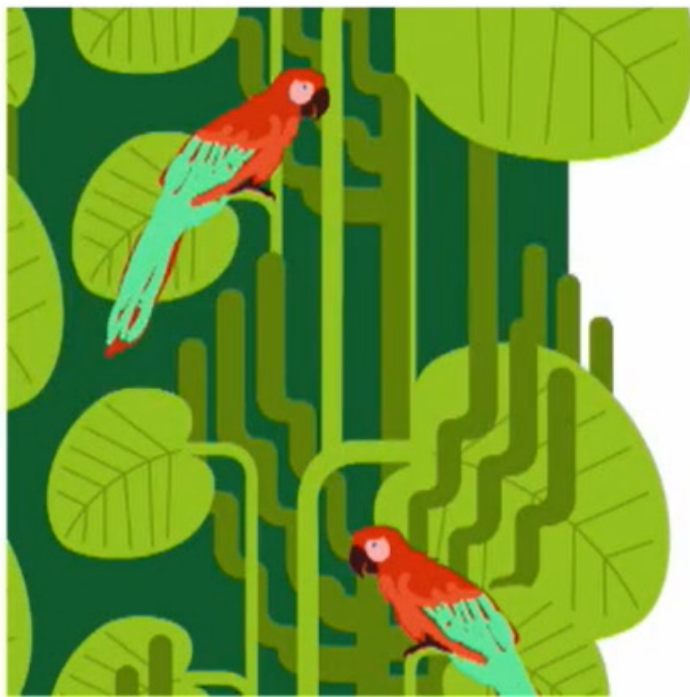




Rachel Scheck - Weill Cornell Medicine

On behalf of the ACTG A5386 study team

Cure and control

IL-15 superagonist N-803, with or without bNAbs, reduces the intact and inducible reservoir

Rachel Scheck, Itzayana Miller, Hanna Mar, Ronald Bosch, Adam R. Ward, Parul Sinha, Huizheng Zhang, Nainika Chada, Ethan Naing, Cristian Ovies, Sandra Terry, Charles S. Venuto, Robin DiFrancesco, Michael L. Freeman, Joshua C. Cyktor, John W. Mellors, Gene D. Morse, Bobby Reddy, Jonathan Berardi, Randall Tressler, Marina Caskey, R. Brad Jones, Timothy Wilkin



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Summary

What is your main question?

- Can an immune-intervention with IL-15 superagonist N-803 ± bNAbs impact viral rebound, the HIV reservoir and the immunologic HIV response?

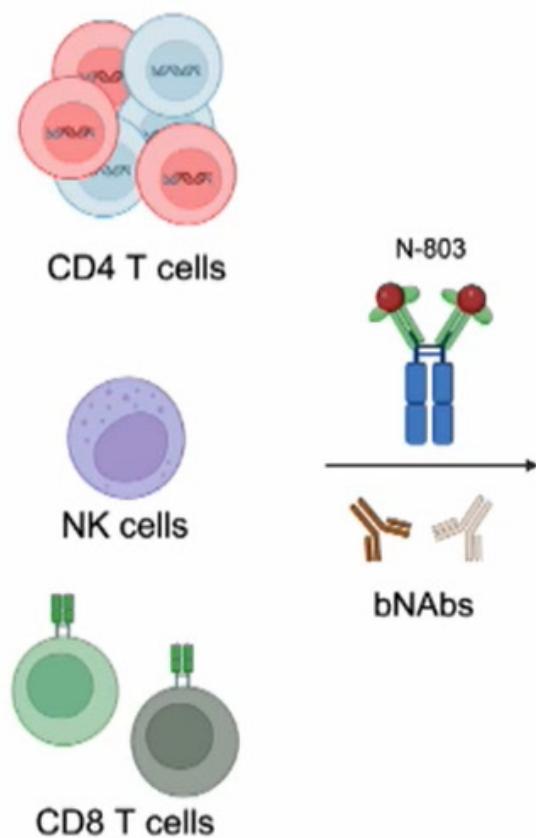
What did you find?

- N-803 reduced the HIV reservoir and enriched for T cells associated with HIV control.
- 11% of participants controlled HIV at week 8 after ART interruption (<200 copies/mL) and to date, 14% of participants remained off ART ≥ 20 weeks

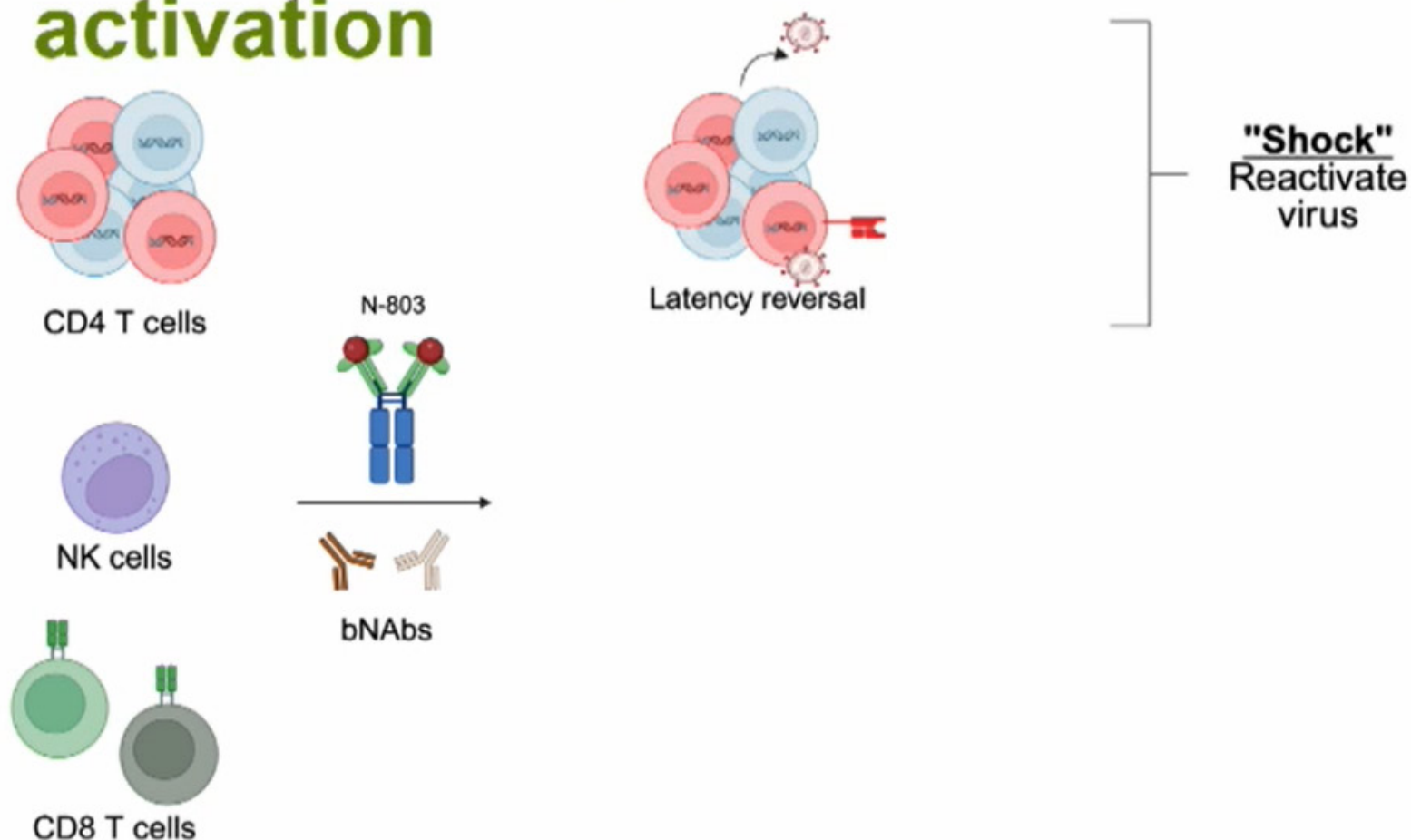
Why is it important?

- Reservoir reduction and immunologic changes that are associated with improved clinical outcomes is possible with N-803.
- This will help us to plan future N-803 trials to achieve more frequent post-intervention control.

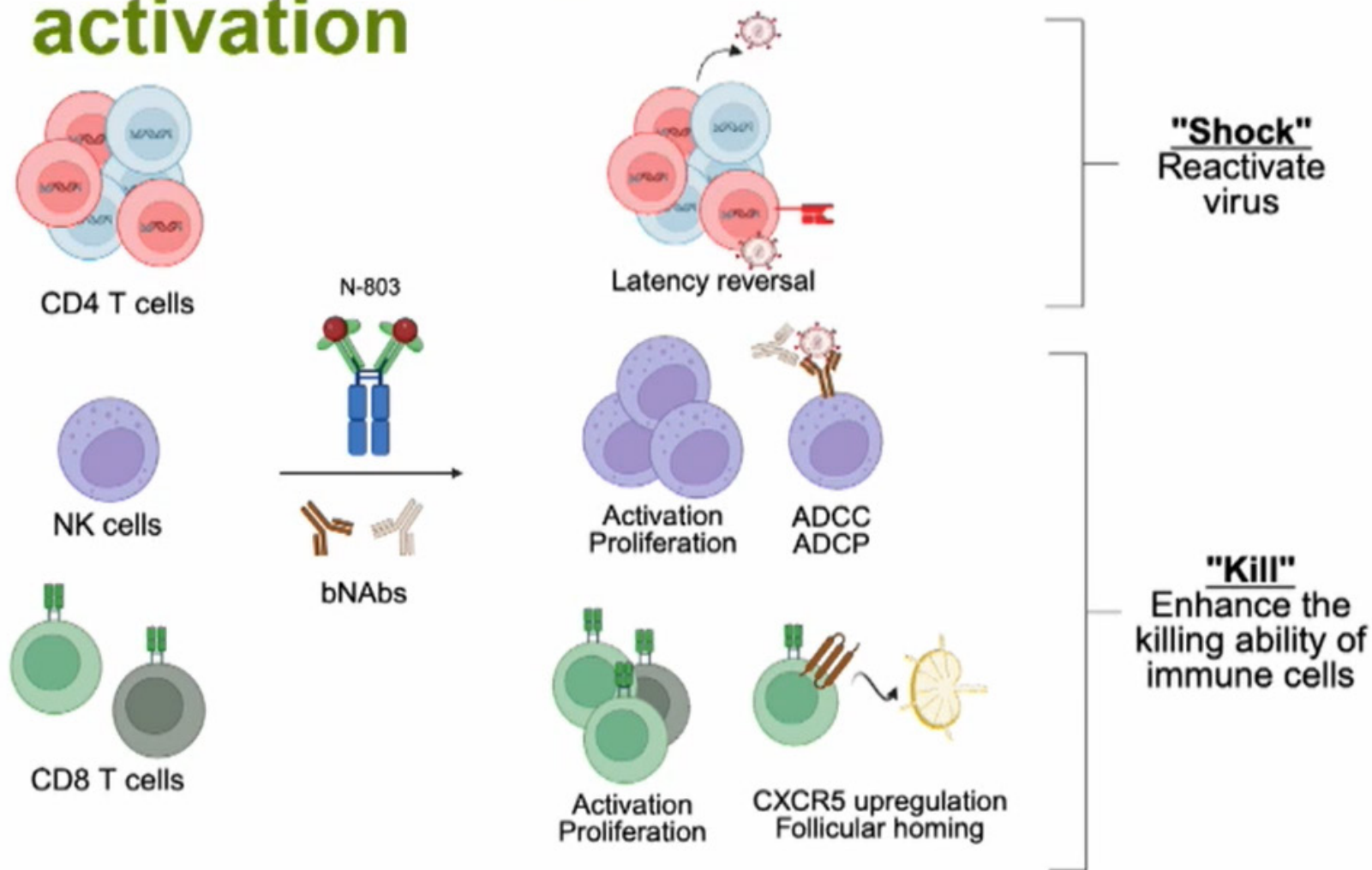
N-803: Latency reversal and immune activation



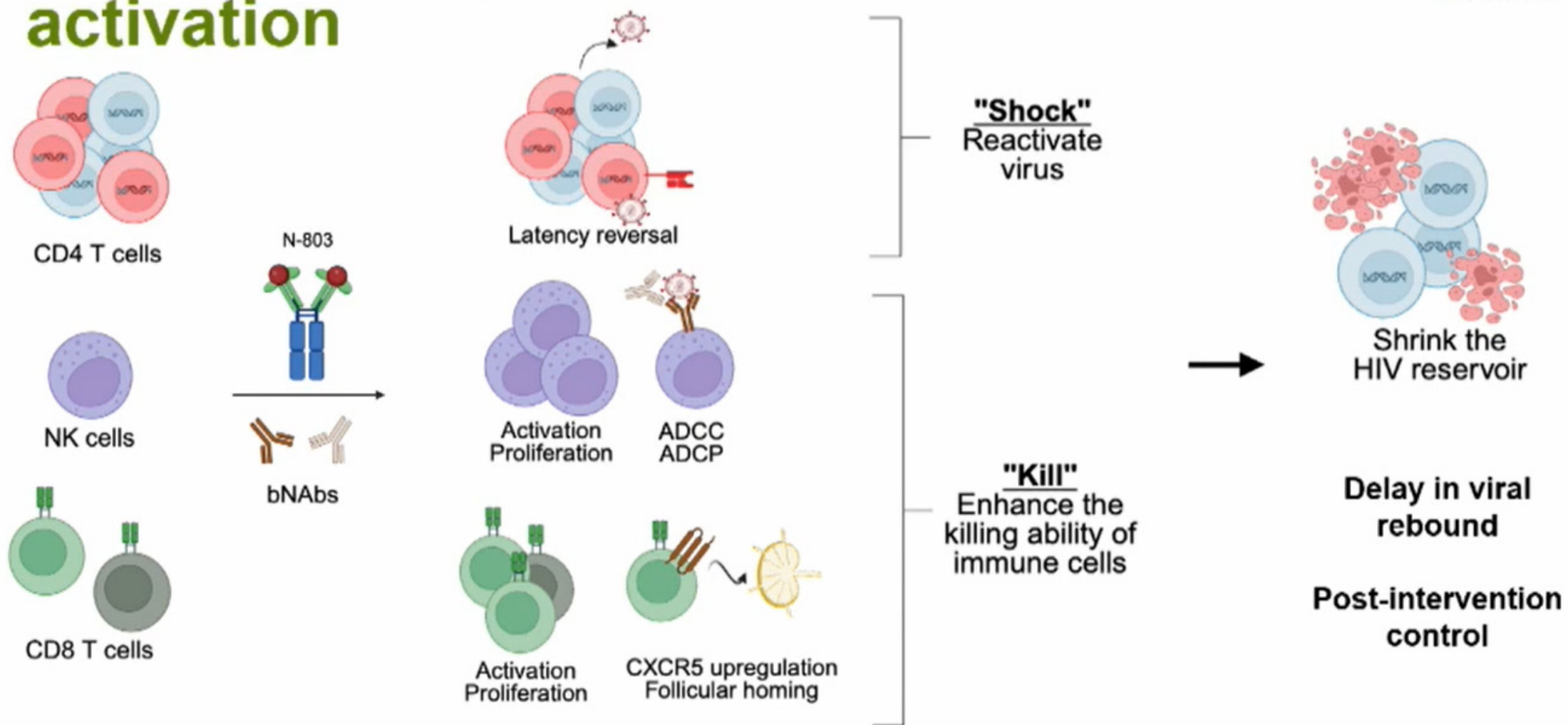
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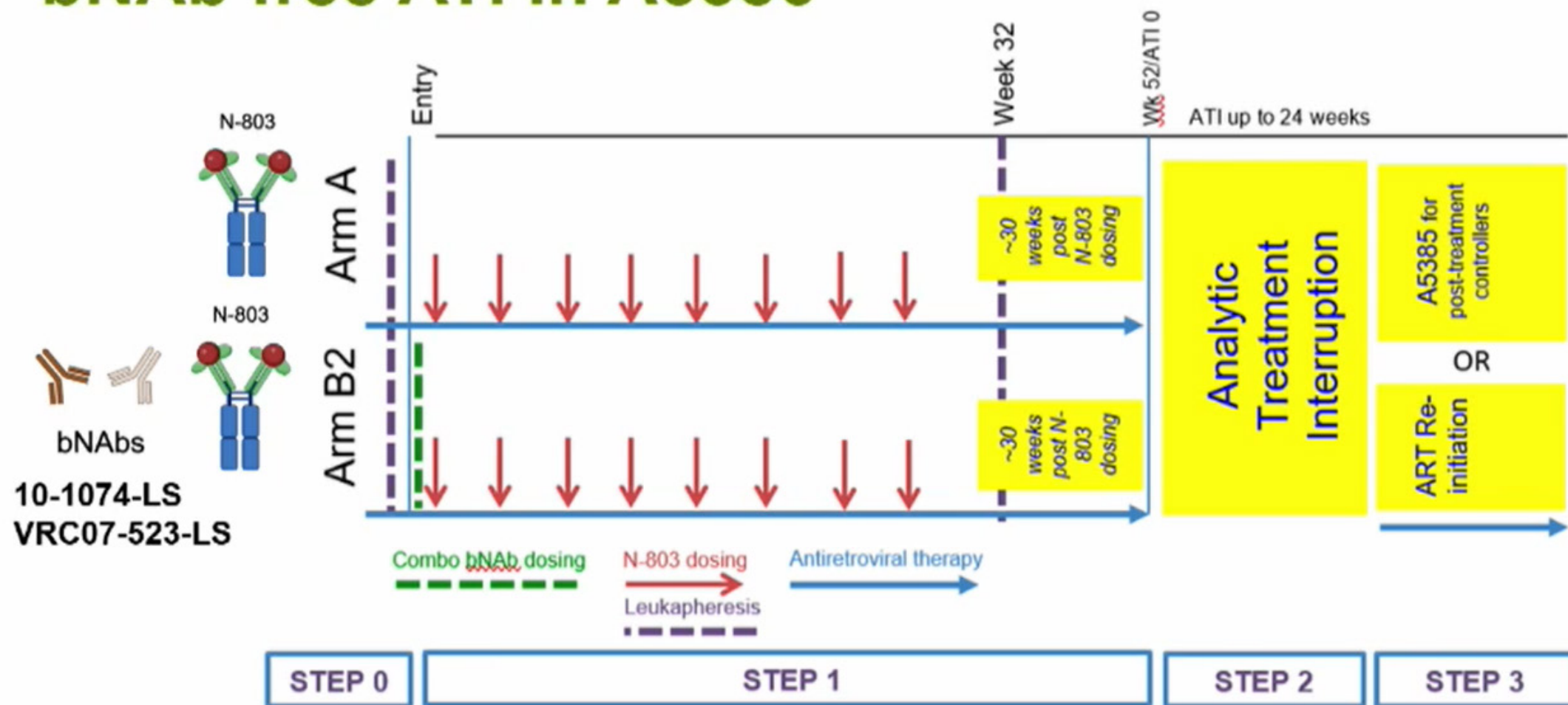
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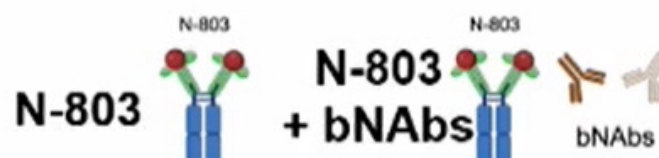
N-803: Latency reversal and immune activation



bNAb free ATI in A5386

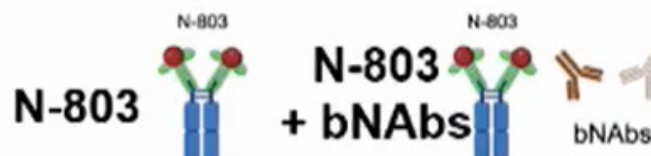


A5386 is fully enrolled: Safety and Tolerability



Characteristic (n=48)	Arm A (n = 25)	Arm B2 (n = 23)
Female sex	4 (16%)	1 (4%)
Age (median, range)	51 (21-70)	51 (25-68)
White race	16 (64%)	13 (56%)
Hispanic / Latino	7 (28%)	2 (9%)
Entry CD4 count (median range)	659 (459-1550)	831 (457-1552)
ART duration (median)	6.4 years	6.7 years

A5386 is fully enrolled: Safety and Tolerability

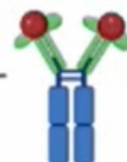


bNAbs



- Well-tolerated
- All completed dosing
- 2 (9%) grade 2 AEs
- Anti-drug antibody results are pending

N-803



- Injection site and systemic reactions were common
- 5 discontinued N-803 after 1 or 2 doses
- 4 received reduced doses
- **43 received ≥ 5 doses**
- 4 (16%) N-803 alone and 4 (17%) N-803 + bNAbs grade 3 or 4 AEs possibly related to N-803

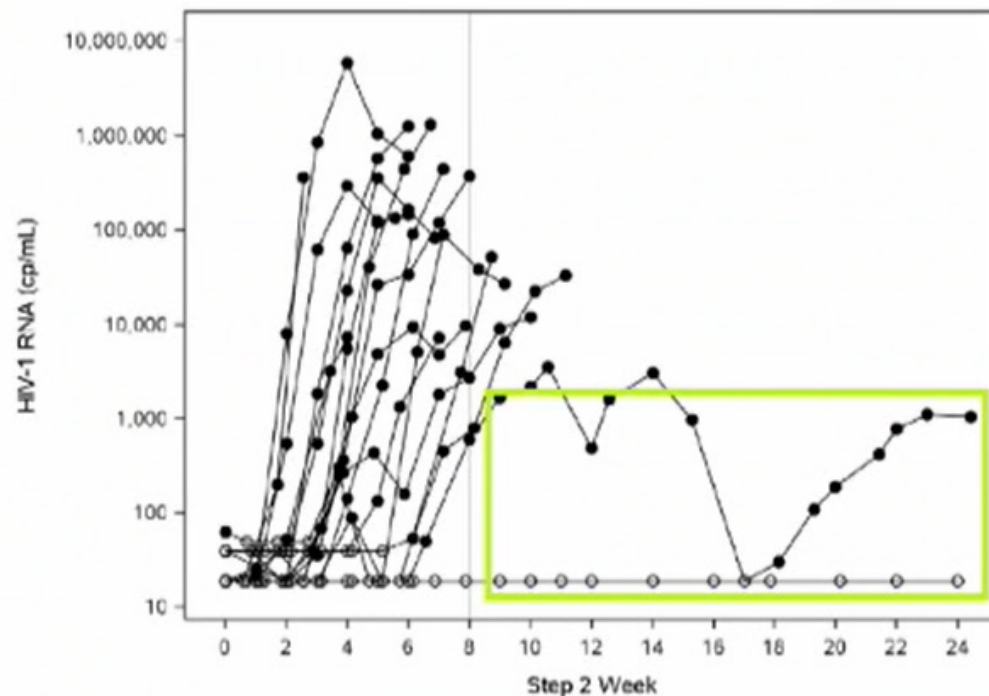
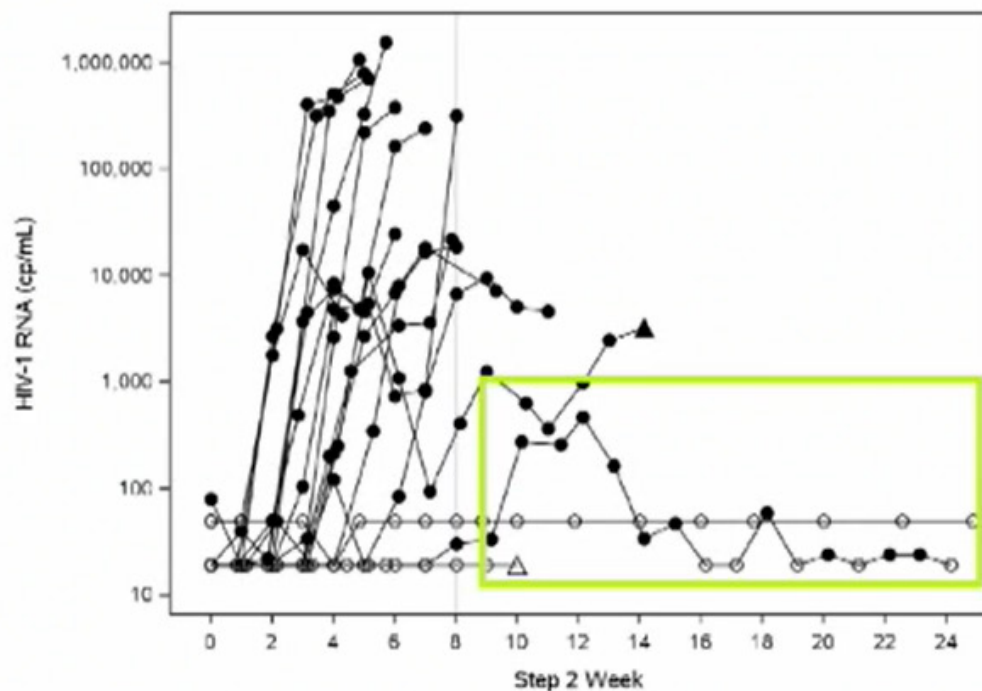
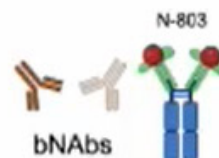
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ATI is ongoing: To date, 14% of participants remained off ART for ≥ 20 weeks

N-803 arm
(n=17)

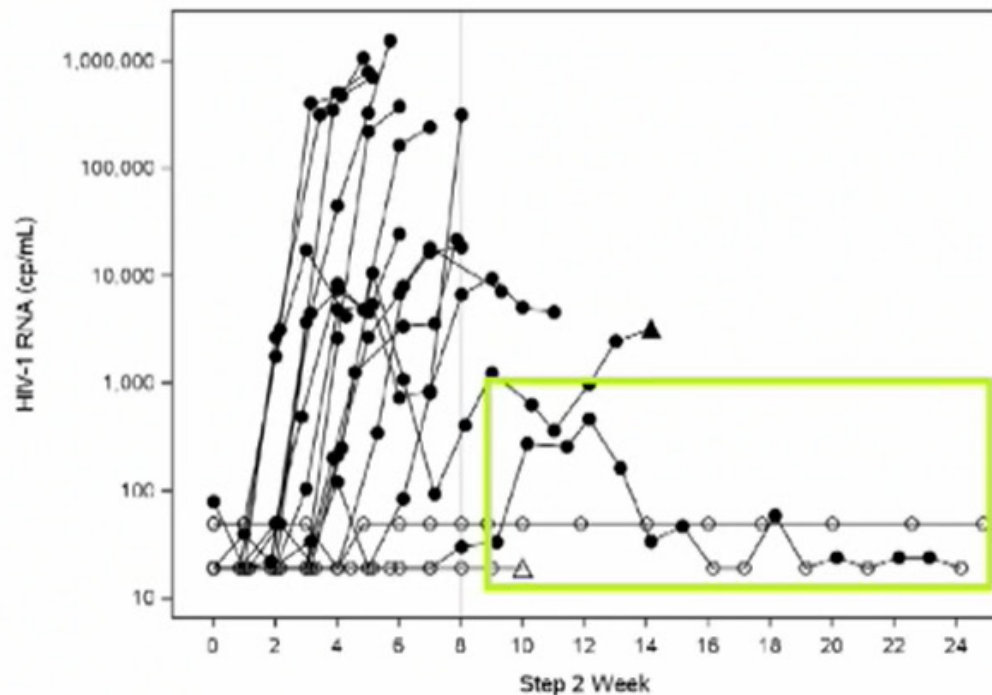


bNAb + N-803 arm
(n=19)

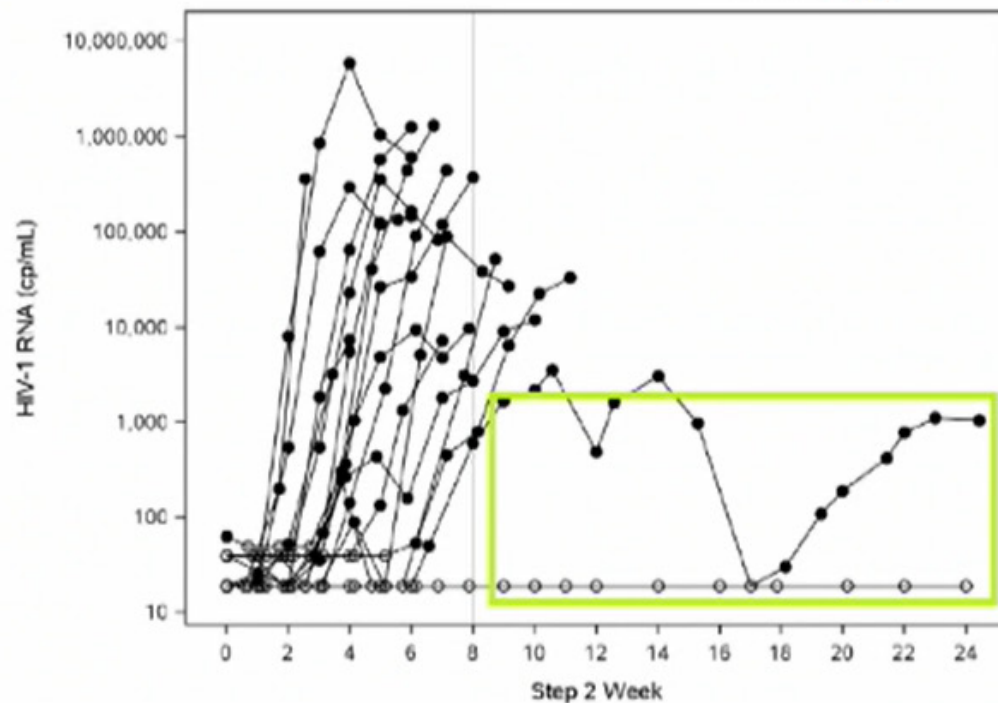
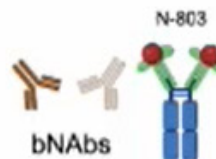


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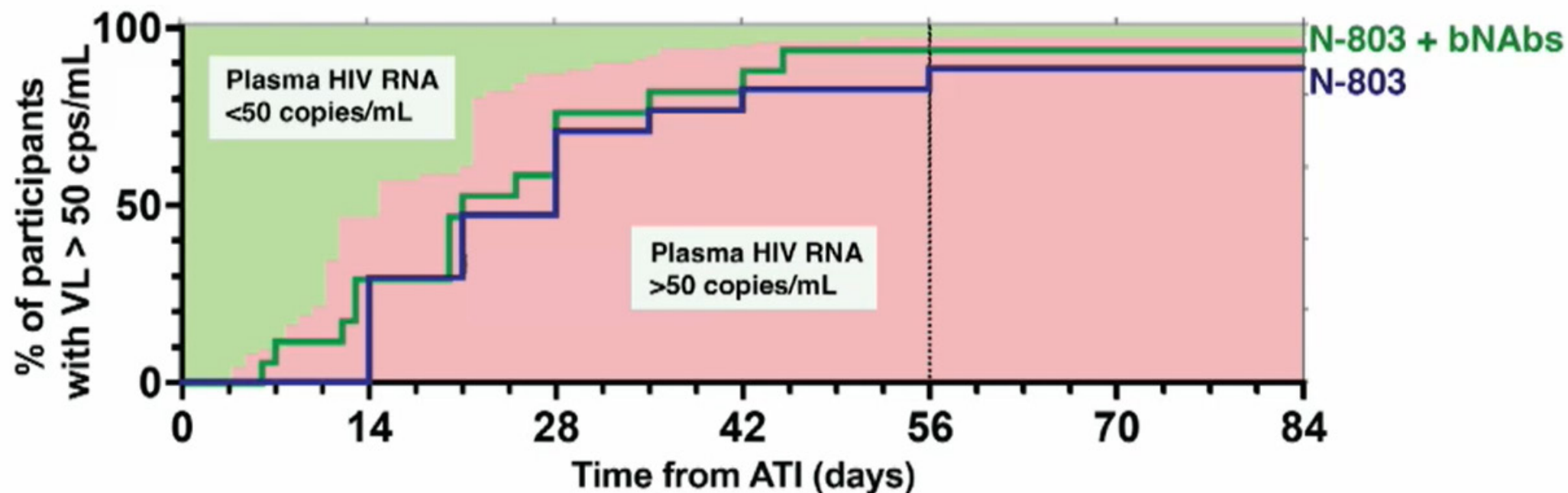


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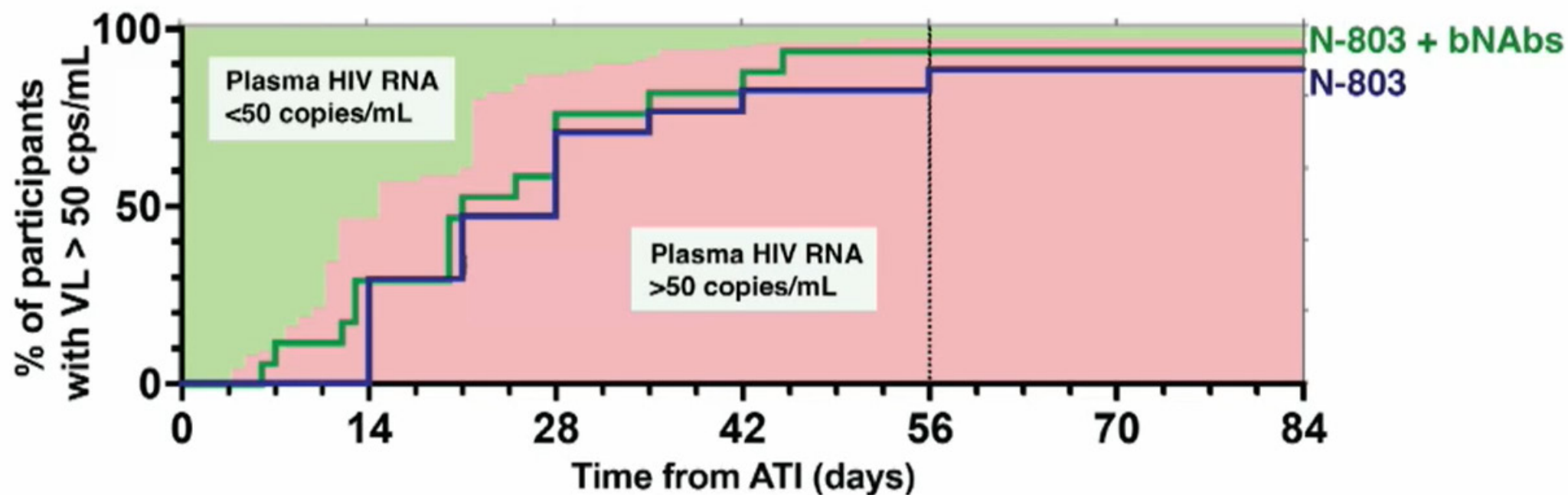


11% reached primary endpoint of <200 cps/mL at week 8

Potentially delayed time to rebound in A5386

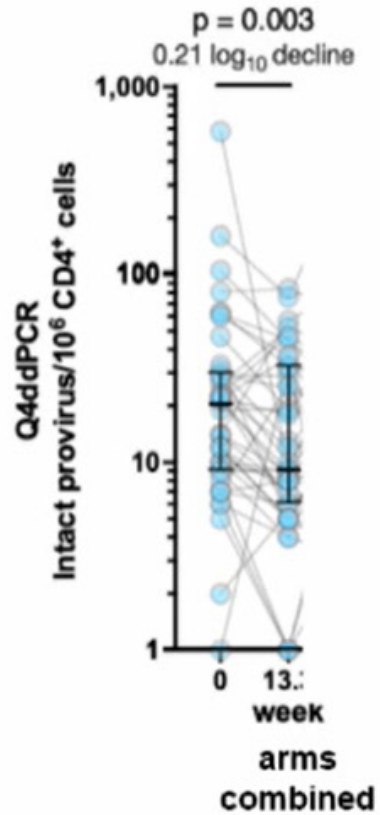


Potentially delayed time to rebound in A5386



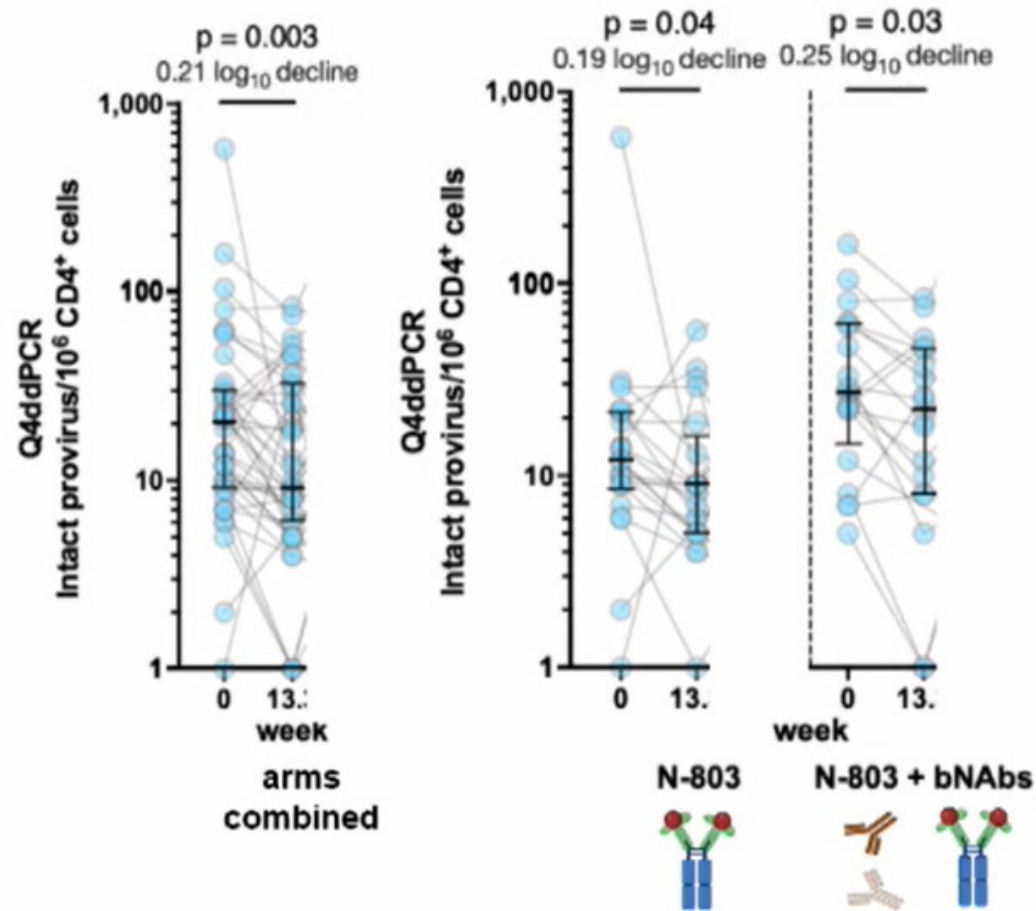
- Median time to rebound (>50 cps/mL) 28 days (IQR 14 – 42) compared to median 16 days (IQR 13 - 25) in historic controls.

N-803 reduces the intact reservoir (n = 42)



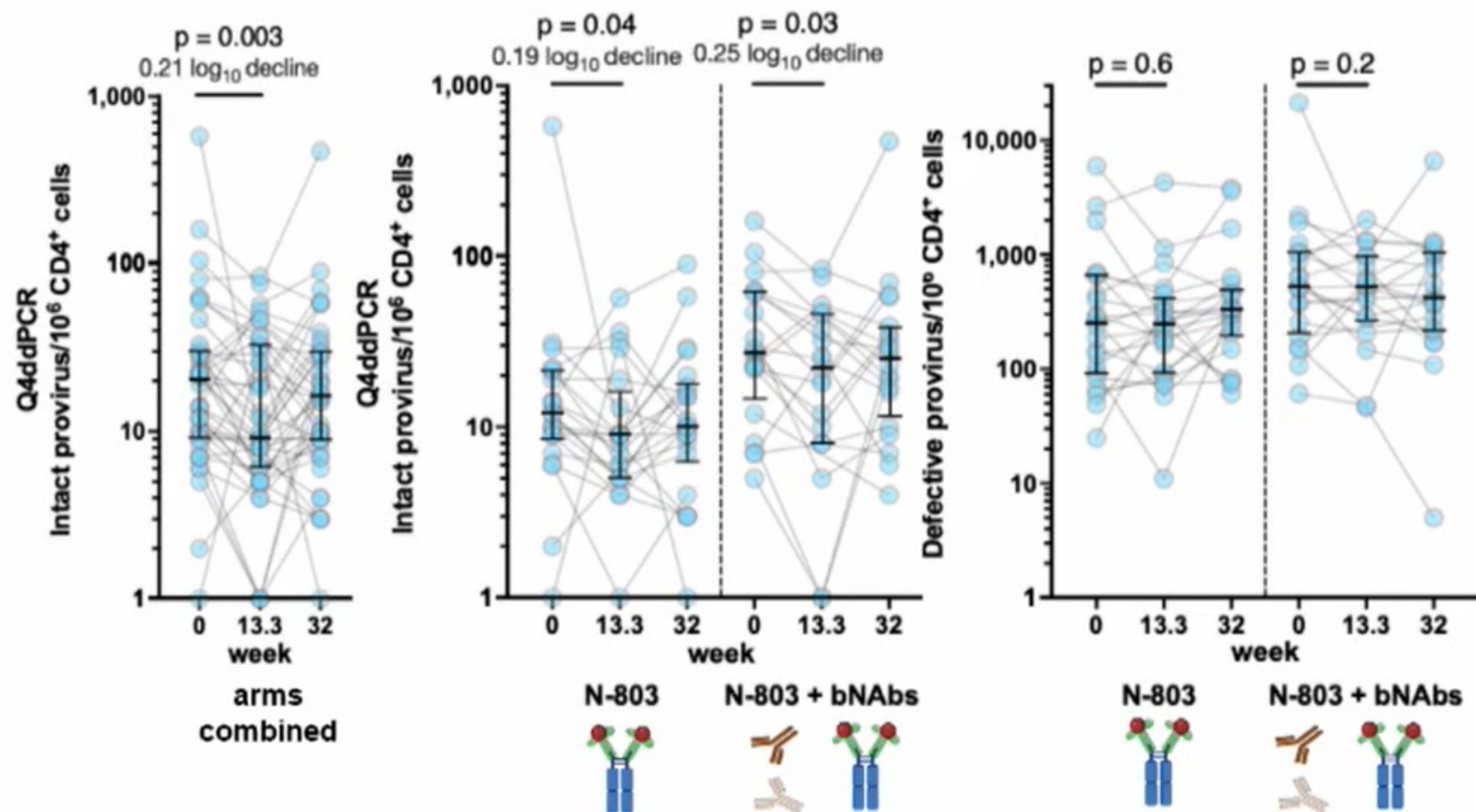
- 37% reduction in intact reservoir after 5 doses N-803 in 71% of participants

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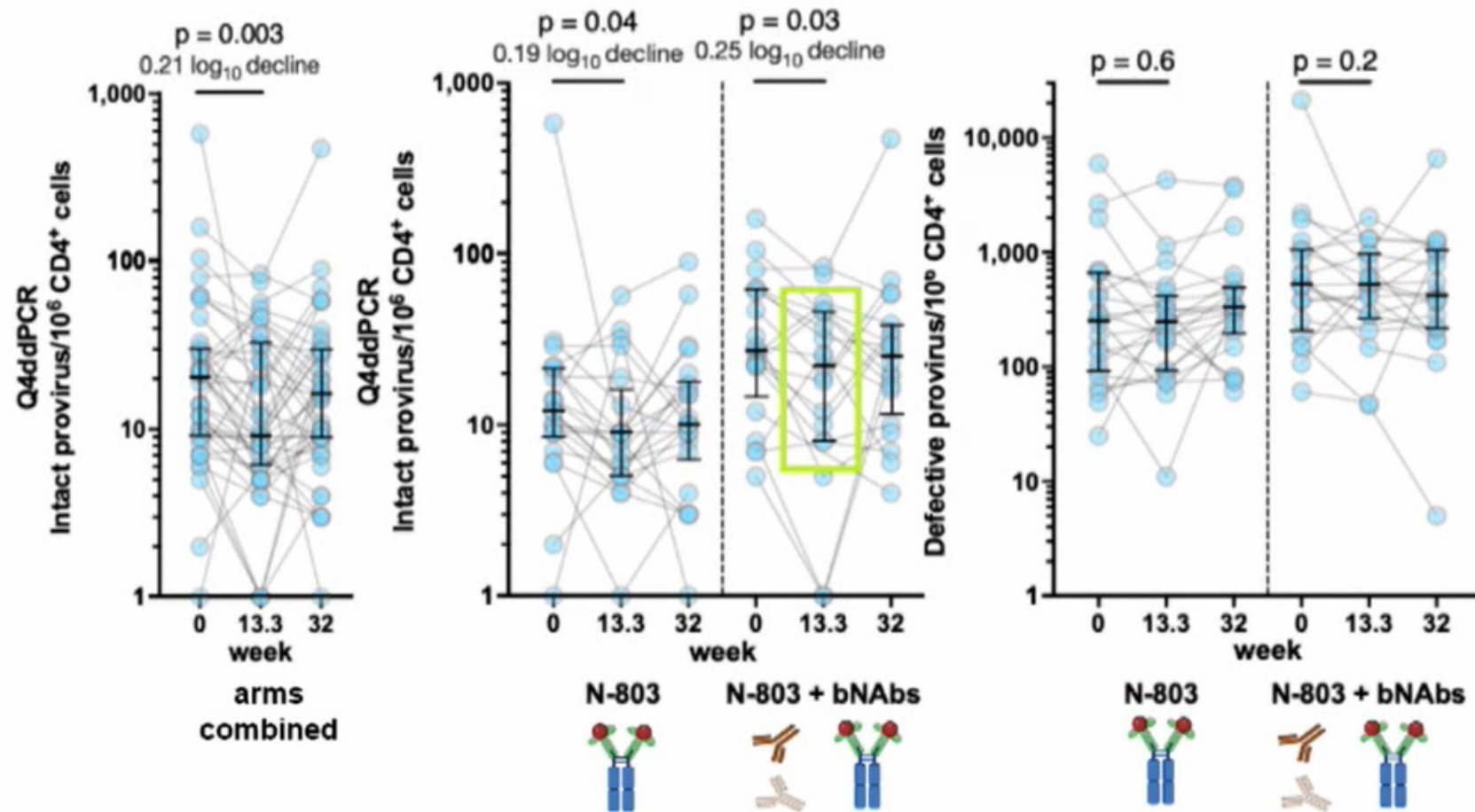
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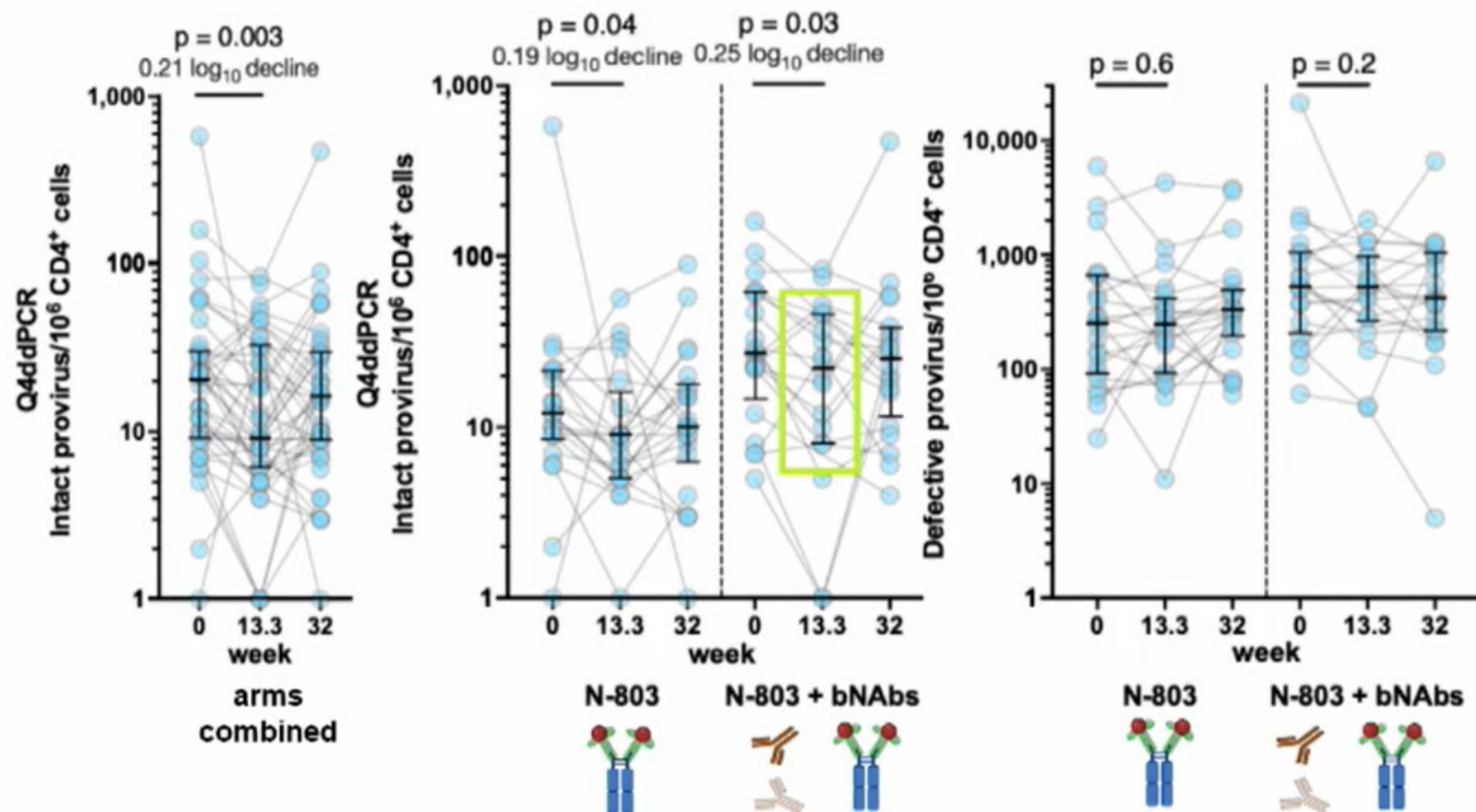
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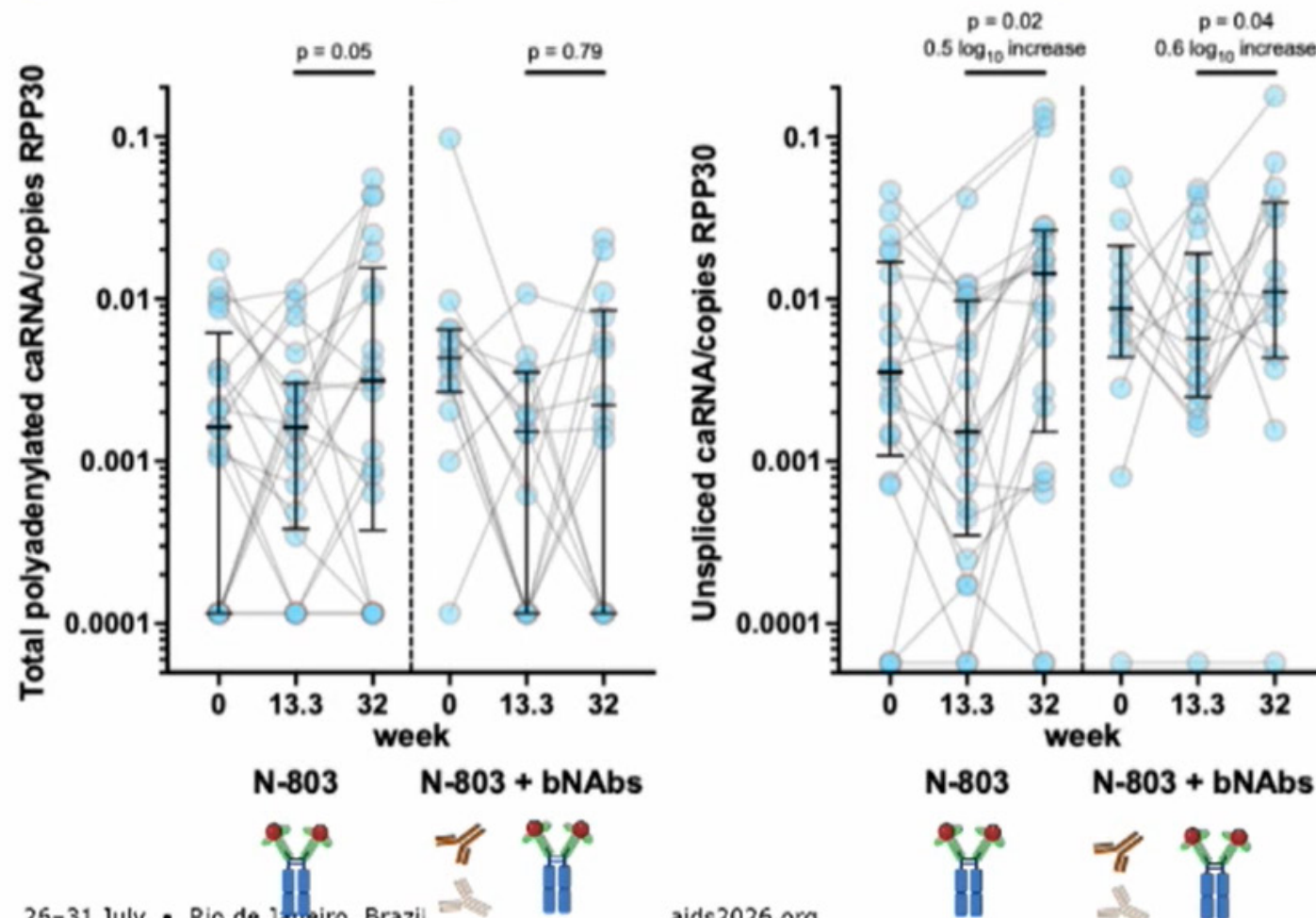
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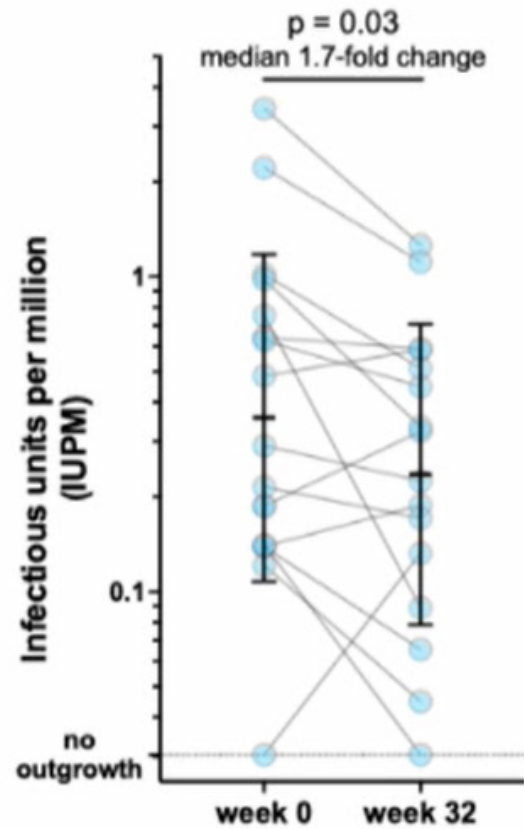
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- **and slope of viral rebound** (Spearman $r = 0.8$, $p = 0.001$, $\beta = 0.64$, $p = 0.02$, $R^2 = 0.33$)

Transcriptional activity follows intact proviral dynamic (n = 35)



- HIV transcripts drop along with intact proviral DNA
- Rebound in transcripts after completion of N-803 dosing

Reduction in the inducible reservoir after N-803 (n = 16, N-803 arm)



- Median 1.7-fold reduction in viral outgrowth after N-803 dosing in 12/16 participants

N-803

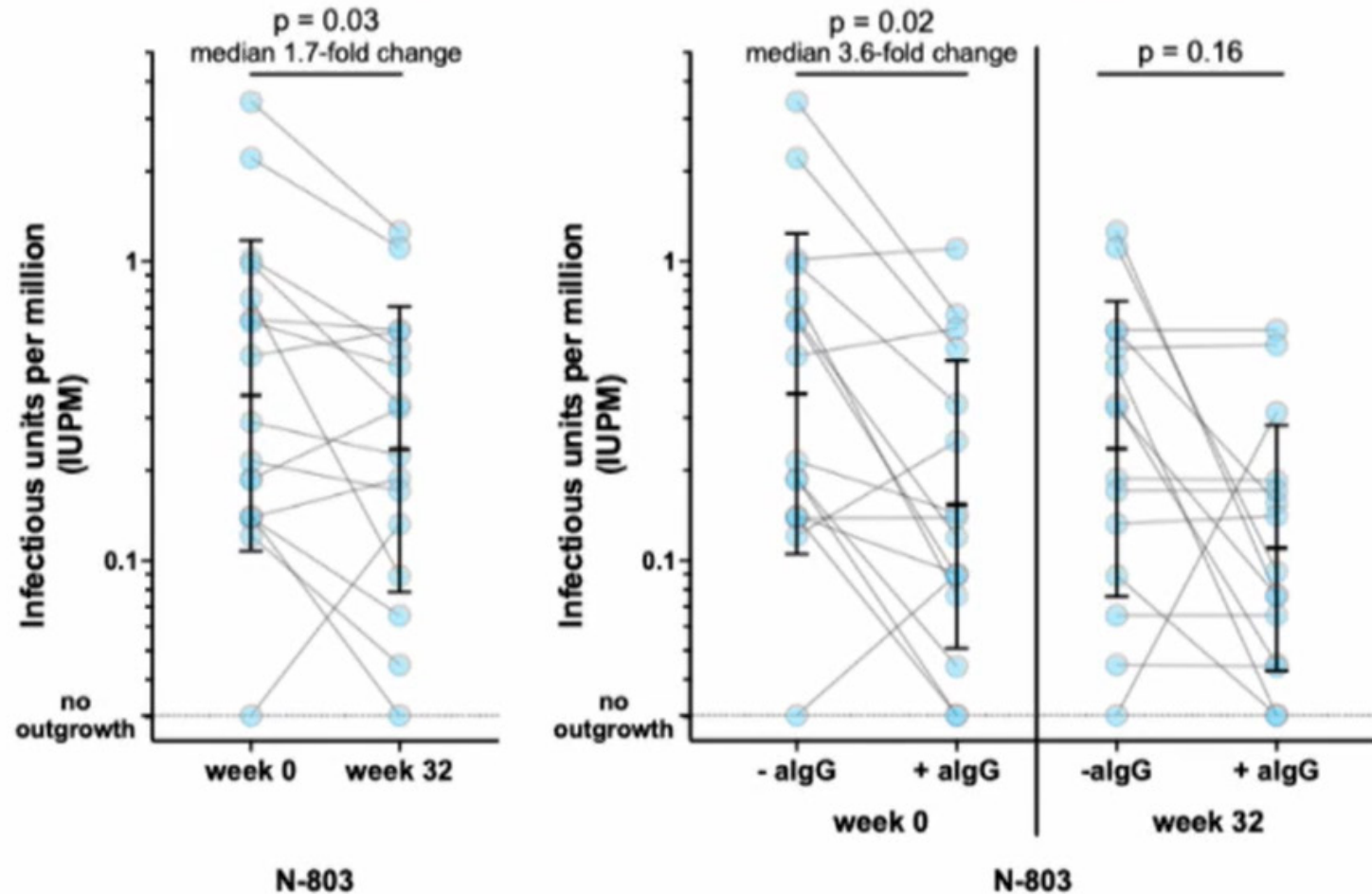
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Medians + IQR

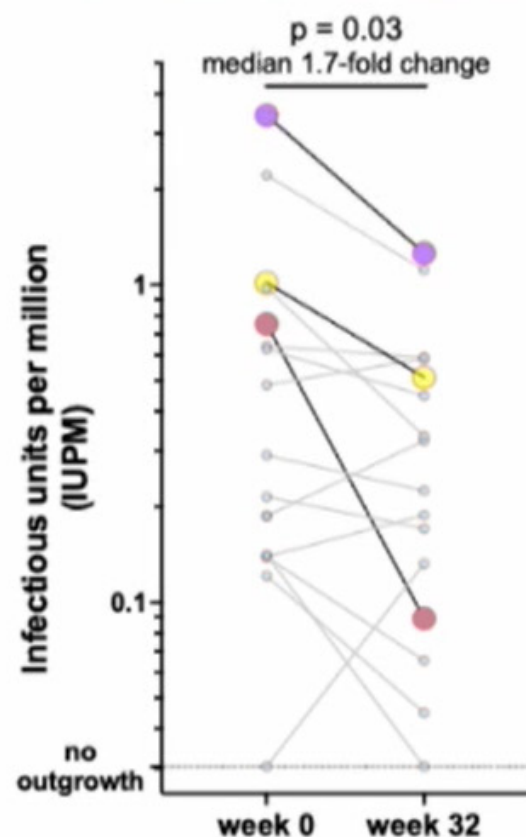
algG = post-intervention autologous IgG

Reduction in the inducible reservoir after N-803 (n = 16, N-803 arm)



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N-803

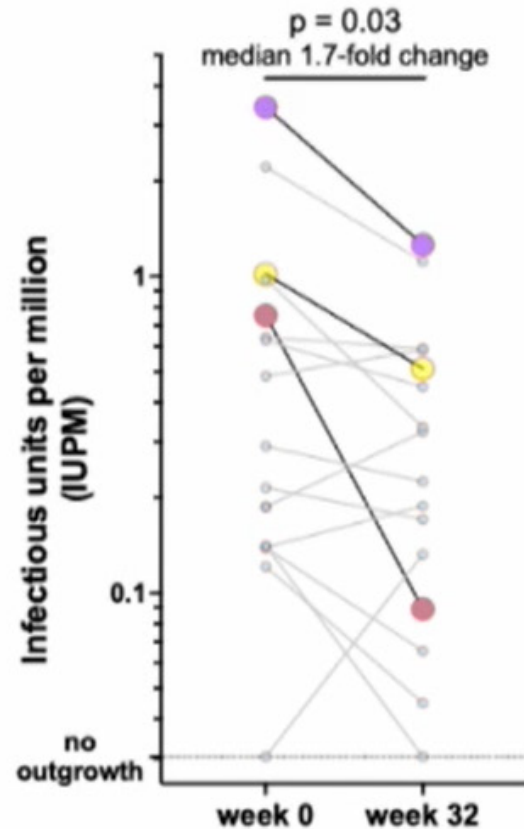
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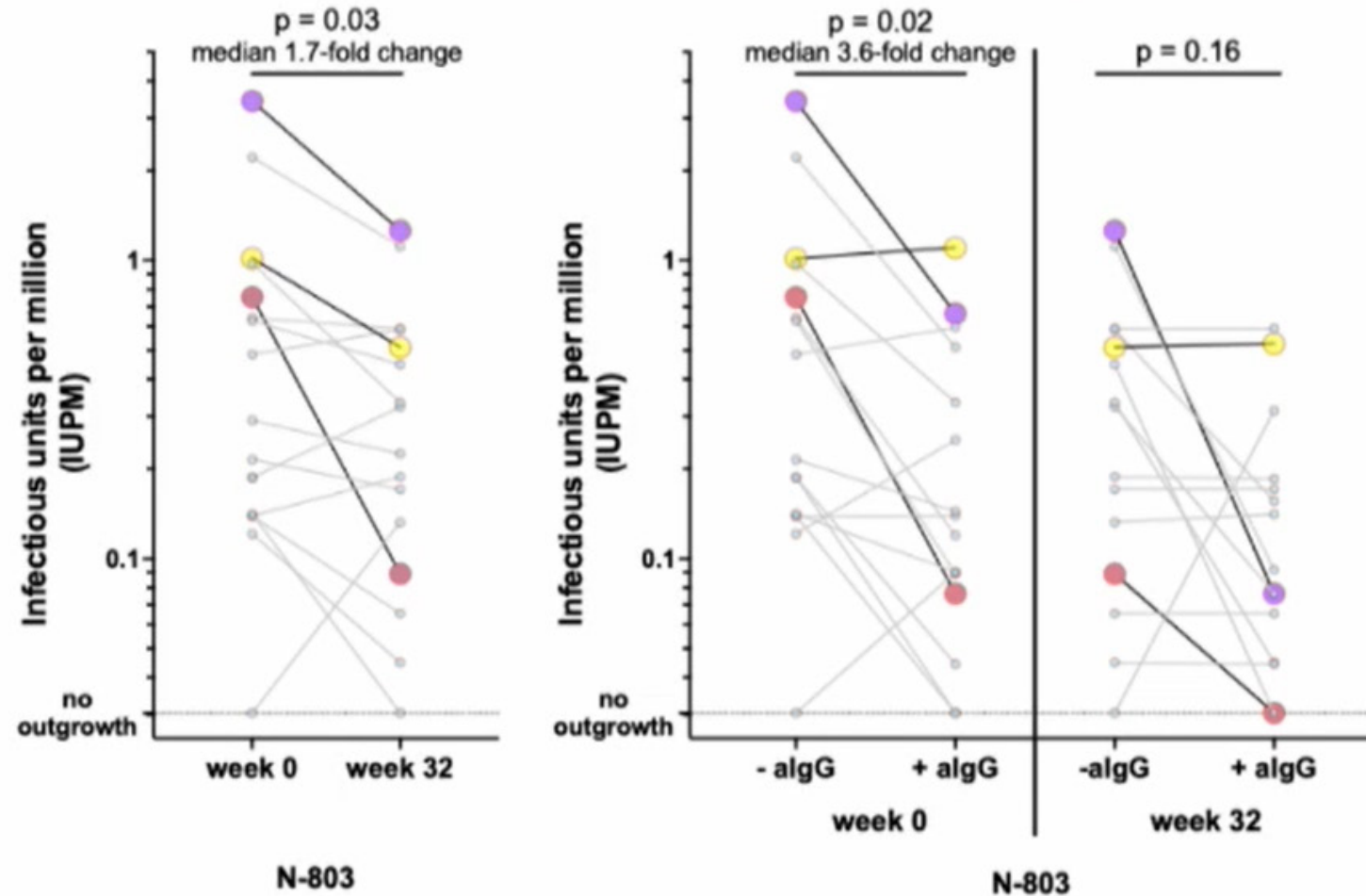
N-803

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Reduction in the inducible reservoir after N-803 (n = 16, N-803 arm)



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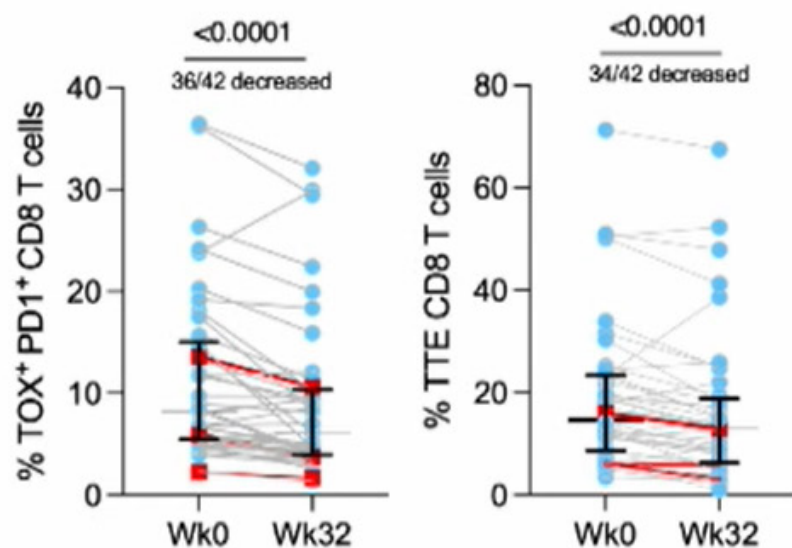
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- Median 1.7-fold reduction in viral outgrowth after N-803 dosing in 12/16 participants
- Strong neutralization by post-intervention IgG against pre-intervention reservoir outgrowth
- Post-intervention controllers (PIC) show stronger reduction in viral outgrowth (2- to 8.5-fold)
- 2/3 PIC tested show exceptionally strong neutralization (5- to 10-fold)

CD8 shift towards stem-like phenotypes and increase in polyfunctional responses

Decrease in exhausted profile



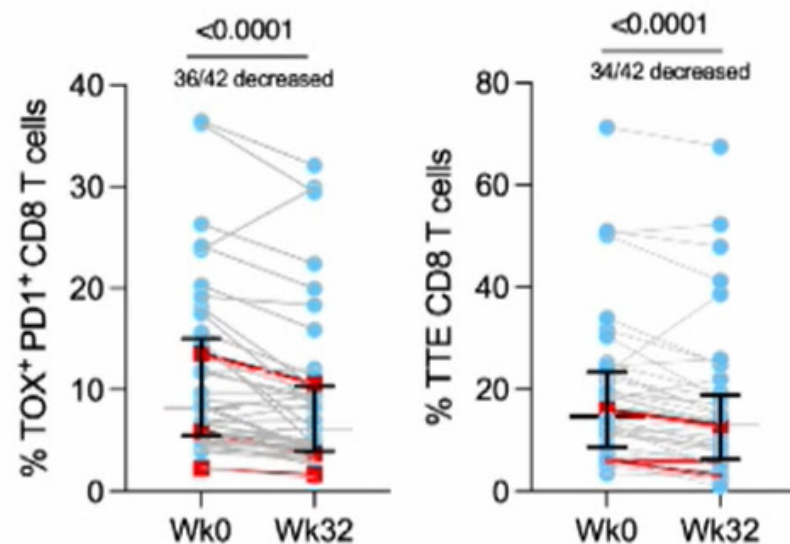
— Post-intervention controllers

Medians + IQR

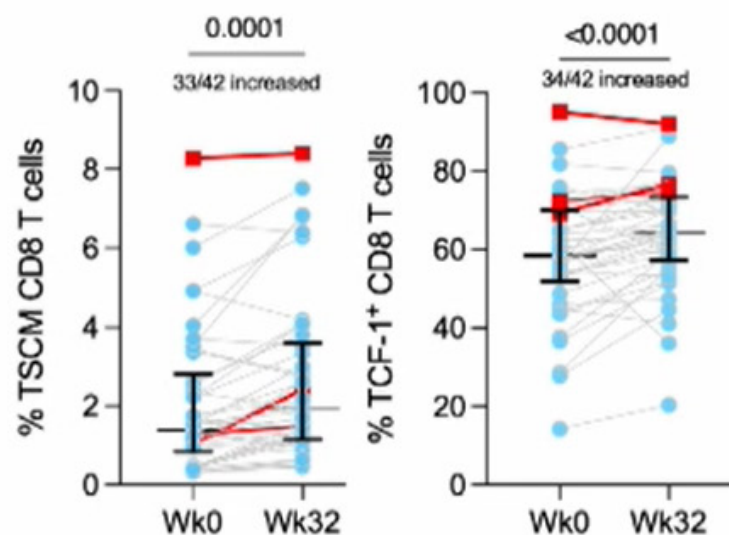


CD8 shift towards stem-like phenotypes and increase in polyfunctional responses

Decrease in exhausted profile



Increase in stem-like profile



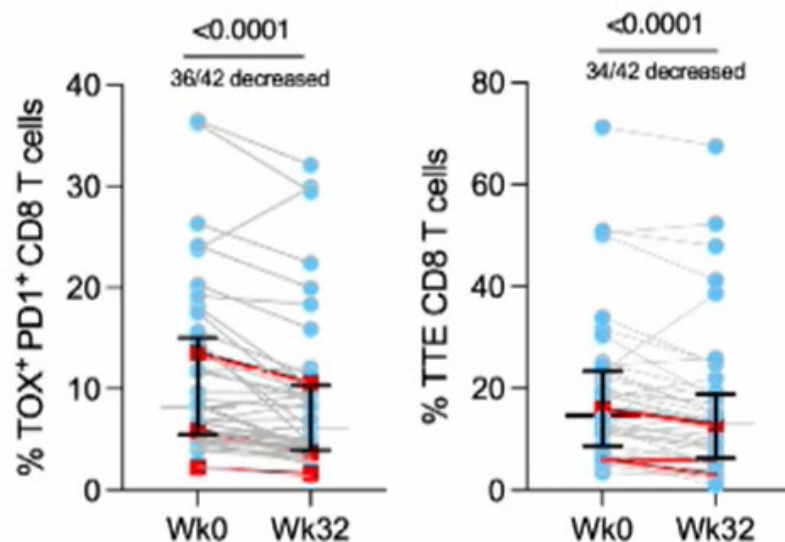
— Post-intervention controllers

Medians + IQR

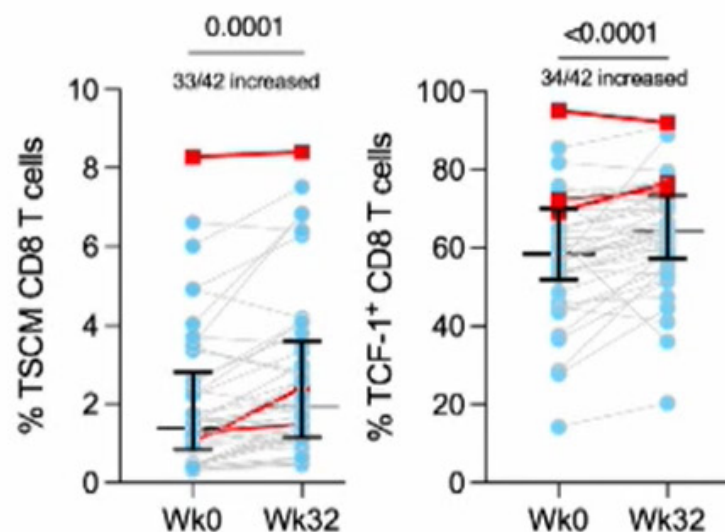


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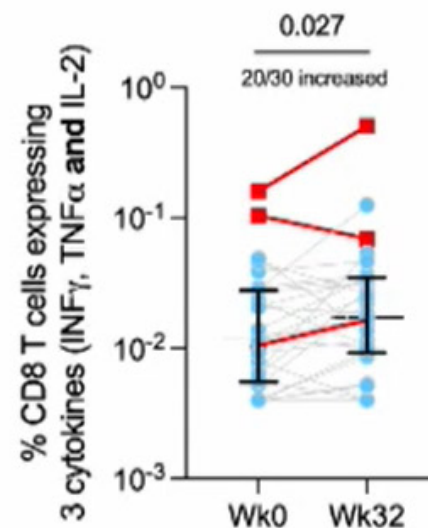
Decrease in exhausted profile



Increase in stem-like profile



Polyfunctional HIV specific CD8

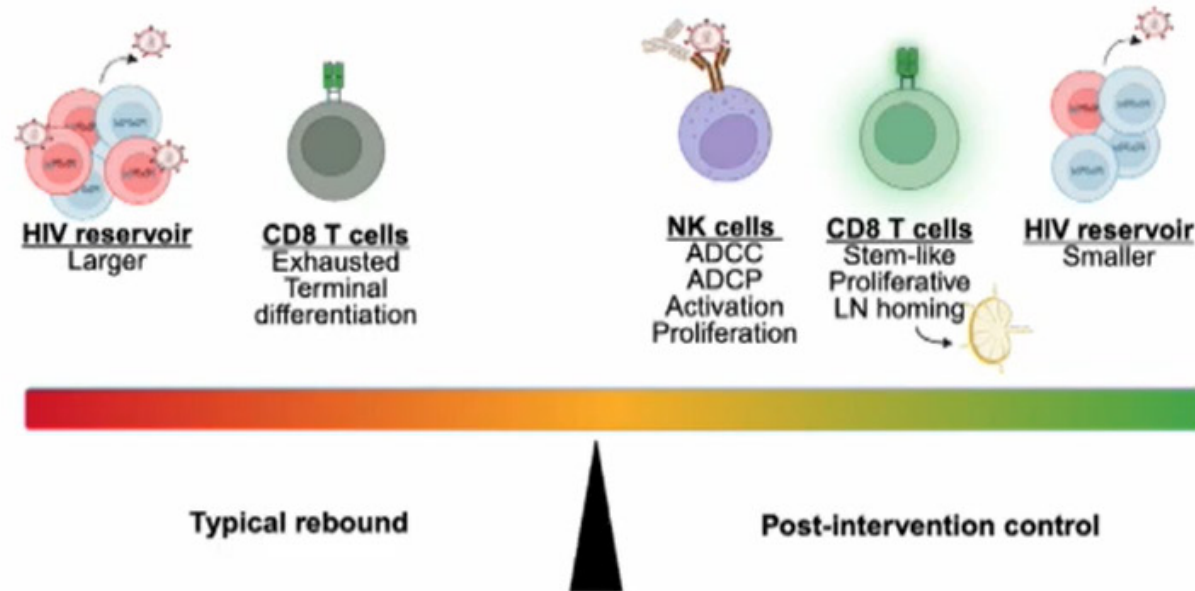


— Post-intervention controllers

Medians + IQR



Summary



1. N-803 ± bNAbs was safe, generally tolerated
2. 4 (11%) of participants controlled HIV at 8 weeks after stopping ART treatment (<200 copies/mL)
3. At least 5 (14%) participants remained off ART for ≥ 20 weeks
4. N-803 potentially delayed viral rebound

Writer - Note – build was interrupted after point 4, as pop-up appeared. Will need to review and finish this last slide



Schematic by Itzayana Miller