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Impact of 10-1074LS and 3BNC117LS on viral rebound dynamics following treatment interruption six months after dosing:

Early results from the open label arm of the RIO trial

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CONFLICTS OF INTEREST

The speaker is a recipient of the UK Medical Research Council Clinical Research Training Fellowship award.
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MC0

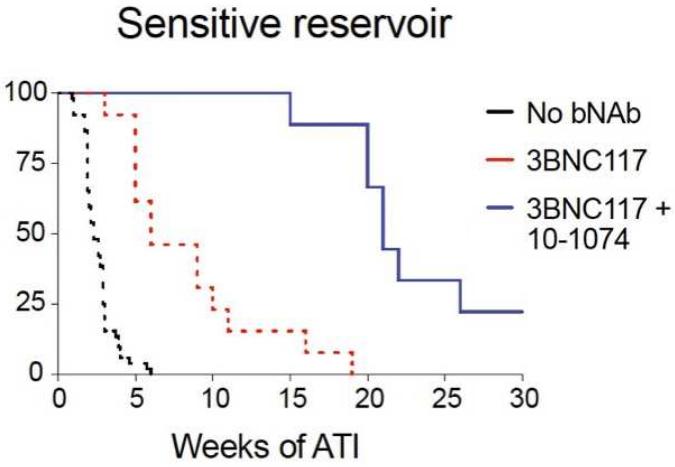
HIV-specific broadly neutralising antibodies (bNAbs) therapy are associated with prolonged ART-free viral suppression

- 3BNC117 and 10-1074 maintained ART-free viral suppression for a median of 21 weeks.

- Long-acting variants using the LS Fc mutation increase half lives by up to four-fold (Caskey CROI 2022)
  - 3BNC117LS: $t_{1/2}$ = 67 days
  - 10-1074LS: $t_{1/2}$ = 80 days

- bNAbs 3BNC117 and 10-1074 maintain viral control at thresholds of serum concentrations above 10µg/ml

(Mendoza et al. Nature 2018, Gaebler et al. Nature 2022)



Mendoza et al. Nature 2018

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Diapositive 3

MC0 We know the LS antibodies have extended half-lives from our first in human studies. Consider re-phrasing as suggested in the slide.

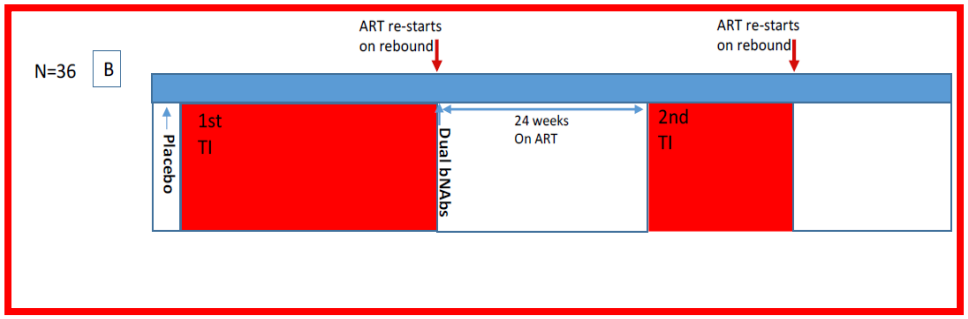
Marina Caskey; 2022-12-06T22:02:28.658

The RIO study

- Phase 2b randomised placebo-controlled trial of long-acting bNAbs 10-1074LS and 3BNC117LS in people diagnosed and treated in early HIV infection.

- bNAbs dosing
  - 3BNC117LS: 30mg/kg
  - 10-1074LS: 10mg/kg

- Early results from participants receiving the open labelled bNAbs are presented today



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Methods

- Participants are monitored until they meet one of the following ART restart criteria
  - **HIV viral load >1000 copies/ml for 6 weeks**
  - **HIV viral load >100 000 copies/ml for 2 consecutive readings a week apart**
  - CD4 count <350 cells/µL
  - Any clinical symptoms, safety or HIV transmission concerns related to ATI
  - Participant preference to restart ART

- Serum bNAb concentrations are measured at regular intervals, using a validated anti-idiotype ELISA.

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Results

- Four participants have entered the 2nd ATI stage to date, all male
- Mean age 39 years (range 26 – 52 years)
- Median time from HIV diagnosis to study enrolment = 6.5 years (range 4 – 10 years)
- All participants had serological evidence of seroconversion at diagnosis and had started ART within 3 months of diagnosis.
- All participants had no evidence of resistance mutations to 10-1074 on baseline screening

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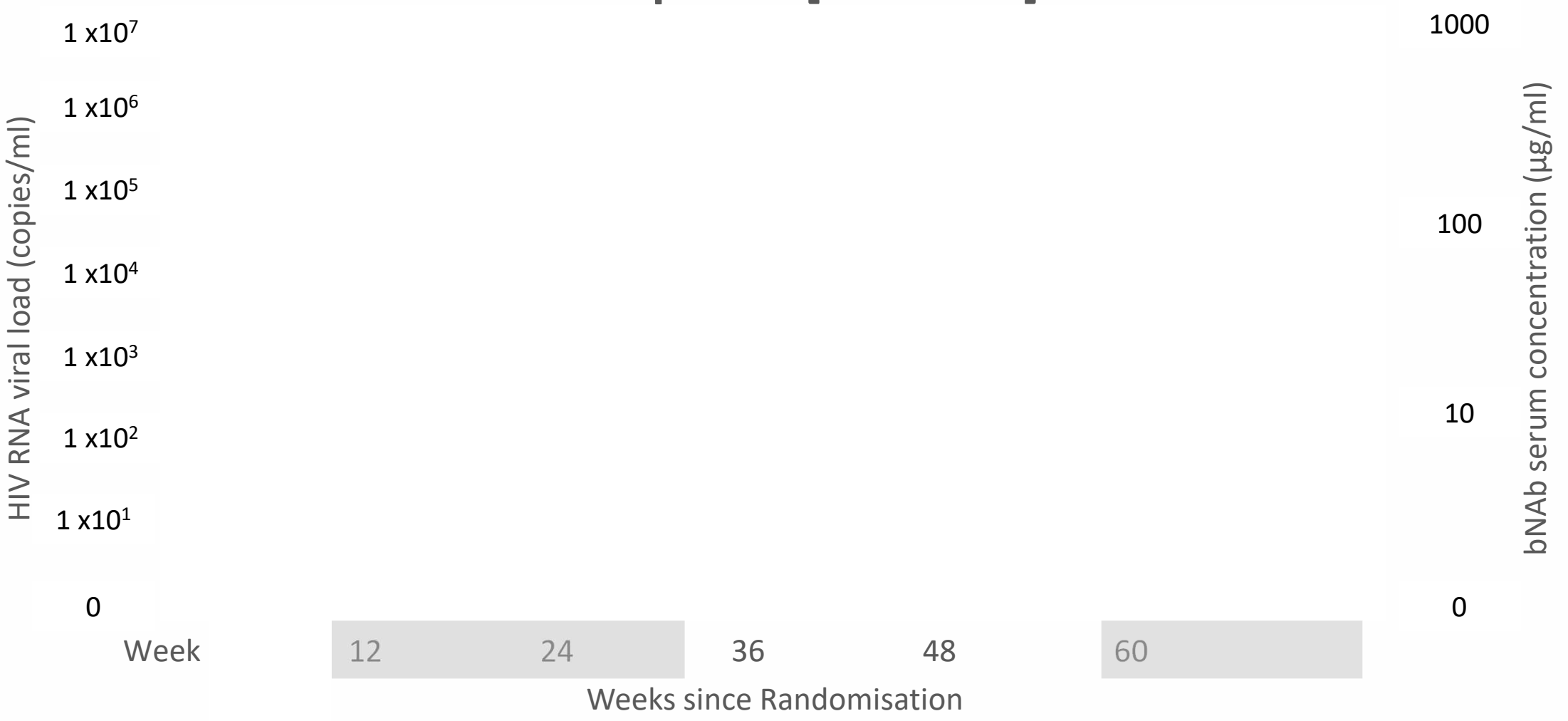
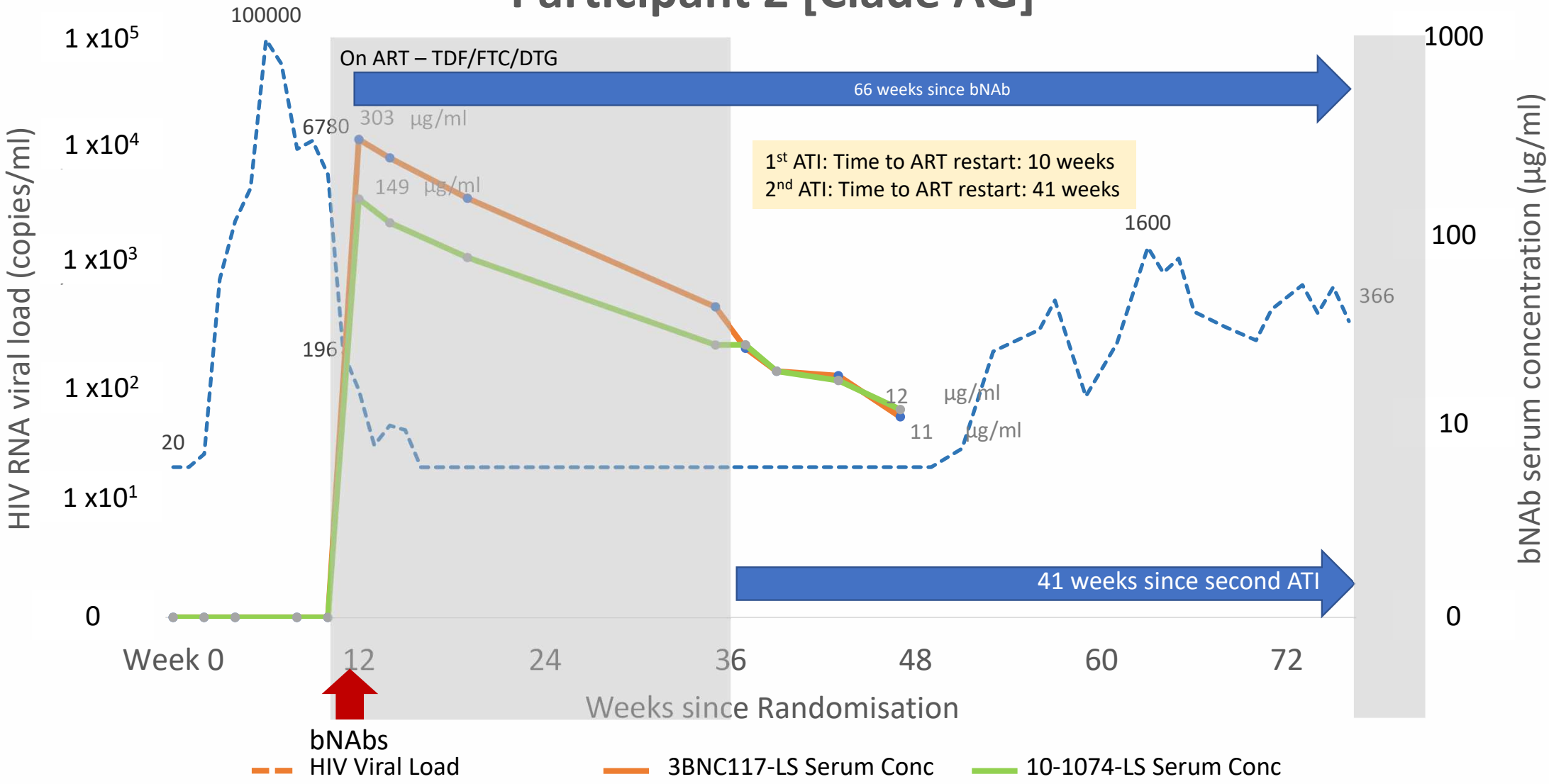
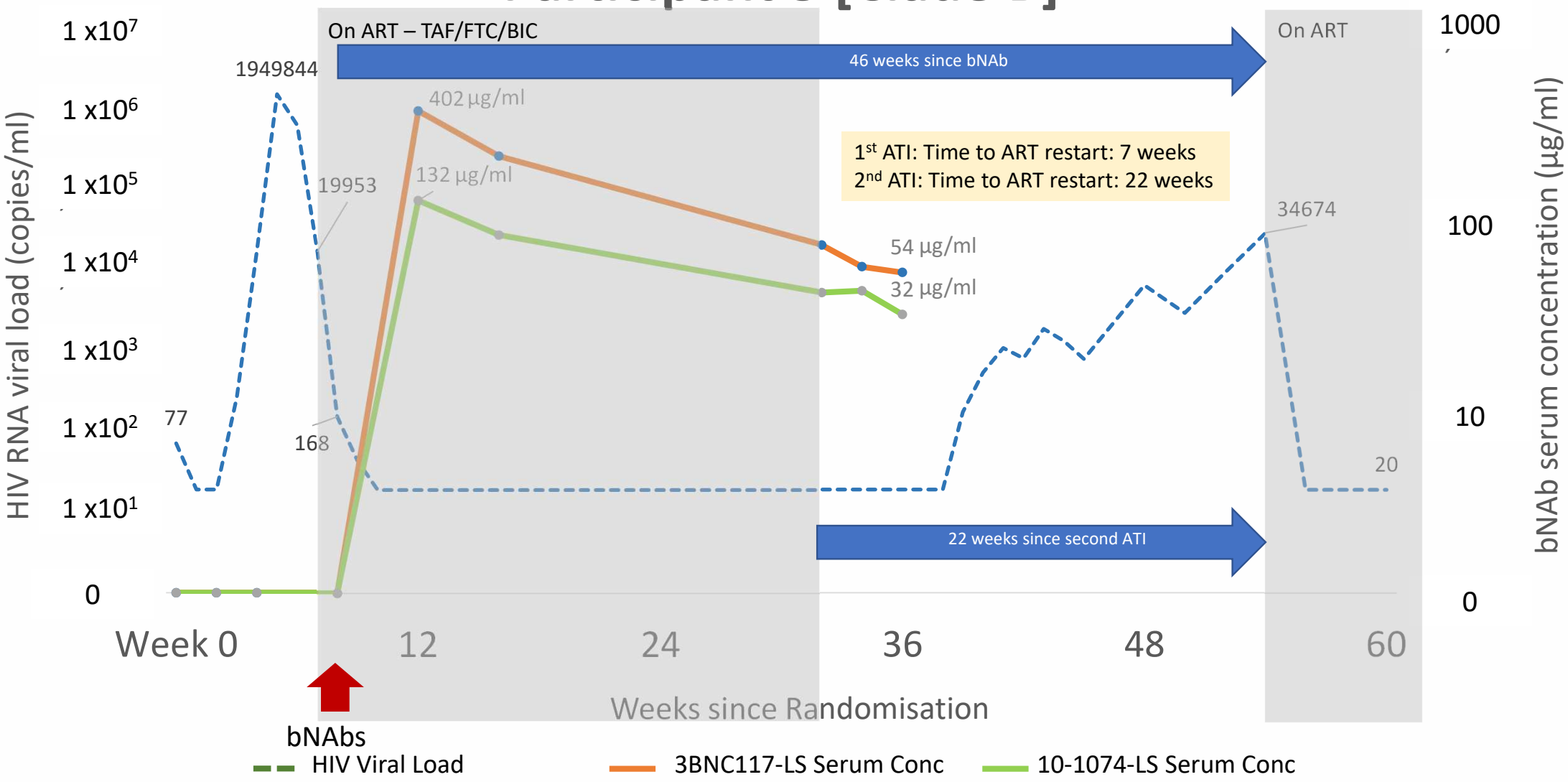
Participant 1 [Clade AG]



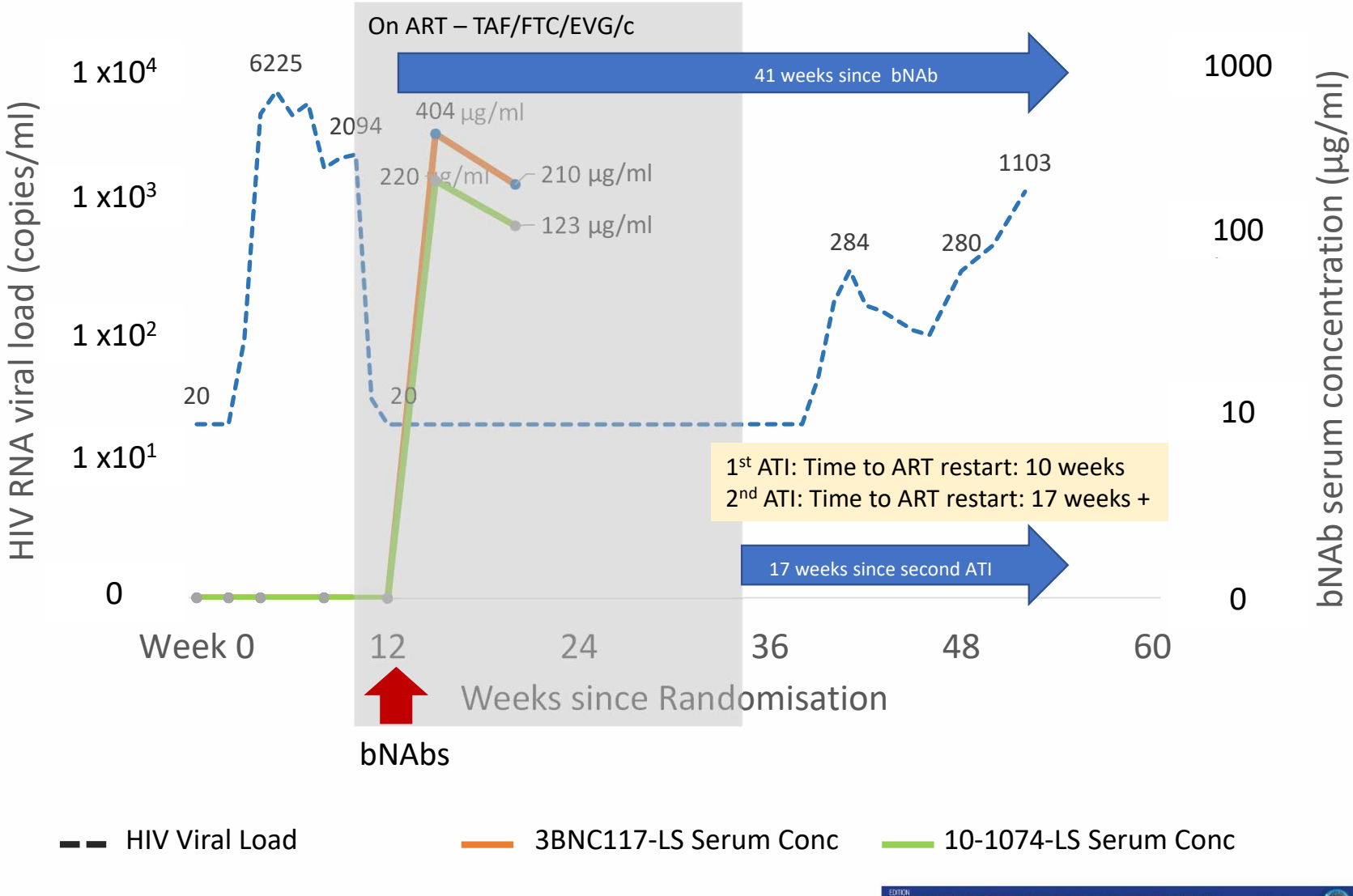
Participant 2 [Clade AG]



Participant 3 [Clade B]



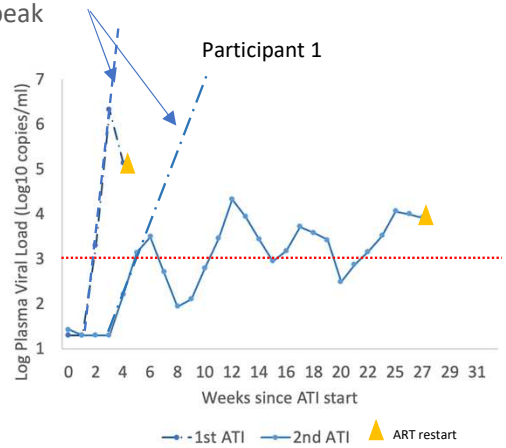
Participant 4 [Clade B]

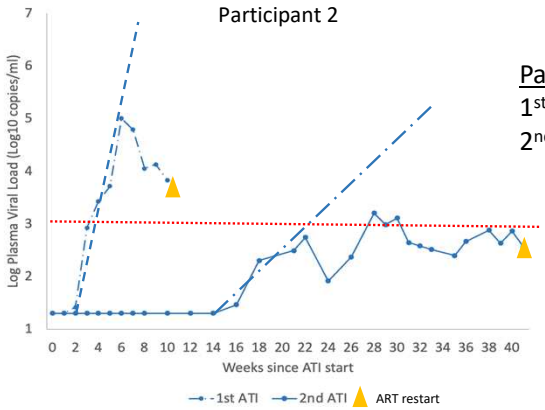


Time to viral rebound was delayed in all four participants

Rate of viral rebound to 1st peak

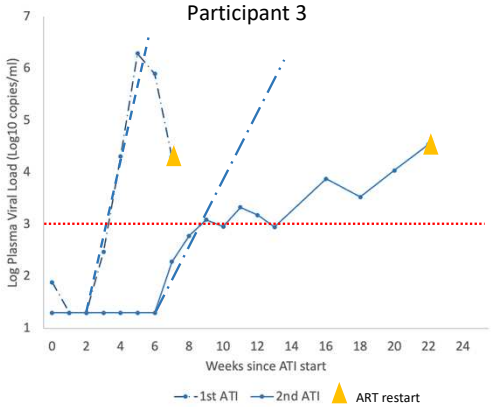
<u>Participant 1</u>
1st ATI: Time to VL>1000 - 2 weeks
2nd ATI: Time to VL>1000 - 5 weeks

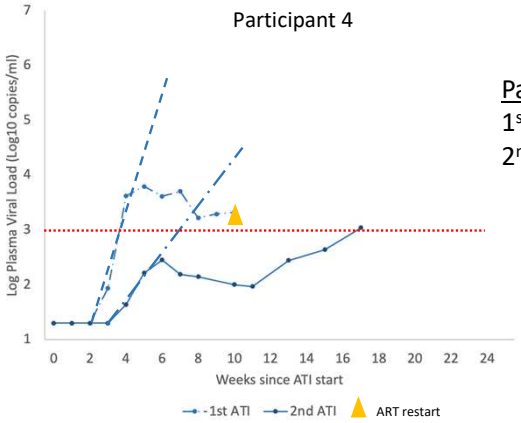




<u>Participant 2</u>
1st ATI: Time to VL>1000 - 4 weeks
2nd ATI: Time to VL>1000 - 28 weeks

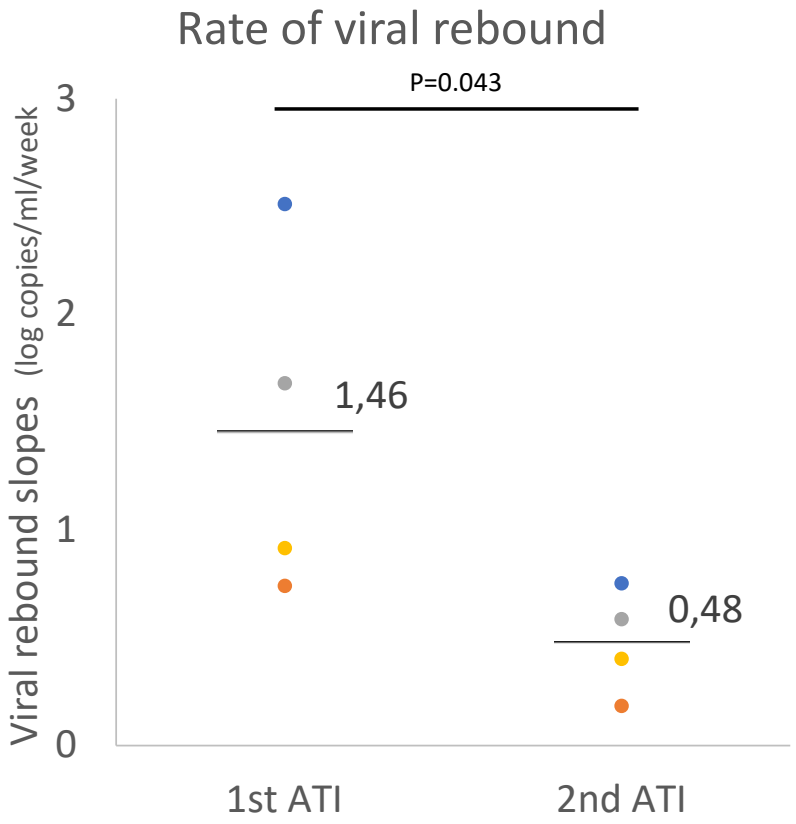
<u>Participant 3</u>
1st ATI: Time to VL>1000 - 4 weeks
2nd ATI: Time to VL>1000 - 9 weeks





<u>Participant 4</u>
1st ATI: Time to VL>1000 - 4 weeks
2nd ATI: Time to VL>1000 - 17 weeks

Rates of viral rebound and peak viral rebound was lower during the second treatment interruption compared to the first



* Participant 4 has not restarted ART at time of analysis

Discussion

- Single infusion of combination 10-1074LS and 3BNC117LS at ART restart resulted in serum concentrations >10µg/ml six months after dosing in all three participants with PK results available during the 2nd ATI

- All four participants lost viral control from undetectable levels after the second ATI, but viral rebound appears slower and delayed compared to the first ATI

- Limitations: small sample size, preliminary nature of analysis, incomplete PK results to date may limit generalisability of results

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- **Key question(s)** : Do people living with HIV who stopped ART and received bNAbs, experience viral rebound differently after stopping ART again 6 months later?

- **Key finding(s):**

  - bNAb levels remained above the previously reported treatment threshold in blood, after 6 months following bNAb infusion and ART restart.

  - Participants who stopped treatment again 6 months after bNAbs infusion eventually experienced viral rebound, but with slower rebound and lower peak viral loads compared to their initial viral rebound on placebo.

With Thanks!

All the RIO study participants

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Questions?

Impact of previous TI on subsequent viral control

- ACTG5068 showed a 0.63 log difference in peak VL in those who had prior structured treatment interruption. (Jacobson et al. J Infect Dis 2006)
- Similar studies by Fagard et al (Arch Int Med 2003), and Oxenius (PNAS 2002) did not show substantial differences in viral control following STI.
- Kaufman et al (PLOS med 2004) reported no consistent effect on serial STIs on subsequent viral control, but transient viral control <5000cp/ml was observed.
- Overall, there may be a small impact on previous TIs on viral control seen in subsequent ATIs, but not to the degree seen in these four participants.

Table 2 Comparison of virological parameters in the non–structured treatment interruption (STI) arms vs. the STI ...

Parameter	Non-STI arms A and C (n = 43)[a]	STI arms B and D (n = 40)[b]	P
End of ATI VL, $\log_{10}$ copies/mL	4.40 (3.81 to 4.88)	4.15 (3.00 to 4.58)	.017[c]
Equilibrium VL, $\log_{10}$ copies/mL	4.37 (4.07 to 4.80)	4.10 (3.29 to 4.43)	.028[c]
Peak VL, $\log_{10}$ copies/mL	5.36 (4.58 to 5.79)	4.73 (4.07 to 4.91)	.0002[c]
Postpeak VL low, $\log_{10}$ copies/mL	4.10 (3.47 to 4.52)‘	3.76 (2.51 to 4.28)	.039[c]
Initial VL rise rate, $\log_{10}$ copies/mL increase per week	1.08 (0.71 to 1.68)	0.85 (0.58 to 1.14)	.009[c]
Doubling time, days	1.95 (1.25 to 2.96)	2.48 (1.85 to 3.63)	
Initial decline rate, $\log_{10}$ copies/mL decrease per week	−0.58 (−1.10 to −0.32)	−0.46 (−0.65 to −0.23)	.059[c]
Time to VL >50 copies/mL, days	21 (13 to 30)	15 (8 to 31)	.94[c]
Time to peak VL, days	44 (34 to 58)	56 (35 to 70)	.27[c]
Time to VL equilibrium, days	54 (42 to 75)	47 (23 to 67)	.29[c]
End-of-ATI VL <1000 copies/mL, ITT, no. (%)	3 (6)[d]	10 (21)[e]	.040[f]
End-of-ATI VL <1000 copies/mL, Obs, no. (%)	3 (7)	10 (25)	.034[f]

NOTE. Data are median (interquartile range) values, unless otherwise indicated. ATI, analytical treatment interruption; ITT, intent-to-treat data; Obs, observed data only; VL, viral load.

[a] Only 42 subjects were included in the peak VL, and 39 subjects were included in the postpeak VL low and initial decline rates.

[b] Only 39 subjects were included in the peak VL, and 38 subjects were included in the postpeak VL and initial decline rates.

[c] Wilcoxon rank sum test.

[d] A total of 49 subjects were included in the end-of-ATI VL for the ITT analysis of STI arms.

[e] A total of 48 subjects were included in the end-of-ATI VL for the ITT analysis of non-STI arms.

[f] Fisher’s exact test.

Jacobson et al. J Infect Dis 2006