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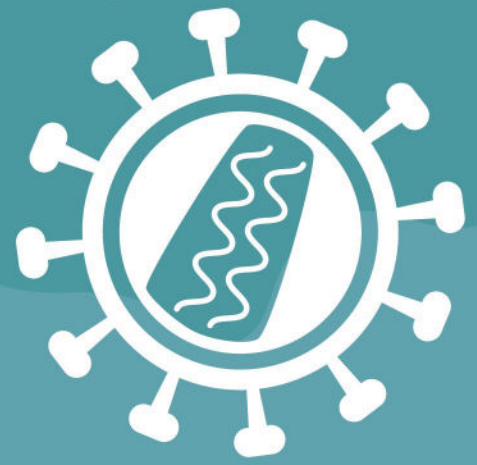
British HIV Association

2025 **Spring Conference**



Wed 23rd – Fri 25th April

Brighton Dome, UK

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The RIO trial: A Randomised Placebo-Controlled Study of 2 LS-bNAbs (3BNC-117-LS & 10-1074-LS) in People Treated in Early HIV

S. Fidler, M. Lee, S. Collins, L. Cherrill, E. Falaschetti, P. Zacharopoulou, M. Altaf, T. Tipoe, G. Taylor, M. Fumagalli, G. Tomaras, M. Caskey, M. Nussenzweig, J. Frater and the RIO Trial Investigators

RIO trial investigators: S. Fidler, M. Lee, S. Collins, J. Fox, A. Clarke, S. Kinloch, S. Pett, K. Ring, C Orkin, M. Bofitto, G. Whitlock, R. Sutherland, A. Uriel, M Balachandran, M. Molina, L. Terry. O. Schmeltz Sogaard, J. Damsgaard Gunst, J. Gohil, H. Box, S. Fletcher, J Frater

Thanks

RIO study participants and clinical teams














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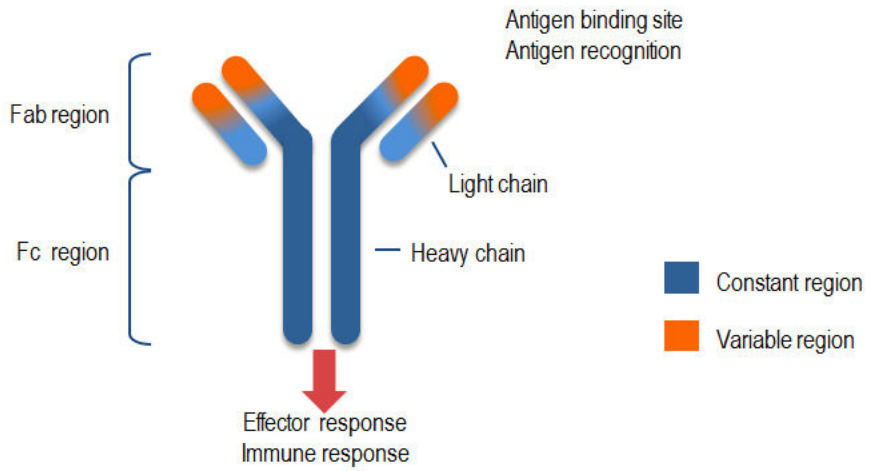
HIV-Broadly Neutralising antibodies (bNabs)

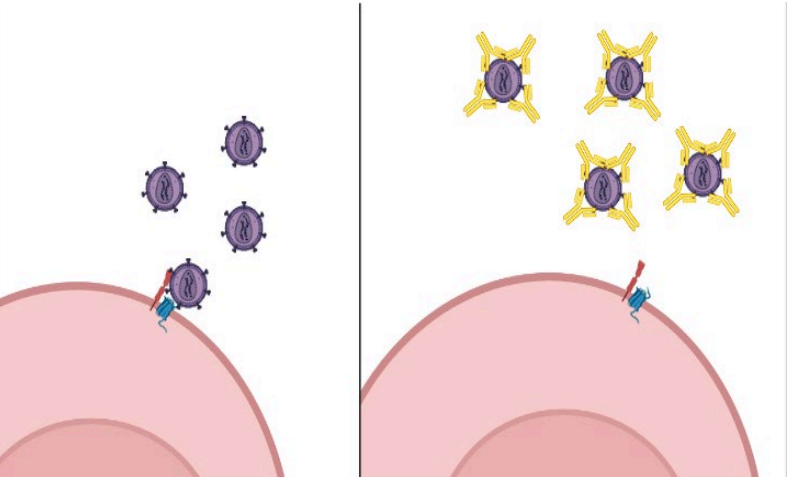


- Broadly neutralising antibodies (bNAbs) recognise and block entry of a **broad** range of different strains of HIV into healthy cells
- antigen binding region is HIV envelope
- The Fc region enhances other immune functions
- Next generation LS-bNAbs have extended half-lives (up to 3-6 months)

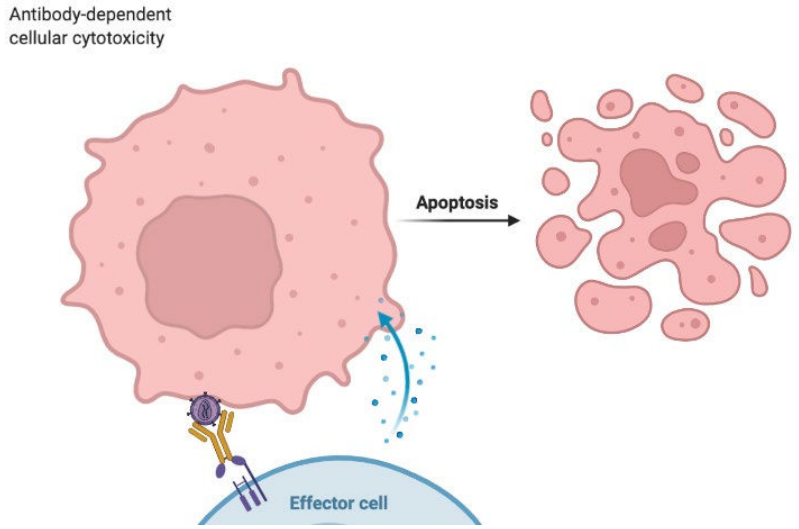
How do antibodies work?

Immune complexes

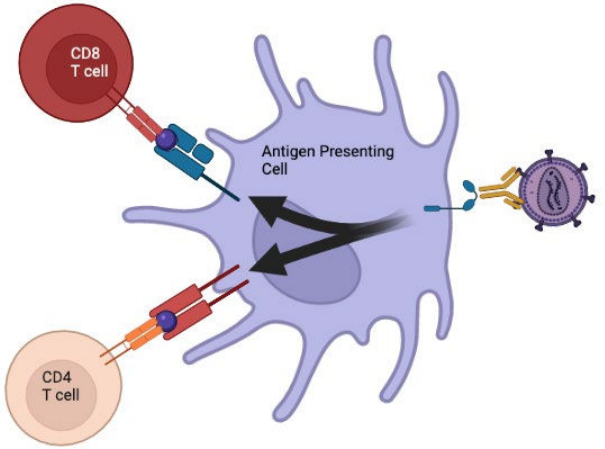
block virus entering cells



Kill infected cells (ADCC)



Boost other cells of the immune system (Vaccinal effect)

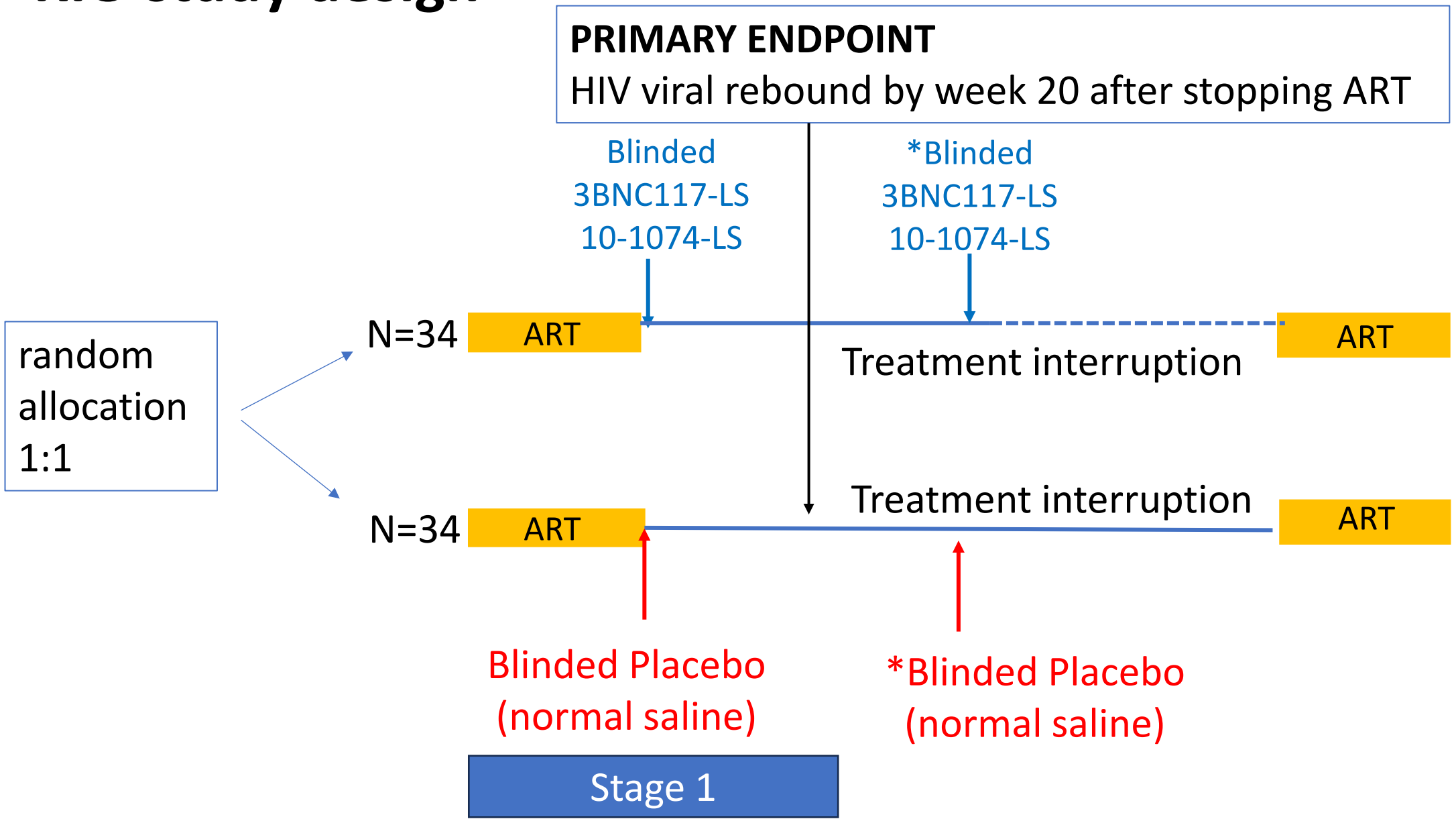


Research question

Can two bNAbs confer significant viral suppression off ART compared with placebo?

- If so, for how long

RIO study design



*Optional blinded second dose of either bNAb or placebo after 20 weeks

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

Exclusions:

- co-infections or co-morbidities
- Predicted resistance to 10-1074 excluded by envelope DNA sequencing
- Free access to PrEP and appropriate protection to prevent transmission

Primary endpoint: viral rebound 20 weeks after stopping ART

Viral rebound definitions

a) >1,000 copies/mL for 6 consecutive weeks

b) >100,000 copies/mL for two readings, one week apart

c) Instances outside of the above two reviewed by an independent panel

ART restart criteria

- Viral rebound
- CD4 count falls <350 cells/uL
- Clinical symptoms attributable to ATI
- Participant preference
- Concerns over risk mitigation for HIV transmission

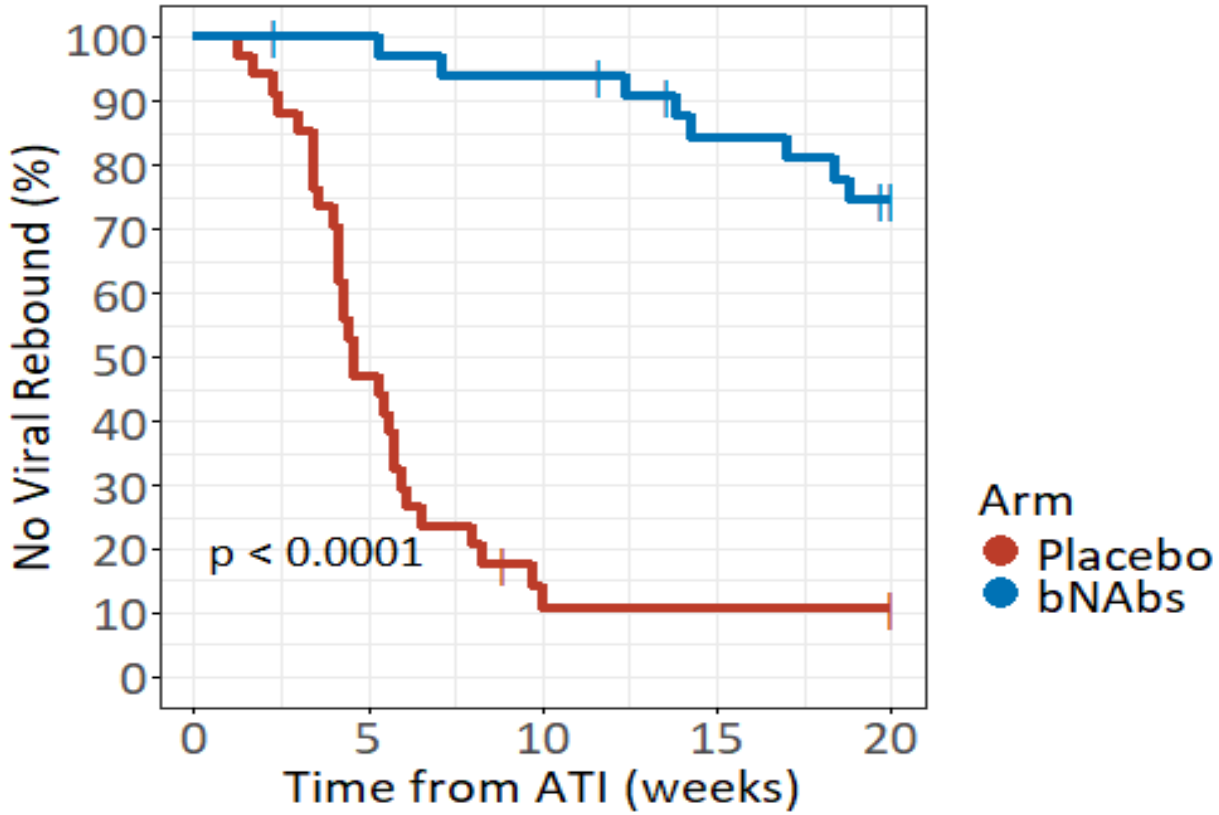
Demographics

Variable	bNAb	Placebo	All
Sex (M)	34 (100)	34 (100)	68 (100)
Gender identity (Cis-male)	**34 (100)**	**34 (100)**	**68 (100)**
Age (y)	36 (22 - 58)	42.5 (23 - 56)	39.5 (22 - 58)
Weight (kg)	77 (52 - 108)	81 (60 - 118)	79 (52 - 118)
BMI (kg/m^2)	25 (20 - 37)	26 (21 - 33)	25 (20 - 37)
Ethnicity (White or White British)	28 (82)	30 (88)	58 (85)
Ethnicity (Black or Black British)	1 (3)	2 (6)	3 (4)
Ethnicity (Asian or Asian British)	3 (9)	0 (0)	3 (4)
Enrolment CD4 count (cell/µL)	**799 (511 - 1468)**	**801 (272 - 1352)**	**800 (272 - 1468)**
ART regimen (II)	17 (50)	23 (68)	40 (59)
ART regimen (RBPI)	1 (3)	1 (3)	2 (3)
HIV clade (A)	1 (4)	2 (8)	3 (6)
HIV clade (B)	**19 (76)**	**21 (84)**	**40 (80)**
HIV clade (Other)	5 (20)	2 (8)	7 (14)
Primary	32 (94)	29 (88)	61 (91)

* N (%) Median (min, max) mean (Min, max)

Primary Endpoint: viral rebound to week 20

Hazard ratio: 0.09, 95% CI (0.04, 0.21)



By week 20

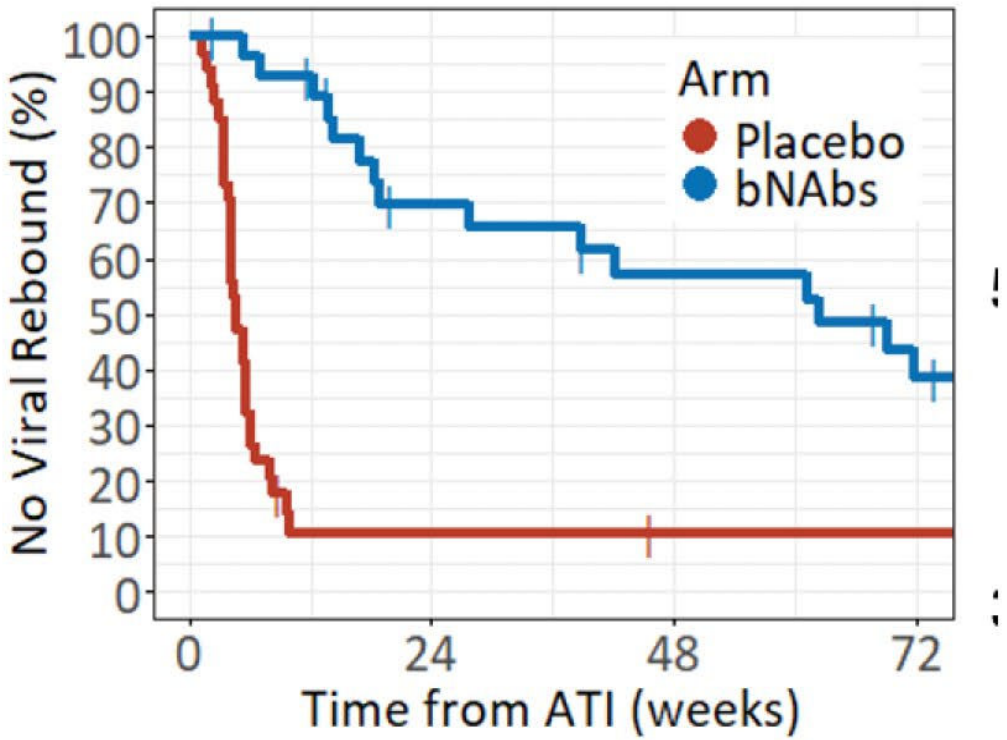
- bNAbs 75% not rebounded
- Placebo 8.8% not rebounded

Number of participants

Weeks from ATI	0	5	10	15	20
bNAbs	34	33	31	26	22
placebo	34	16	4	3	3

Viral rebound by study arm to week 72 after 2 doses

Hazard ratio: 0.24, 95% CI (0.13, 0.44)

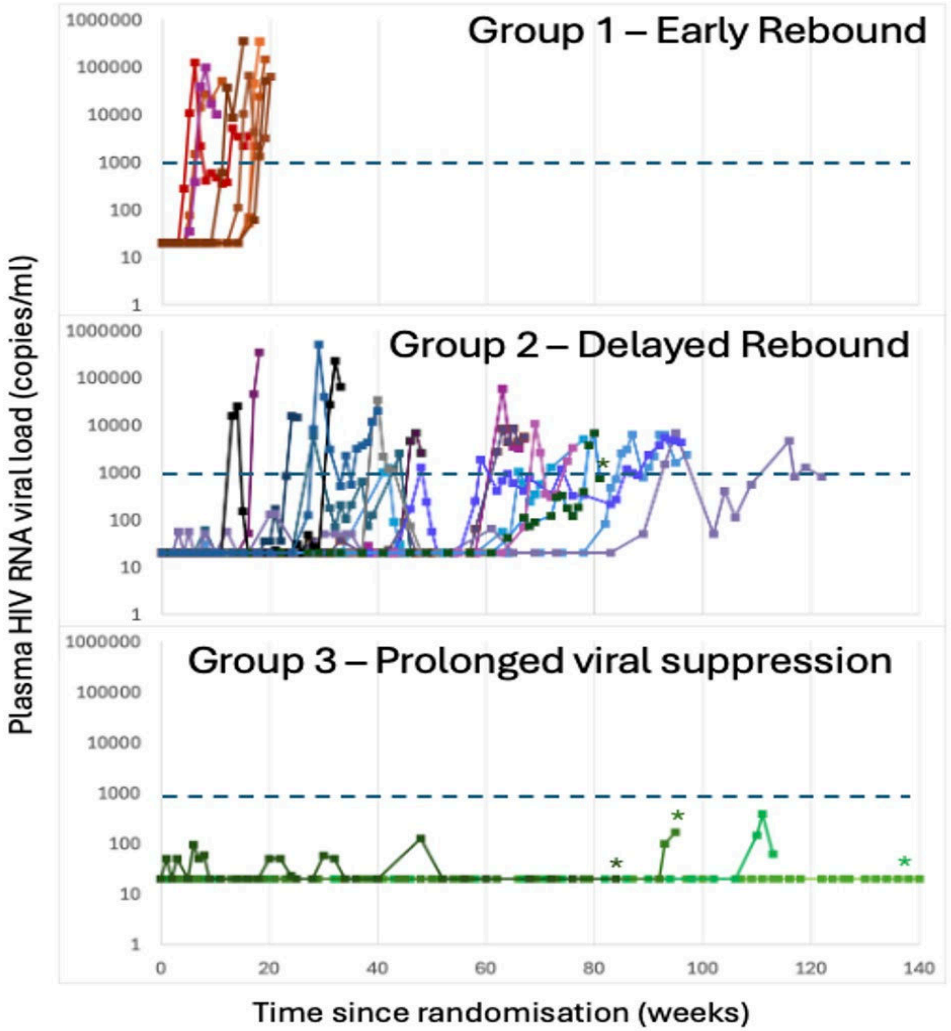


- 57% not rebounded week 48
  - 95% CI (0.41, 0.8)
- 39% not rebounded week 72
  - 95% CI (0.23, 0.65)
- Placebo: 2/34 (6%) not rebounded

Number of participants

	0	24	48	72
bNAbs	34	20	13	8
placebo	34	3	2	2

Three patterns of virological responses to bNAbs



1. **Rapid rebound**

8 participants rebounded within 20 weeks
(4 with bNAb resistance)

2. **Delayed rebound**

14 participants not rebounded
before 72 weeks

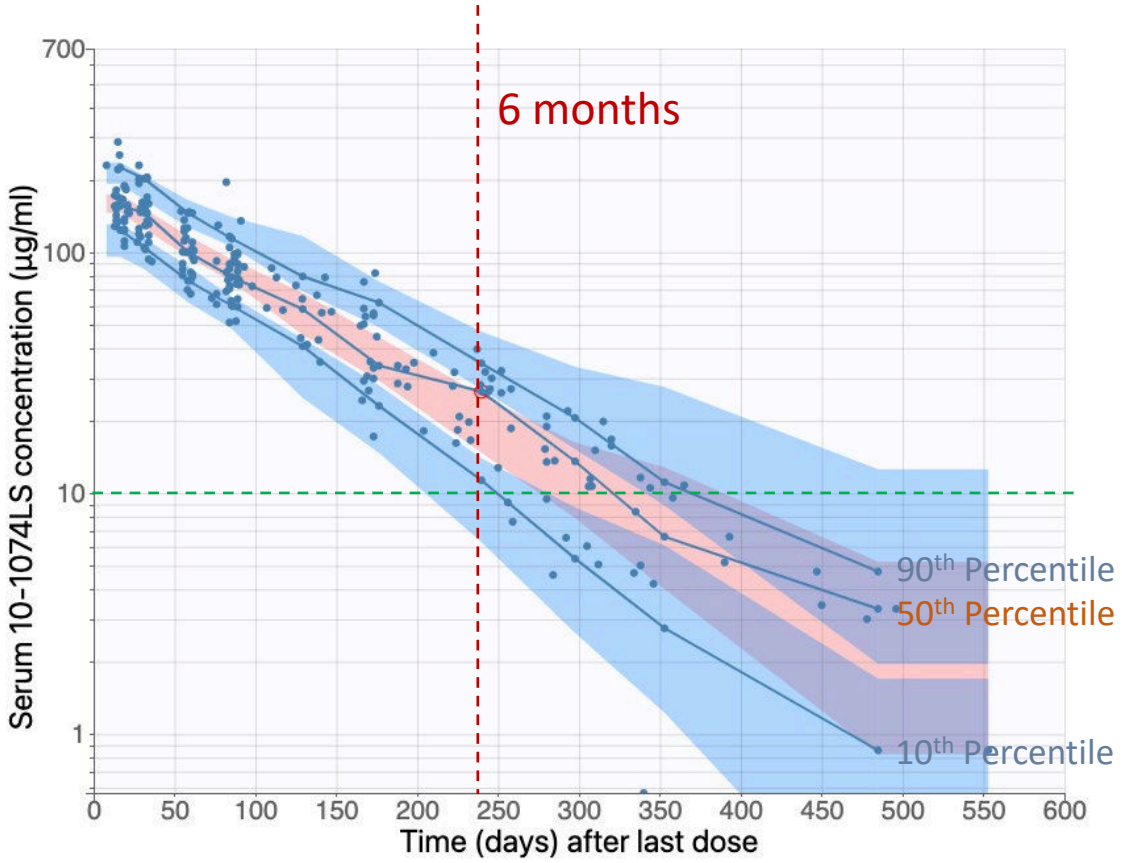
3. **Viral control**

4 have not rebounded > 72 weeks

LS-bNAb Pharmacokinetics

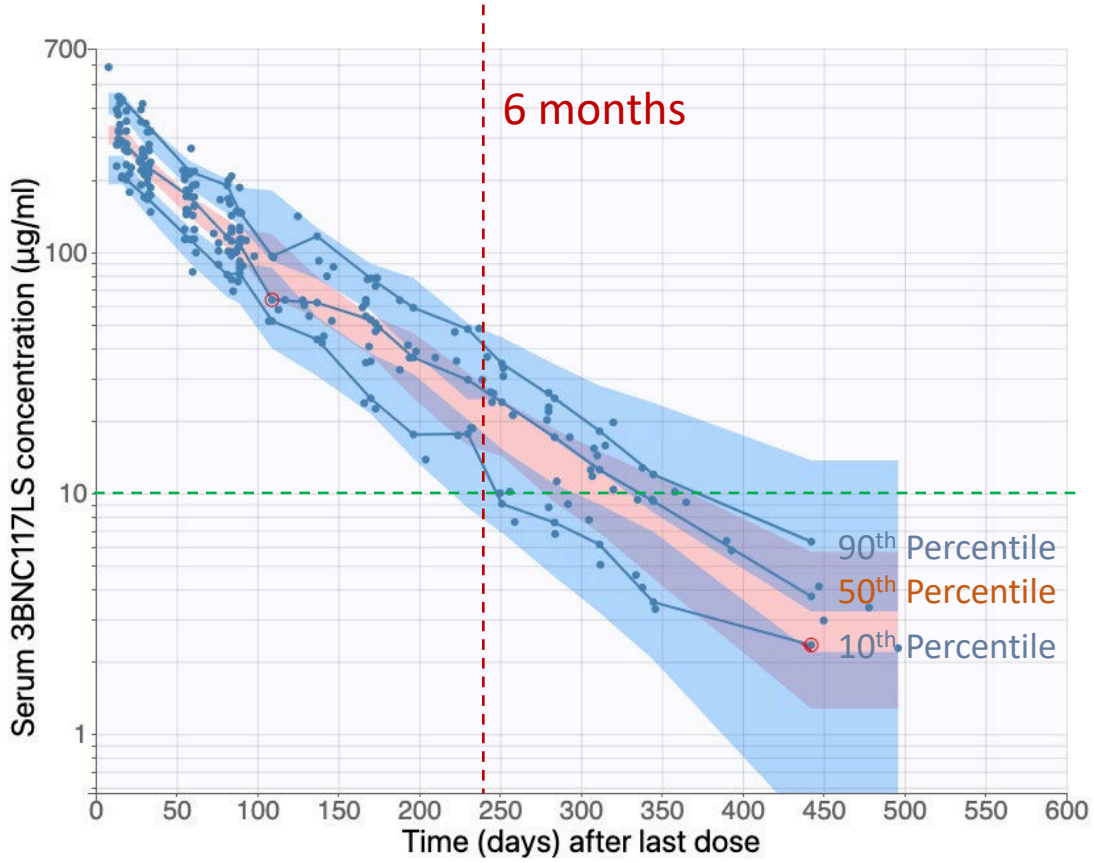

10-1074LS (Dose 10mg/kg)

	Estimate	90% prediction interval
Half-life	**72.5 days**	69.1 – 76.2 days



3BNC117LS (Dose 30mg/kg)

	Estimate	90% prediction interval
Half-life	**64.8 days**	61.8 – 66.6 days



Adverse events associated with bNAbs and ATI

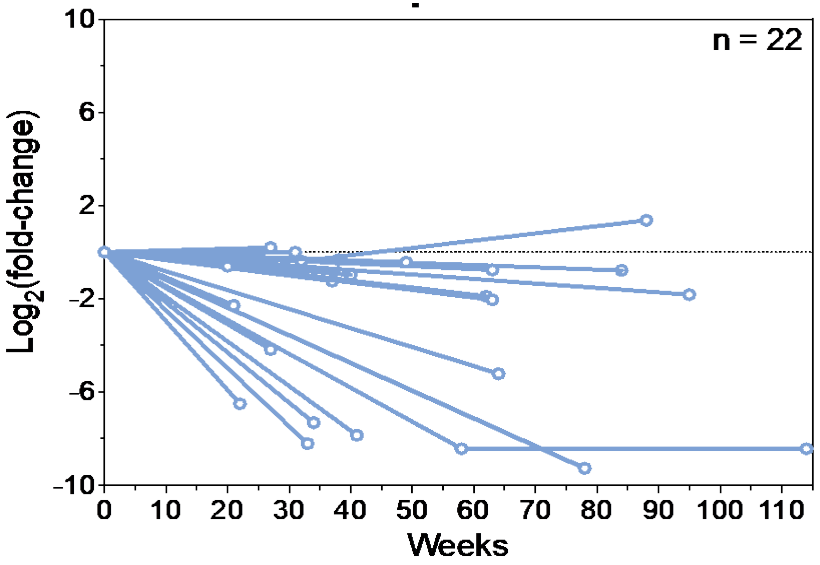
- 8 Serious Adverse Events, one death. None related to bNAb or ATI. No infusion reactions.
- No-one restarted due to CD4 count decline.
- No HIV transmission.

	Statistics	bNAbs	Placebo	All
Viral load peak (copies/ml)	Median (min, max)	55,245 (5060 – 125000)	1,000,000 (21900 – 10,000,000)	63,525 (3236 – 10,000,000)

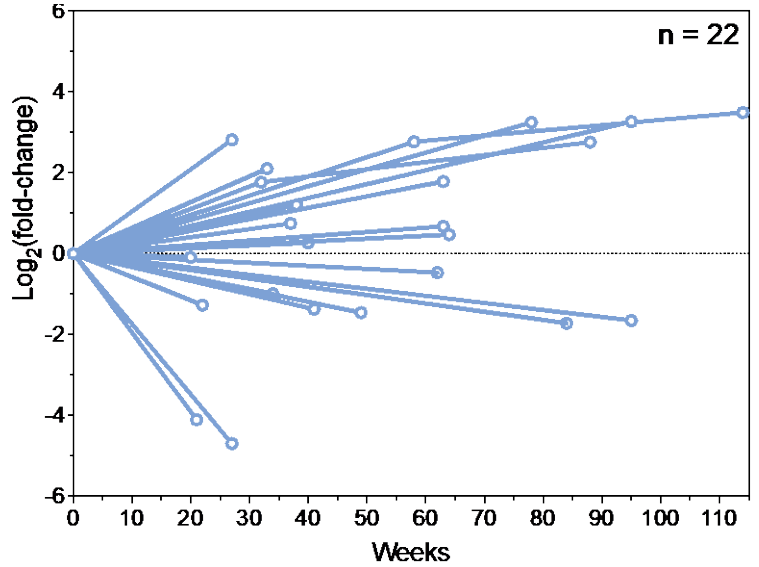
- 94% achieved viral suppression by 12 weeks after ART restart
- No difference to viral suppression on ART restart by study arm
- 5 participants had peak VL > 1,000,000 at rebound; time to viral suppression was 2-24weeks

Impact of bNAbs on HIV Reservoir size

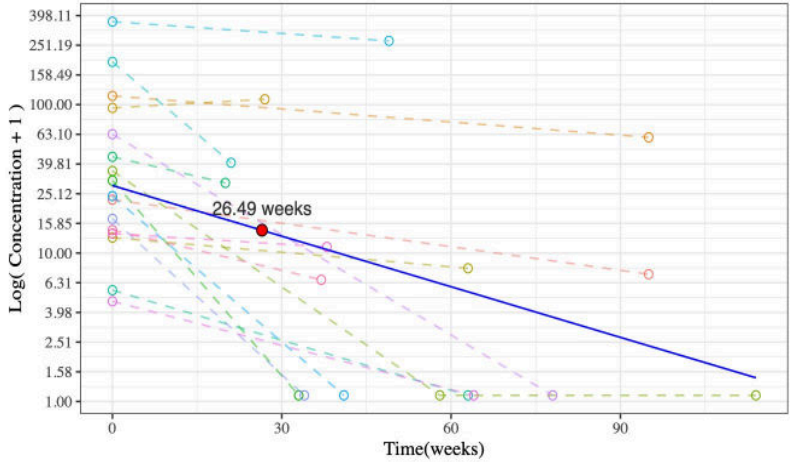
Marcilion Fumagallo
Nussenzweig lab



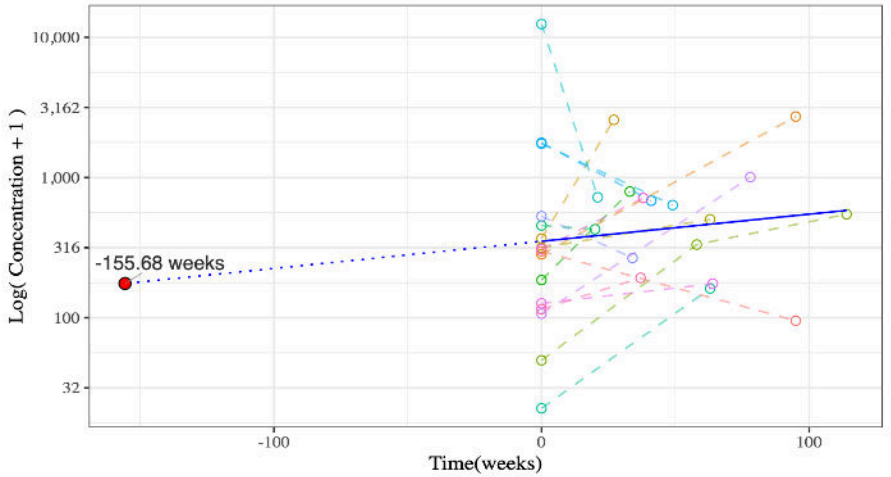
Fold change in intact provirus



Fold change in defective provirus



Half life of intact provirus over time
26.5 weeks

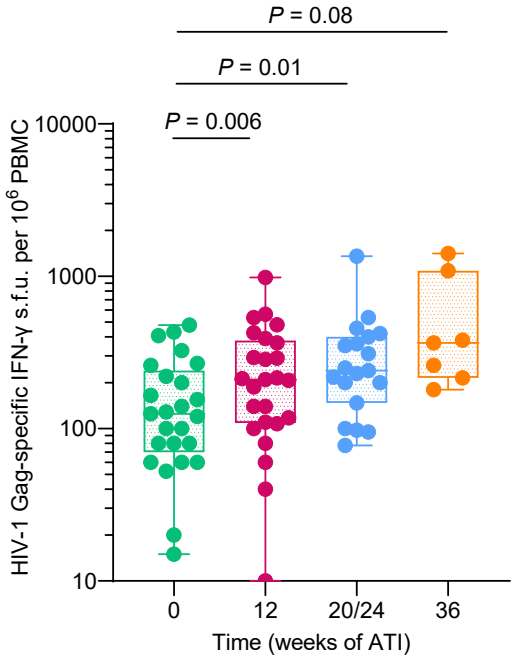


Half life of defective provirus over time
155.68 weeks

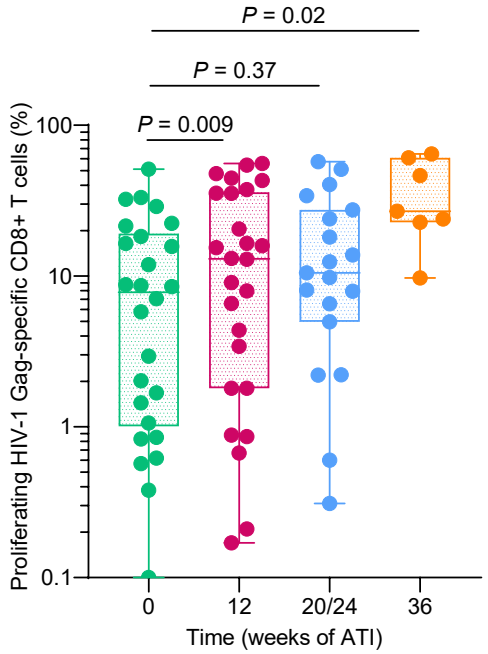
T cell immunology in RIO – a ‘vaccinal’ effect?

Mohammed Altaf
John Frater,

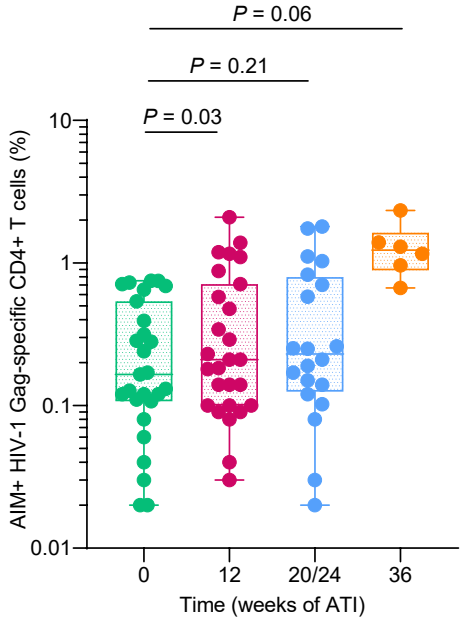
ELISPOT
(Gag Pools)



CD8 Proliferation
(Gag Pools)



CD4 AIM
(Gag Pools)



Only participants Arm A (bNAb) off ART VL < 50 copies RNA/ml

Community Summary and Key Findings

- Three quarters of people who received bNAbs did not rebound by week 20.
- 1 in 3 people who had bNAbs have stayed off ART for over 72 weeks.
- bNAbs boosted new HIV-specific immune responses.
- There were no serious events (from either bNAbs or stopping ART).
- Everyone resuppressed after restarting ART.
- Even with close monitoring, VL rebounded much higher than planned in the protocol
- bNAbs stimulated new immune responses.
- bNAbs impacted the size of the HIV reservoir.

With Thanks! All the RIO participants

Imperial College London: ***Sarah Fidler (Chief Investigator),*** Graham Taylor, Ming Lee, Marcelo Molina, Maryam Khan, Jacquie Ujetz, Ishrat Jahan, Maathini Balachandran, Katie Topping

University of Oxford: ***John Frater (Co-PI),*** Helen Brown, Mohammed Altaf, Panagiota Zacharopoulou, Nicola Robinson, Timothy Tipoe, Ane Ogbe, Carla Nel

Rockefeller University: ***Michel Nussenzweig (Co-PI),*** Marina Caskey, Jill Horowitz, Adriana Barillas-Batarse, Christian Gaebler, Cintia Bittar Oliva , Marcilio Fumagalli

Imperial Clinical Trials Unit (ICTU):
Hanna Box, Stephen Fletcher, Daphne Babalis, Emanuela Falaschetti, Louise-Rae Cherrill, Najwa Soussi, Nicholas Johnson, Toby Prevost, Christina Prechtl, Milaana Jacob, Ambreen Ashraf

NIHR Imperial Clinical Research Facility (ICRF)
Tom Cole, Lisa Hurley, Susanne Fagerbrink, David Owen, Karen Mosley

RIO Clinical Investigators: Sarah Fidler, Julie Fox, Sabine Kinloch, Gary Whitlock, Marta Boffito, John Thornhill, Alison Uriel, Rebecca Sutherland, Chloe Orkin, Amanda Clarke, Sarah Pett, Ole Schmeltz Søgaard, Jesper Damsgaard Gunst, Lisa Hamzah, Paola Cicconi, Kyle Ring, Jesal Gohil

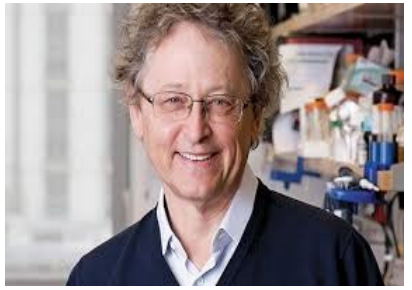
Community Representatives: UK-CAB
Simon Collins (Leadership group, UK i-base), Jo Josh (IDMC), Ben Cromarty (TSC)

Trial Oversight:

Trial Steering Committee (TSC): Frank Post (King's College London, *Chair*), Independent Members: Frank Post (Chair), Caroline Sabin, Clifford Lean, Jaime Vera, Dimitra Peppa, Ben Cromarty
Independent Data Safety Monitoring Committee (IDMC): Abdel Babiker (MRC CTU at UCL, *Chair*), Jane Anderson, Andrew Lever, Jo Josh, *Roy Trevelion (previous member)*
Endpoint Review Committee (ERC): Linos Vandekerckhove (Ghent University, *Chair),* Beatriz Mothe Pujadas, Casper Rokx, Ole Schmeltz Søgaard *(previous Chair)*



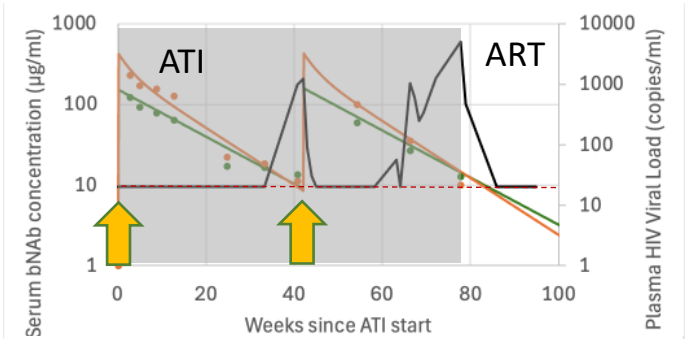


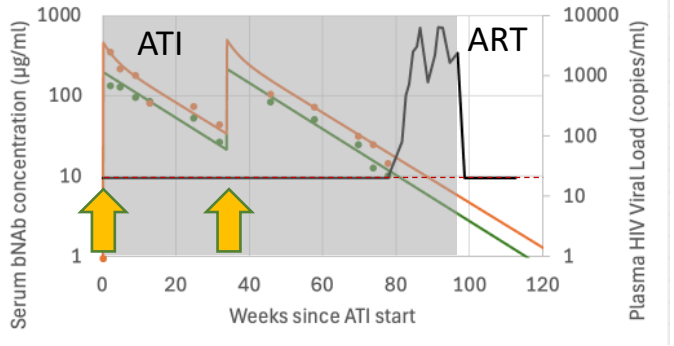



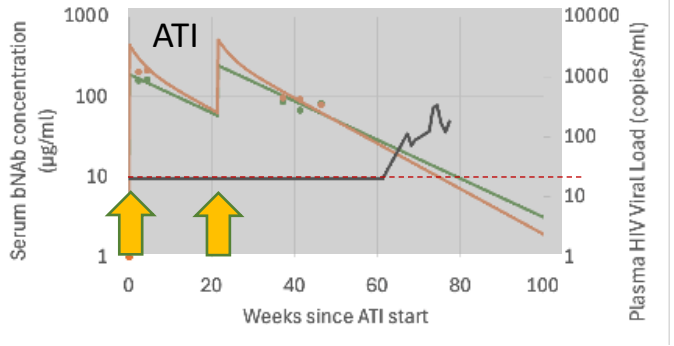

Group 3 participants

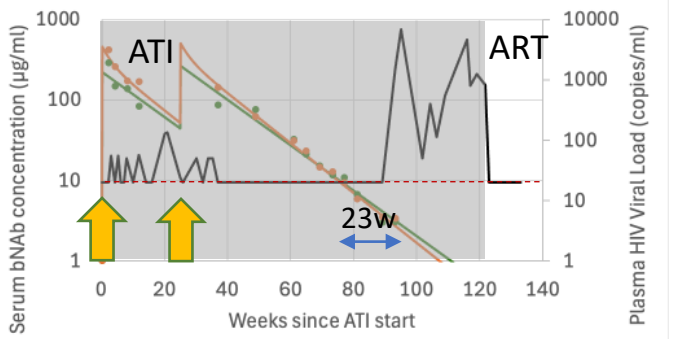
Delayed rebound

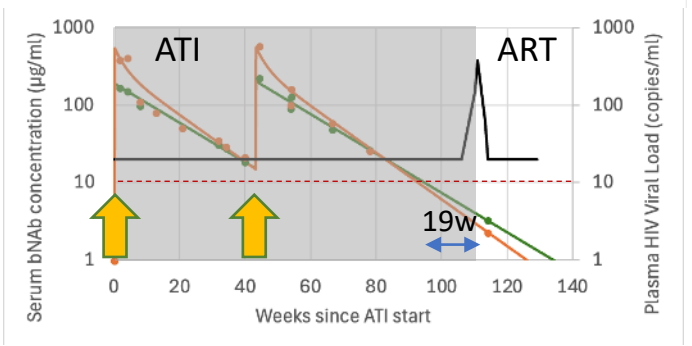
People with ‘post-bNAb’ control

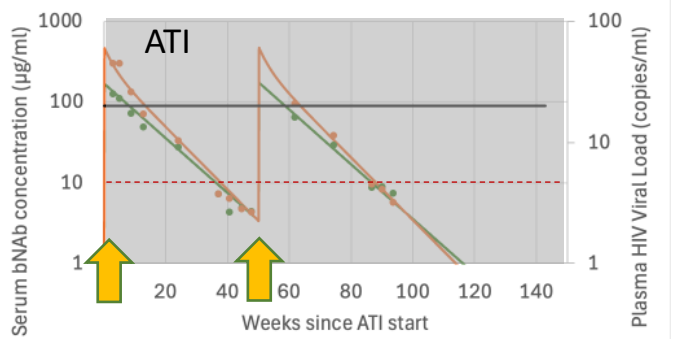


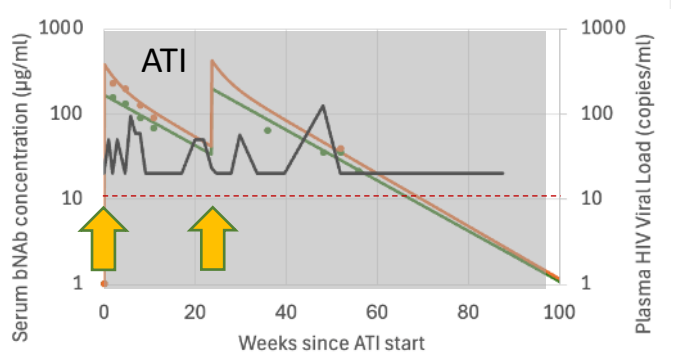


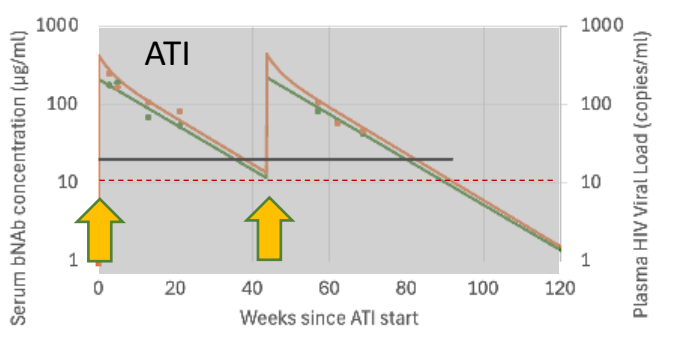








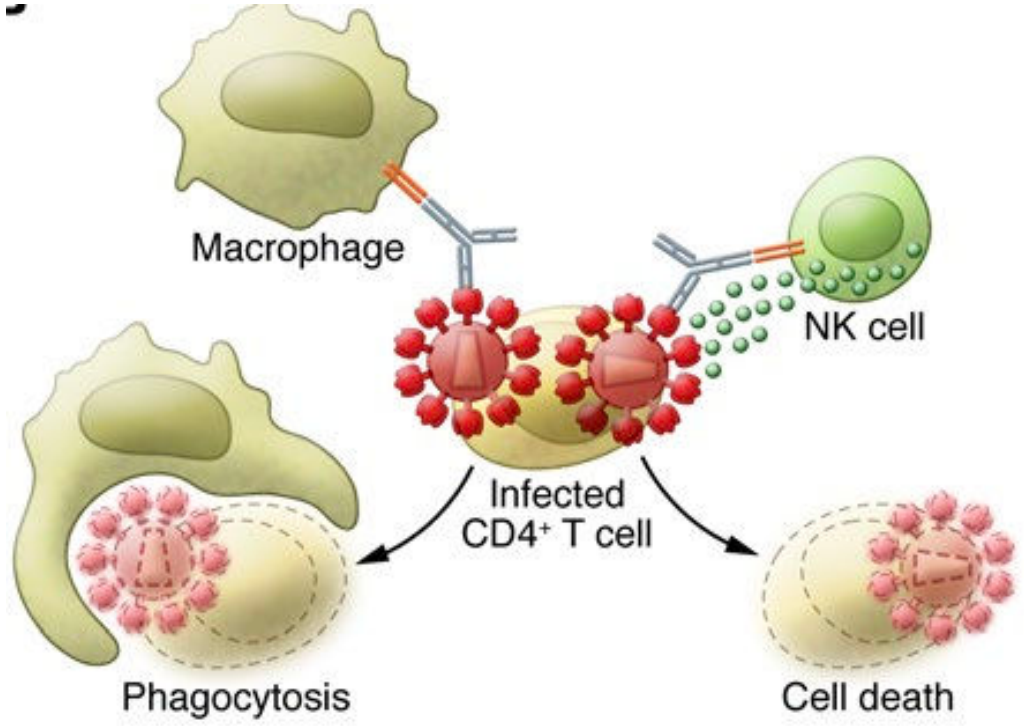




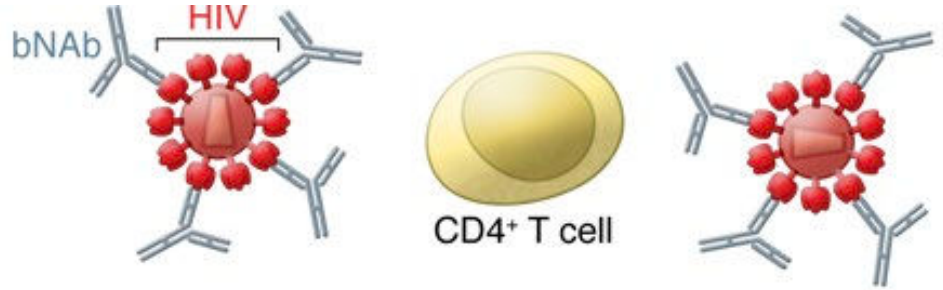
bNAbs — 10-1074LS — 3BNC117LS — HIV VL

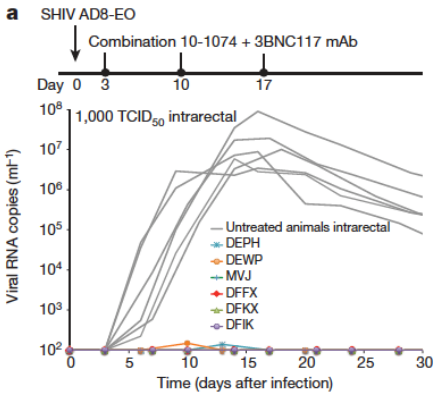
Can HIV bNAbs do more than ART?

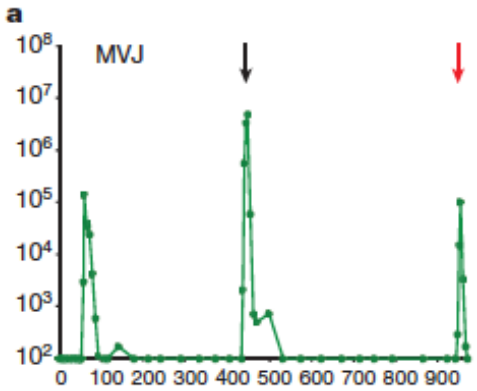
bNAbs can engage innate immune effector cells and facilitate killing of infected cells



bNAb mediated enhancement of HIV-specific adaptive immunity
– a **vaccinal effect** ?







Halper-Stromberg, Nussenzweig 2016 JCI; Nishimura et al 2017 Nature

The rise of HIV-specific Broadly Neutralising Antibodies (bNAbs) as antiviral agents raises a number of key questions:

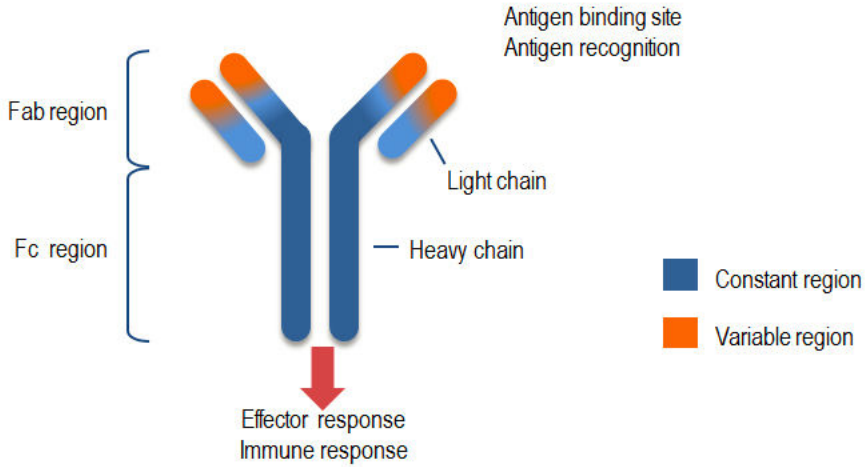
1. Are they effective as antiretroviral agents?
2. Does the ‘LS’ mutations confer long-term sustained antiviral control?
3. Is there a post-bNAb effect that can induce remission or even cure?
4. How long do bNAbs last in blood and tissue, and can we define a post-bNAb effect by measuring bNAb levels?

HIV-Broadly Neutralising antibodies (bNabs)

- antigen binding region is HIV envelope
- The Fc region enhances other immune cell functions
- Next generation bNAbs have extended half-lives (up to 3-6 months)

How do antibodies work?

1. block the entry of a **broad** range of different strains of HIV into healthy cells
2. kill infected cells (ADCC)
3. boost other cells of the immune system “vaccinal effect”



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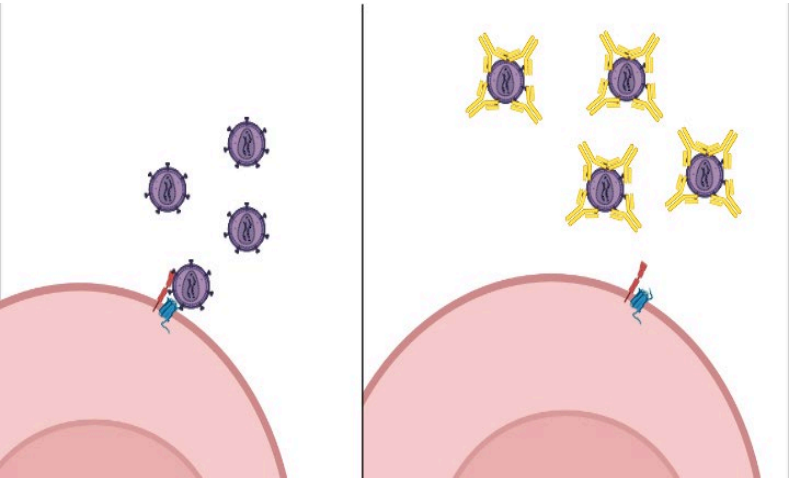

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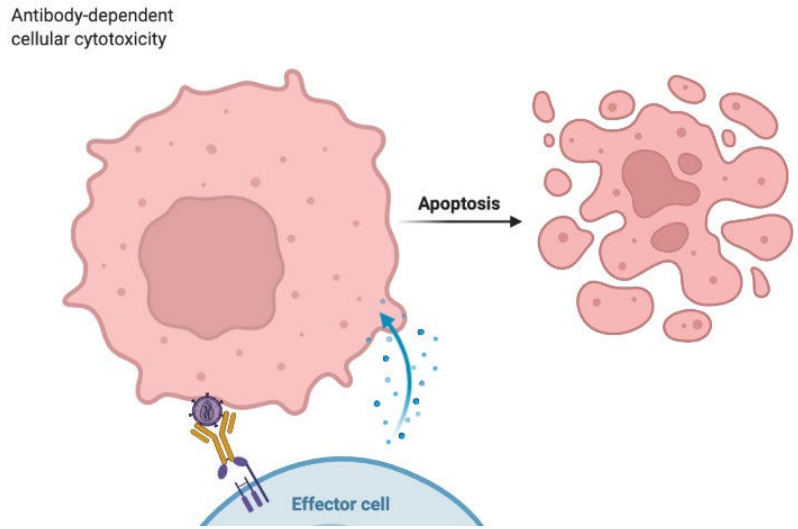

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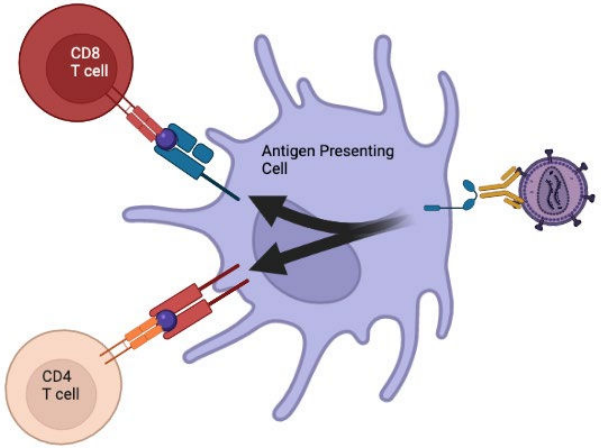

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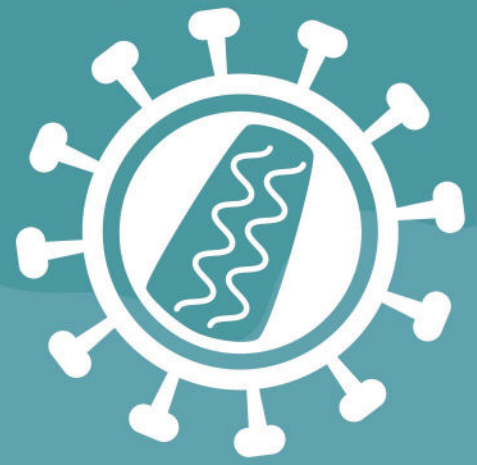
British HIV Association

2025 **Spring Conference**



Wed 23rd – Fri 25th April

Brighton Dome, UK

www.bhiva.org

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