%) remained undetectable >72 weeks



RIO Trial – Immune responses

Increase HIV-specific T-cell responses on bNAbs and viral load < 50 copies/ml

? ‘vaccinal’ effect

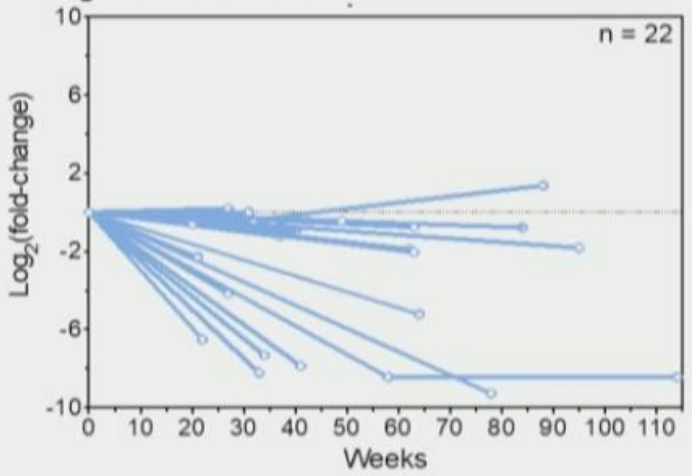


#506 Frater et al. CROI 2025

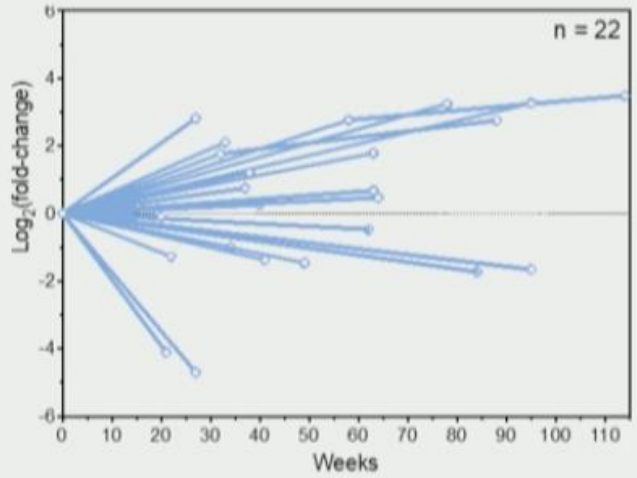
RIO Trial – HIV Reservoir size

Impact of bNAbs on HIV Reservoir size

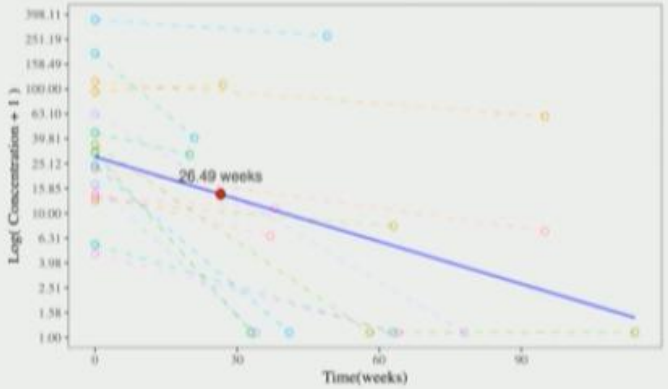
Marcilion Fumagalli
Nussenzweig lab
Poster 513



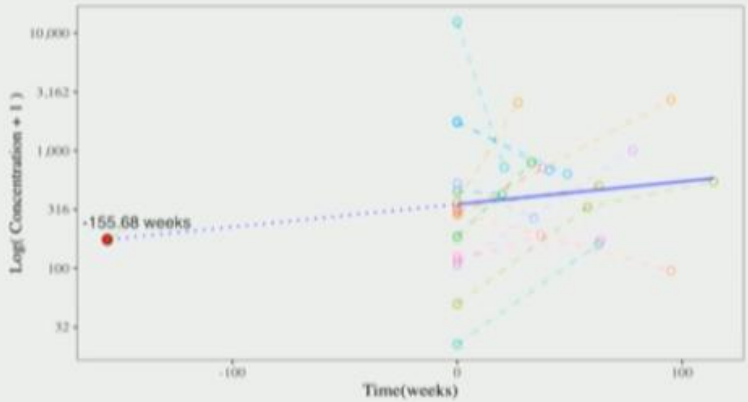
Fold change in intact provirus



Fold change in defective provirus



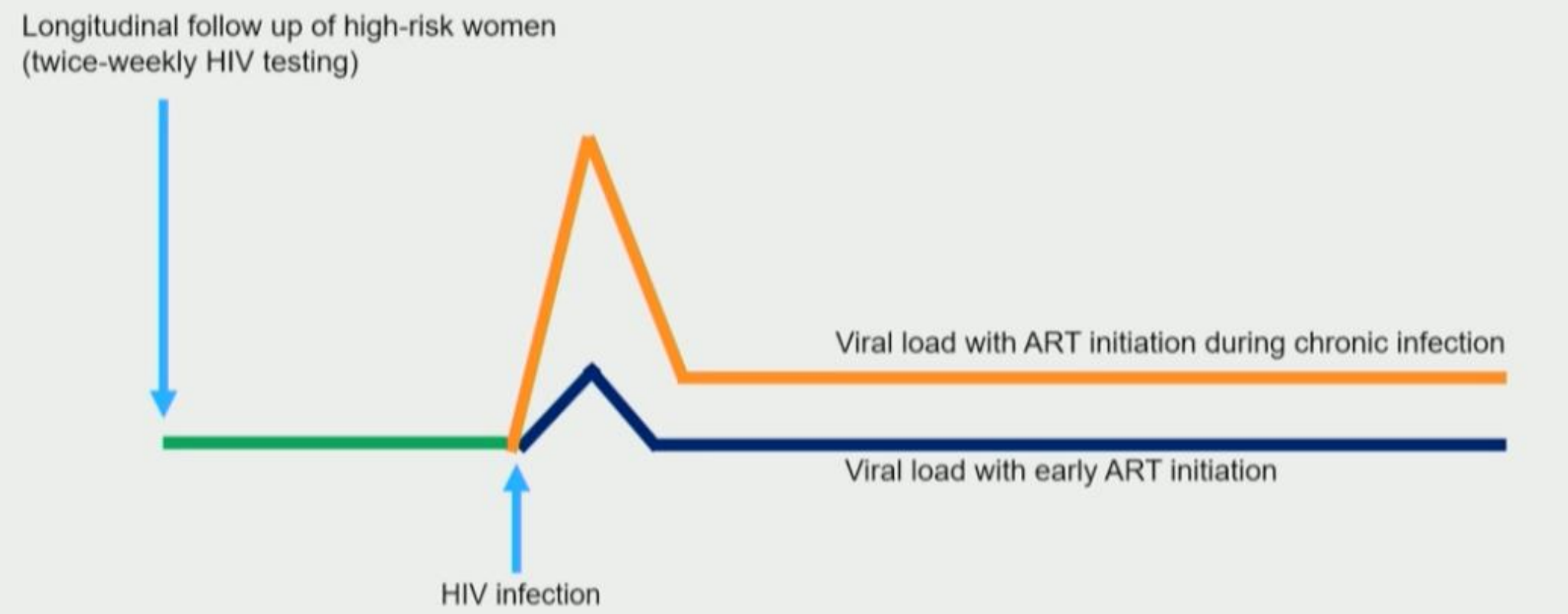
Half life of intact provirus over time
26.5 weeks



Half life of defective provirus over time
155.68 weeks

Vesatolimod + 2 bNAbs in early treated Sth African women

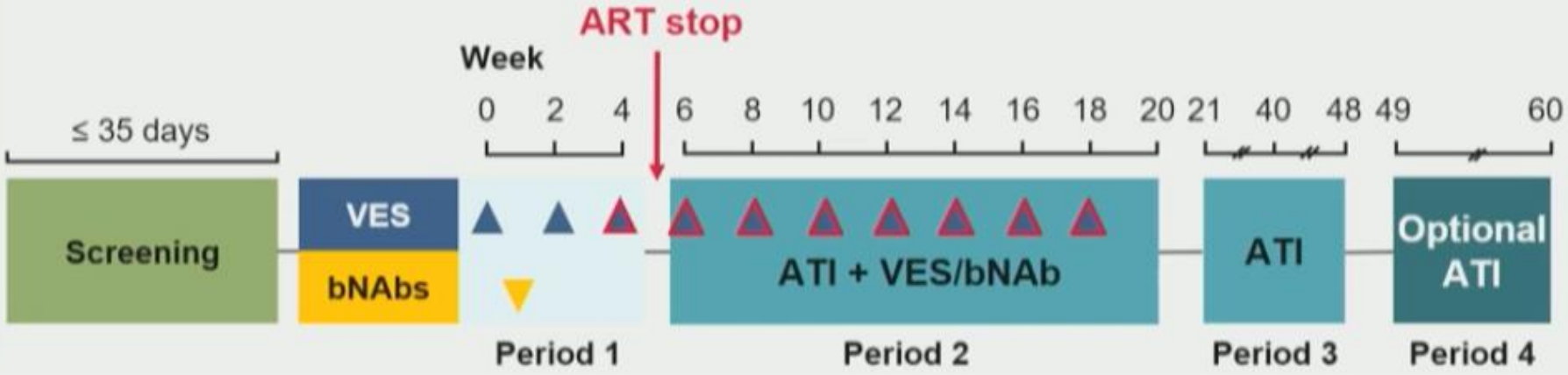
FRESH Cohort - Begin ART in Hyperacute infection



Design: Single arm, open label

Inclusion criteria

- Females from FRESH cohort
- Virally suppressed on ART > 12 months
- Sensitive to at least 1 of the 2 bNAbs
- CD4+ T-cell count ≥ 500 cells/μL



▲ VES (oral) ▲ Possible VES dose escalation[a] from 6 to 8 mg ▼ bNAbs: VRC07-523LS + CAP256V2LS (NIH) (20 mg/kg IV each bNAb)

ART restart criteria

- Plasma HIV-1 RNA measurements ≥ 1000 copies/mL for **8 consecutive weeks** without a drop of 0.3 $\log_{10}$ from previous week
- Confirmed plasma HIV-1 RNA > 100,000 copies/mL
- Confirmed CD4+ T-cell count < 350 cells/μL
- Pregnancy, participant request, or investigator/sponsor discretion due to other clinical criteria

During ATI, viral load was monitored every 2 weeks until initial rebound, then every week

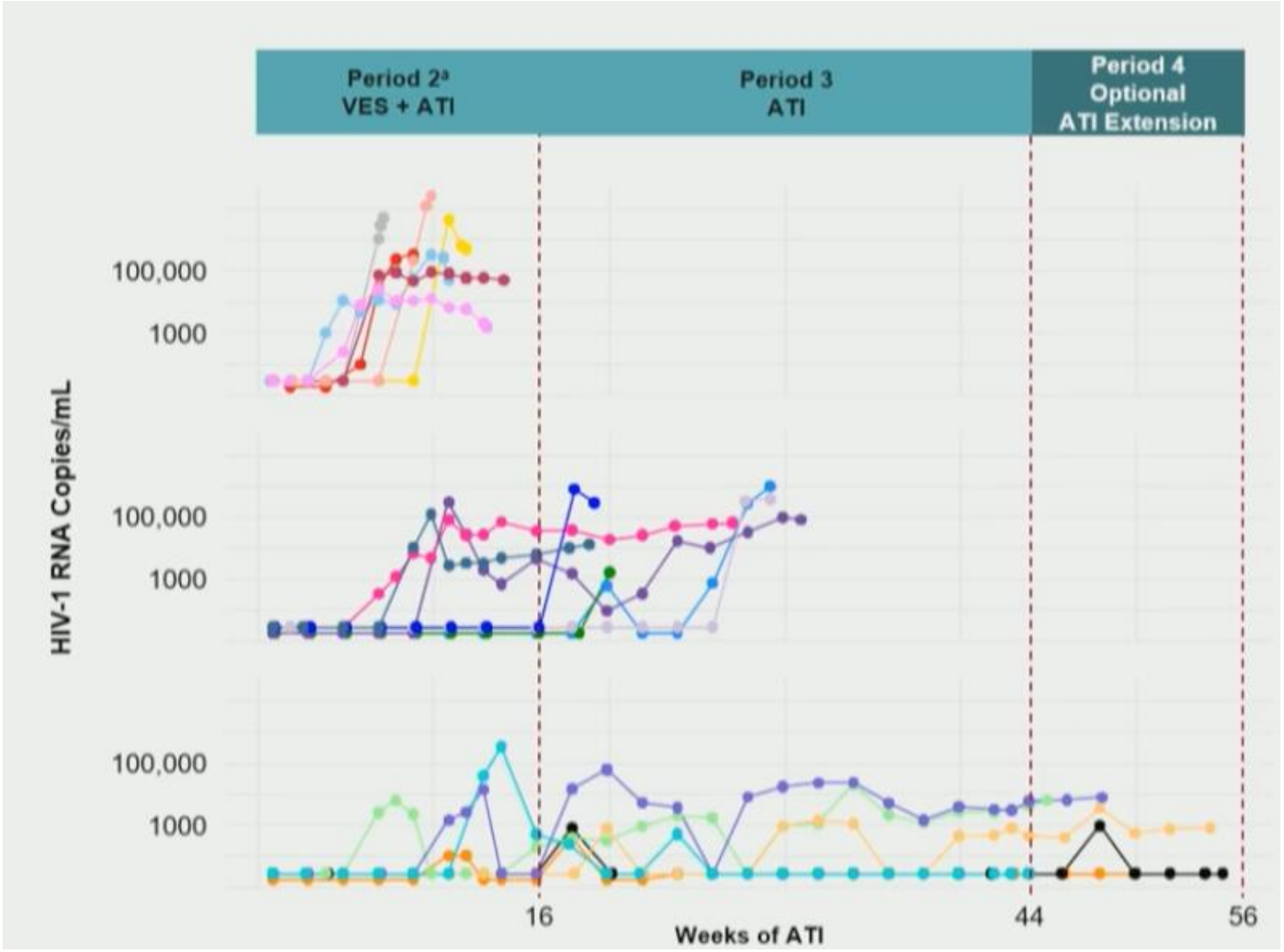
TLR-7 agonist vesatolimod - activate NK and dendritic cells leading to IFN-α and other cytokine production → antiviral effect

Characteristic	Enrolled Participants (N = 20)
CD4+ count at screening, cells/μL, median (range)	880 (520-1472)
Time to ART initiation, median (range), days	1 (0-3)
Time on ART before enrollment, median (range), years	6.9 (1.7-8.5)
Peak HIV-1 RNA before ART start, copies/mL, n (%)	
≥ 50 to < 2000	9 (45)
≥ 2000 to ≤ 5000	4 (20)
> 5000	7 (35)
Fiebig stage at ART initiation, n (%)	
I (HIV RNA+)	17 (85)
II (HIV RNA+ and p24+)	0
III (Ab+/WB-)	3 (15)
IV (Ab+/WB+/p31-)	0
Baseline bNAb susceptibility, n (%)	
Susceptible to both bNAbs	11 (55)
Susceptible to VRC07-523LS only	7 (35)
Susceptible to CAP256V2LS only	2 (10)

Primary endpoint – safety

- Well tolerated
- No SAEs
- Many mild transfusion reactions

Patterns of Viral rebound



Early ART restart 7/20 (35%)

Delayed ART restart (bNAb waning) 7/20

Late

- 6/20 (30%) off ART through week 48 (44 weeks of ATI)
- 4/20 off ART at 55 weeks ATI. These 4 people off ART median 1.5 years (range 1.2-2.4)

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Studies reporting viral control off ART post bNAbs

Study	bNAbs received / Months detectable in plasma	Other interventions tested	Viral control post bNAbs
Mendoza et al. Nature 2018	3BNC117, 10-1074 / 4	Nil	2 / 9 (18%)
Gaebler et al. Nature 2022	3BNC117, 10-1074 / 6	Nil	2 / 12 (17%)
Gunst et al. Nat Med 2022	3BNC117 / 3	Latency reversal agent Romidepsin	4 / 11 (36%)
Gunst et al. Nat Med 2023	3BNC117, 10-1074 / 4	TLR9 agonist Lefitolimod	4 / 23 (17%)
Julg et al. Nat Med 2024	PGT-121, VRC07-523, PGDM1400 / 12	Nil	5 / 12 (41%)
Peluso et al. Res Sq 2025	VRC07-523-LS, 10-1074 / 4	TLR9 Agonist Lefitolimod, Therapeutic vaccine	2 / 10 (20%)
Fidler et al. CROI 2025	3BNC117-LS, 10-1074-LS / 12	Nil	6 / 29 (21%)
Ndung'u et al. CROI 2025	VRC07-523-LS, CAP256V2-LS / 6	TLR7 Agonist Vesatolimod	6 / 20 (30%)
Caskey et al. IAS 2025	3BNC117-LS, 10-1074-LS / 12	IL-15 superagonist N-803	7 / 23 (30%)

Immune checkpoint inhibitors

Anti-CTLA-4

Tremelimumab (AZ) & Ipilimumab (BMS)

Approved

YERVOY™

Anti-PD-1

Nivolumab (BMS) & Pembrolizumab (MSD)

Approved

OPDIVO™

KEYTRUDA®

Anti-PD-L1

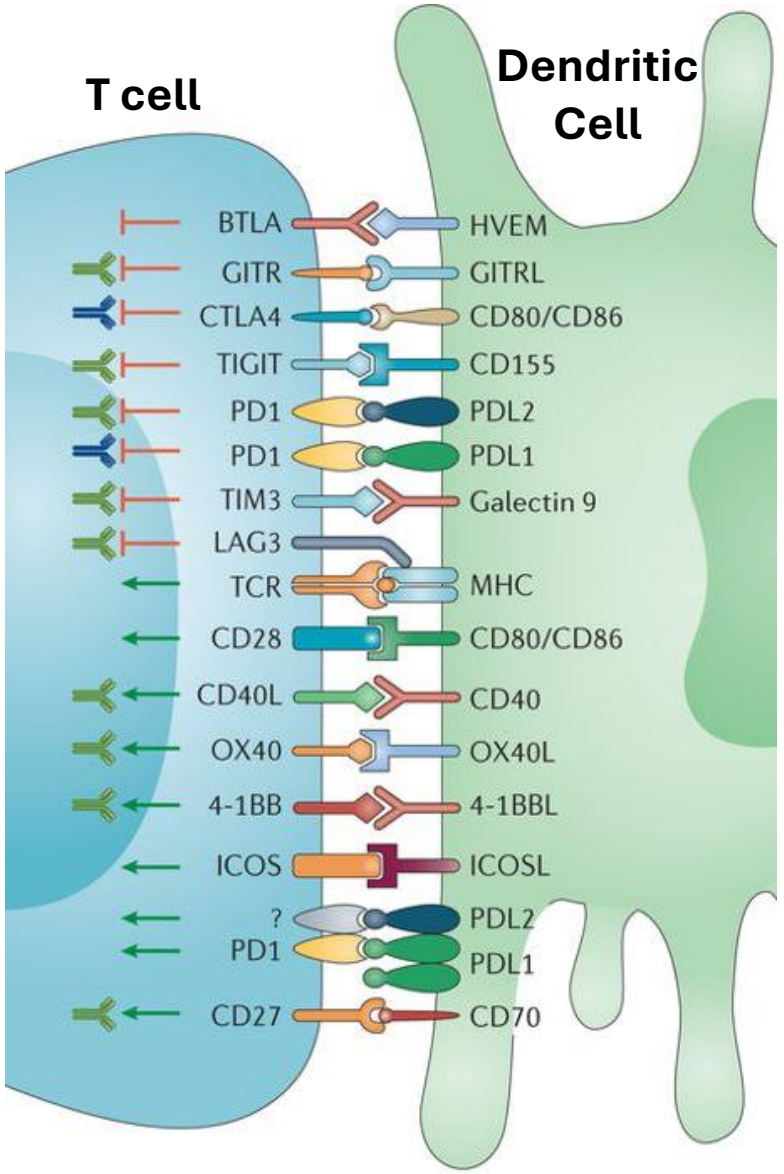
Durvalumab (AZ/Medimmune)
Avelumab (Pfizer)
Atezolizumab (Roche/Genentech)

Approved

TECENTRIQ™

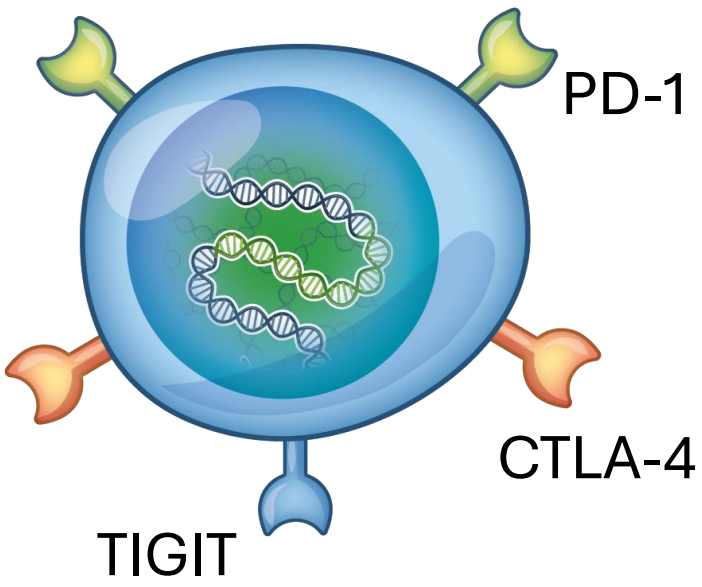
BAVENCIO®

IMFINZI™



Wykes 2018 Nat Rev Immunol

The rationale for anti-PD1 in HIV cure



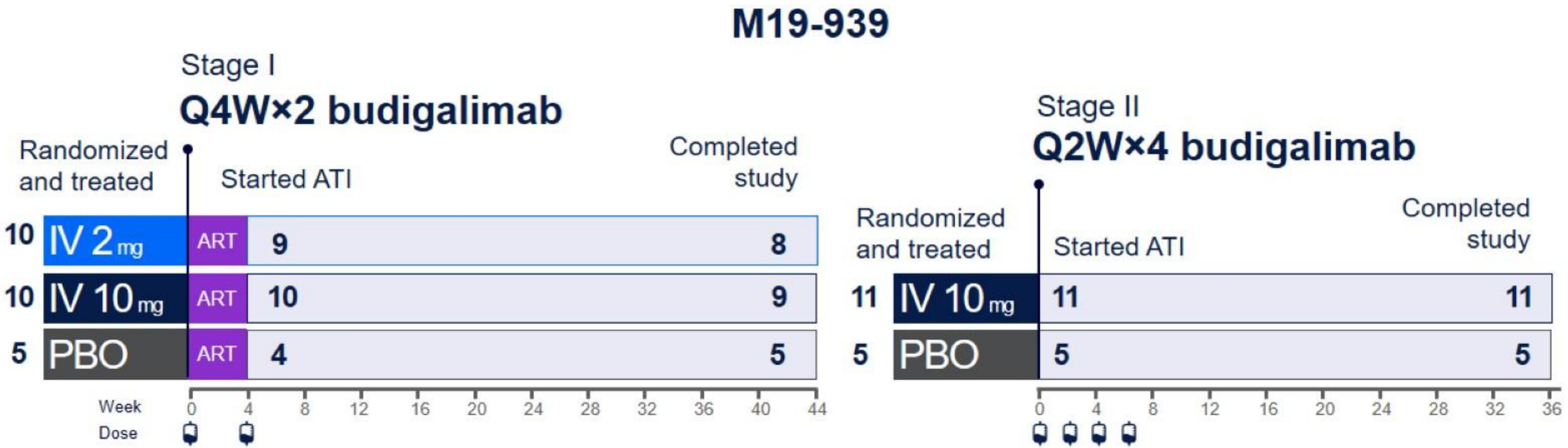
- Latent virus is enriched in cells that express PD-1 and other immune checkpoints (CTLA-4, TIGIT)
- Exhausted T-cells express PD-1 and other immune checkpoints and these cells persist on ART
- PD-1 and other immune checkpoints put the brake on T-cell activation and potentially put the brakes on the virus

- Evidence of HIV latency reversal in people with HIV and cancer receiving anti PD-1
- Anti PD-1 followed by ART interruption lowered viral setpoint in a macaque model

- Therefore Anti PD-1 could both reverse latency AND enhance immune function

Chomont, Nat Med 2009; Fromentin, Plos Path 2016; McGarry, Immunity 2017; Fromentin Nature Comms 2019; Uldrick Sci Trans Med 2022; Okoye, CROI, 2020

M19-939 and M19-972: Phase 1b randomized double-blind studies of budigalimab in PLWH



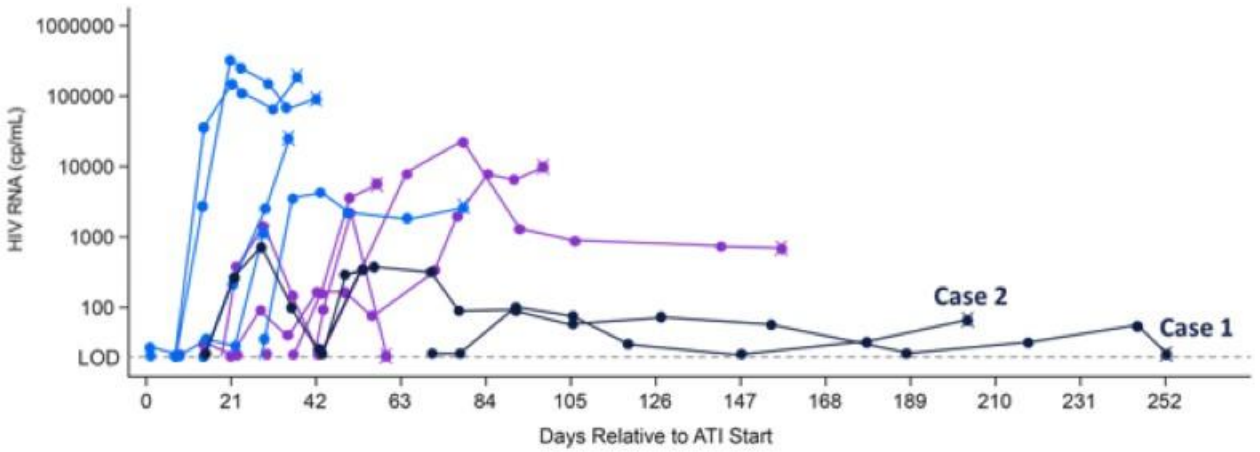
NCT04223804 (clinicaltrials.gov)

Routy JP et a. EACS 2023; oral: abstract 1077

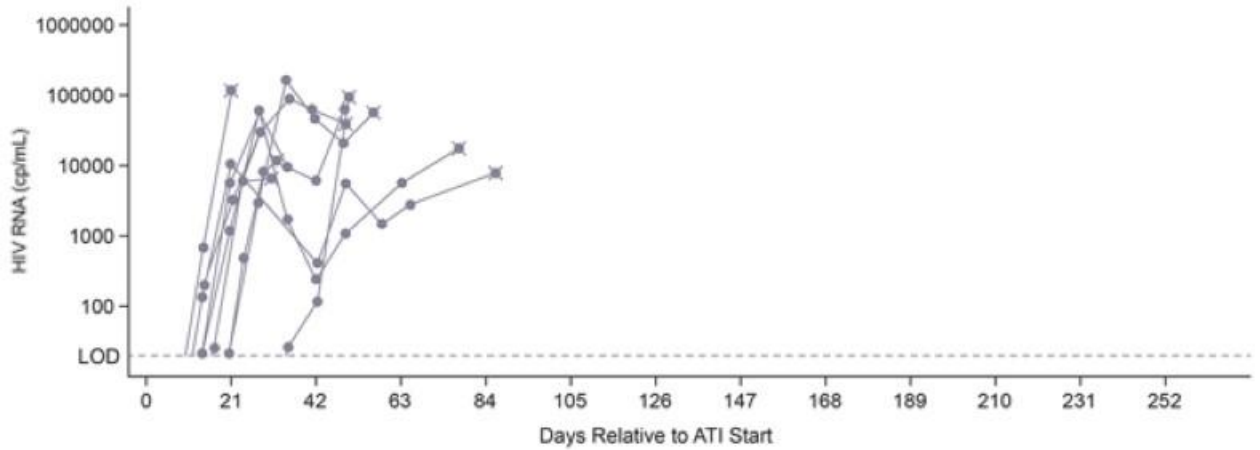
Week 0 indicates baseline/start of treatment.
ART, antiretroviral treatment; ATI, analytical treatment interruption; IV, intravenous; PBO, placebo; PLWH, people living with HIV; Q2W, every 2 weeks; Q4W, every 4 weeks.

Exploratory efficacy: Viral load kinetics during ATI (M19-939)

10-mg Q2W×4 Budigalimab (n=11)



Pooled Placebo (n=9)



6 people defined as delayed viral rebound off ART

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

Routy JP et a. EACS 2023; oral: abstract 1077

Left graphs in log scale; day 0 corresponds to baseline; in stage II, 2 participants discontinued study drug: 1 for protocol violation (prohibited live vaccination); 1 for AE (grade 1 reversible hyperthyroidism).
[a]Defined as experiencing delayed viral rebound (>21 days) and/or off-ART viral control (<1000 cp/mL).
ART, antiretroviral therapy; ATI, analytical treatment interruption; LOD, limit of detection (20 cp/mL); Q2W, every 2 weeks.

NIVO-LD Clinical Trial – Melbourne, Singapore

Low dose nivolumab

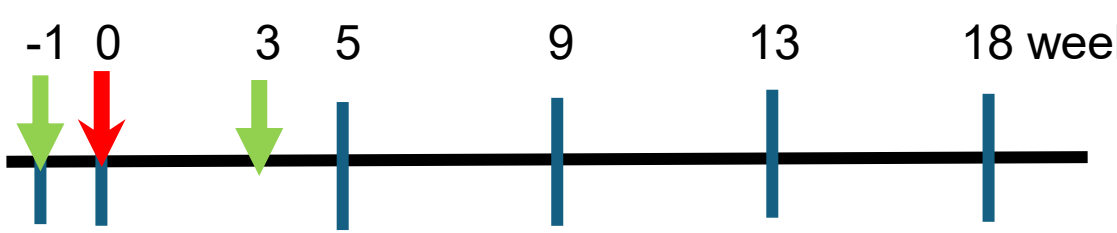
FNA

Placebo

HIV-infected, on ART; VL <50 copies/ml for 2 years; CD4 > 350 cells/ul

Cohort A:
Safety Cohort

0.1 mg/kg
0.3 mg/kg
1 mg/kg
anti-PD1
n=6 in each



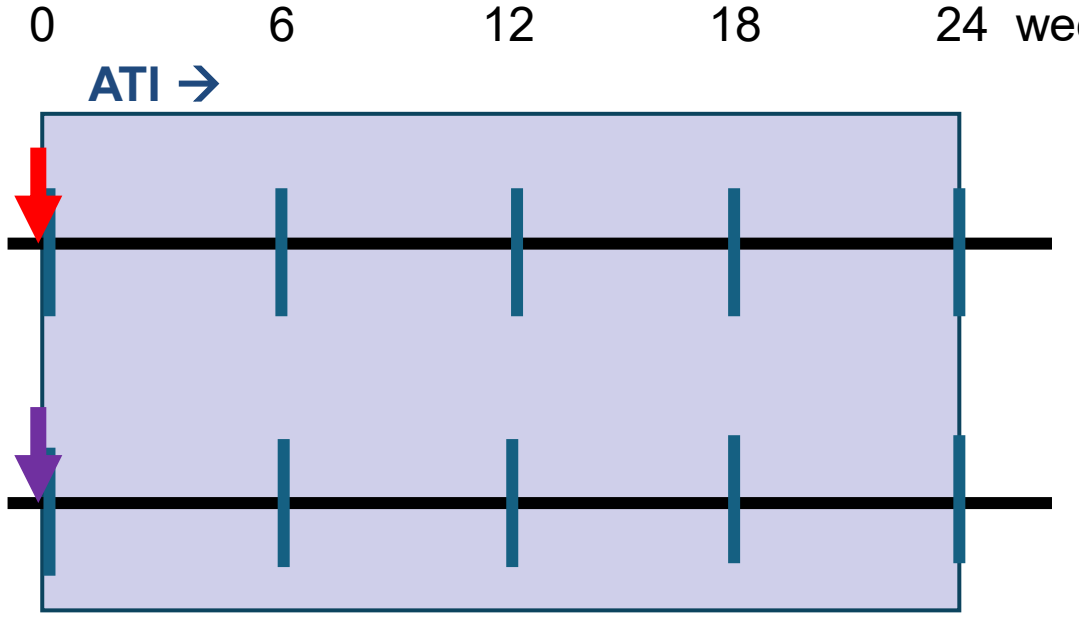
Endpoints

Safety
PD-1 occupancy

Cohort B:
Immunogenicity Cohort

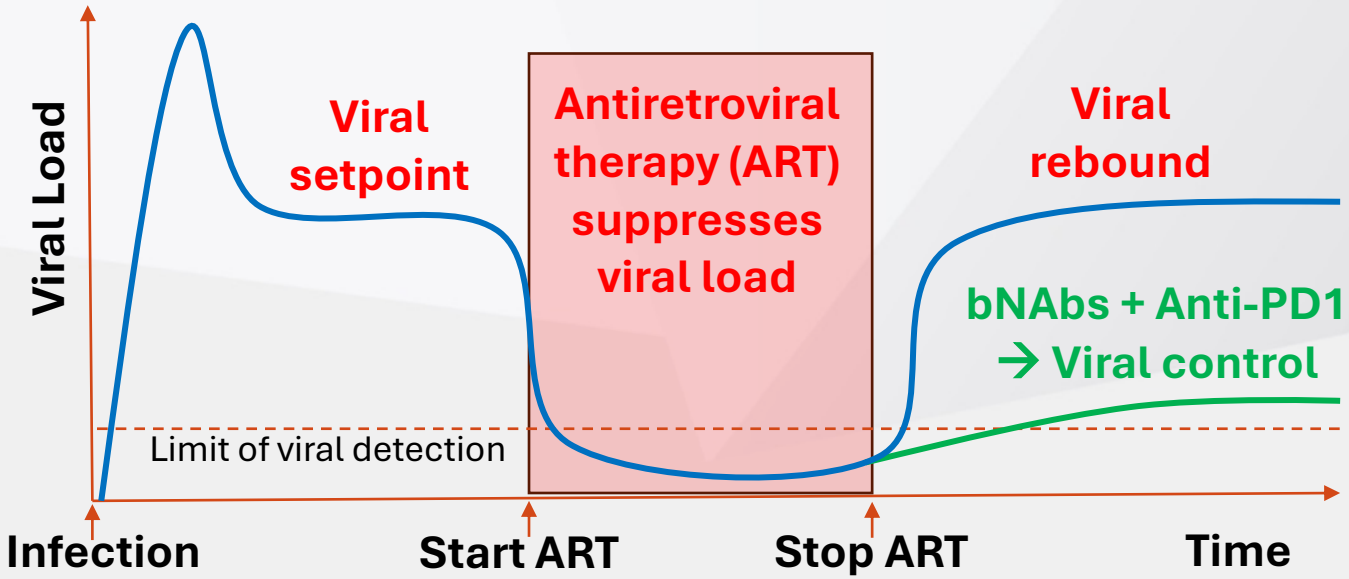
anti-PD1
Dose TBD
n=12

Placebo
n=12



Safety
Immunogenicity

Could combination immunotherapy control HIV replication without antiretroviral therapy ?



HIV Cure Volunteer database

HIV Cure Volunteer Database Newsletter

NOVEMBER 2024 | Newsletter FOR VICTORIAN HIV CURE VOLUNTEER DATABASE | EDITION #3

What's in this edition of the newsletter!

- Update from **AIDS 2024** which was held in Munich in July 2024
- HIV cure studies on display at the Australasian HIV/AIDS conference for **HIV unwrapped**

Publication alert! Immunotherapy in HIV cure research

Updates on HIV cure from AIDS 2024

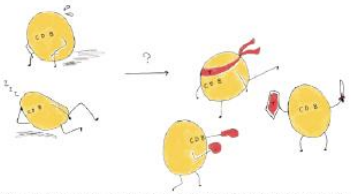
AIDS 2024, the largest global HIV conference was held in Munich this July, with over 11,000 delegates gathered from across the world, including people with HIV, advocates, doctors, and researchers. In this edition we highlight HIV cure research from Australian and International researchers.
Read the full report of HIV cure science at AIDS2024 by Heather Ellis:
https://hivcure.com.au/2024/09/10/unpacking-the-hiv-science-at-aids2024/

Another case of cure

Another case of an HIV cure from a stem cell transplant was announced at AIDS2024. "The Next Berlin Patient" was named after the city where he had the procedure (the first "Berlin Patient" was Timothy Ray Brown, who was the first person to be cured of HIV with a stem cell transplant). This person, who remains anonymous, received a stem cell transplant from a donor who has a **single copy** of the "delta-32" gene. The previous people cured had transplants from donors who had two copies of this gene, which blocks most strains of HIV from entering and infecting their immune cells.
The Next Berlin Patient has been off HIV treatment for over 5 years and has no detectable virus anywhere in his body, indicating a likely cure.
However, this isn't a cure strategy for everyone - stem cell transplants are dangerous procedures and can't be performed in most people with HIV, unless they have a life-threatening cancer requiring transplantation.

Understanding HIV immune responses following Nivolumab

In people with HIV on antiretroviral therapy (ART), immune responses are impaired despite effective treatment. Dr Celine Gubser (now based at the Lausanne University Hospital in Switzerland) presented work done in Melbourne, investigating the effects of an anti-PD-1 drug called **Nivolumab** on immune cells in six people with HIV on ART who were receiving this drug for cancer therapy.
Participants received anti-PD-1 every two weeks and donated blood which was studied to describe changes in the makeup of proteins on the surface of these cells, known as T cell receptors. Three of the participants showed an increase in number of CD8 exhausted T-cells (TEX cells), which do not work as well as regular T cells. These participants also had unique T cell Receptors that recognised different parts of the HIV virus to help induce anti-HIV immune responses.



More research is ongoing to understand what role these receptors may play in controlling HIV if ART is stopped. A clinical study of Nivolumab is currently seeking volunteers in Melbourne now (see last page of newsletter)

Acknowledgements

The Alfred Hospital
Jill Lau
Marti Kaiser
Paul Beech
Janine Roney
Joel Le Couteur
Mei Tang
Maggie Moore
ID Department research co-ordinators

Doherty Institute, Uni Melb and Royal Melbourne Hospital
Sharon Lewin
Judy Chang
Lauren Wallace
Ajantha Solomon
Barbara Scher
Thomas Rasmussen
Michael Roche
Hannah King

Aarhus University
Thomas Rasmussen

Alfred Health - John F Marriott Trust

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