Broadly Neutralizing Antibodies in Cure Strategies: 3BNC117 and 10-1074 Studies

Marina Caskey

The Rockefeller University

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Conflict of Interest Statement

- Gilead Biosciences – Ad-Hoc SAB

Community Slide

➢ Key Questions:

- Can bNAbs maintain viral suppression?
- Can bNAbs decrease the reservoir or improve control of the reservoir by immune responses?

➢ Key Findings:

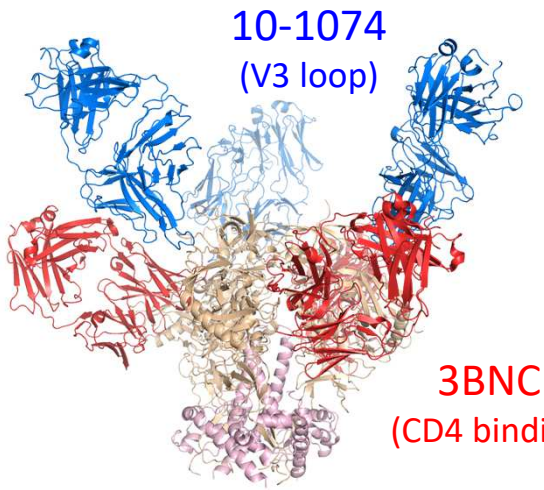
- Combinations of bNAbs can maintain suppression of sensitive viruses
- Early results suggest that bNAbs may:
  - Decrease the reservoir
  - Improve immune responses
- But the effects have not been sufficient to induce ART-free suppression (or control) of viral loads….consistently.

➢ What comes next?

- Samples from completed trials are being studied carefully to better understand the effects
- We plan to evaluate bNAbs in **different study populations** (e.g in sub-Saharan Africa), and to test if **treatment for a longer period of time or in combination with other strategies** that improve immune response have greater effects.

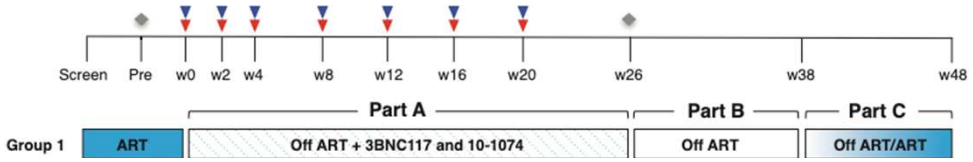
3BNC117 and 10-1074: Clinical experience

- Well-tolerated following SC and IV administration, including repeated doses
- The bNAb combination leads to significant but transient decline in viremia.
- After ART discontinuation, the antibodies maintain viral suppression in individuals with sensitive viruses.
- Across all studies a subset of participants harbored viruses with baseline bNAb resistance.
- The LS variants have > 2-fold longer half-lives than parental antibodies

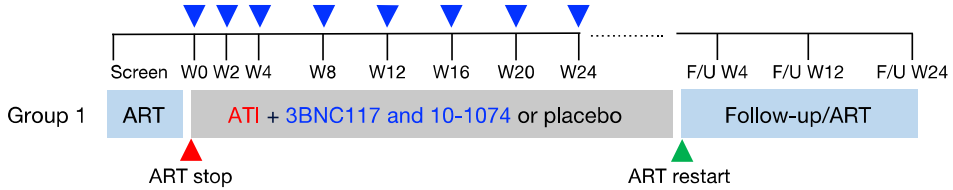


Caskey, Klein, et al. Nature. 2015
Scheid, et al. Nature 2016
Caskey, Schoofs, et al. Nat Med. 2017
Mendoza, et al., Nature 2018
Bar-On, et al., Nat Med. 2018
Cohen, et al., JEM 2018
Cohen, et al., PlosOne 2019
Gaebler, et al., Nature 2022
Sneller, et al., Nature 2022

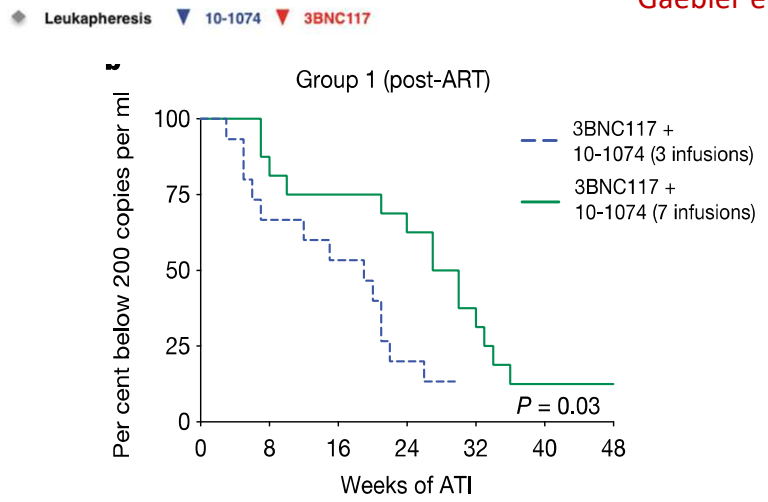
Repeated doses of two bNAbs can maintain suppression of sensitive viruses in the absence of ART

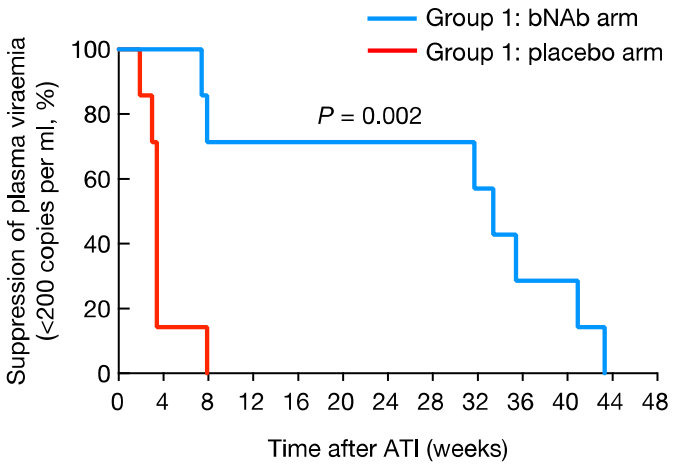


Gaebler et al., 2022



Sneller et al., 2022



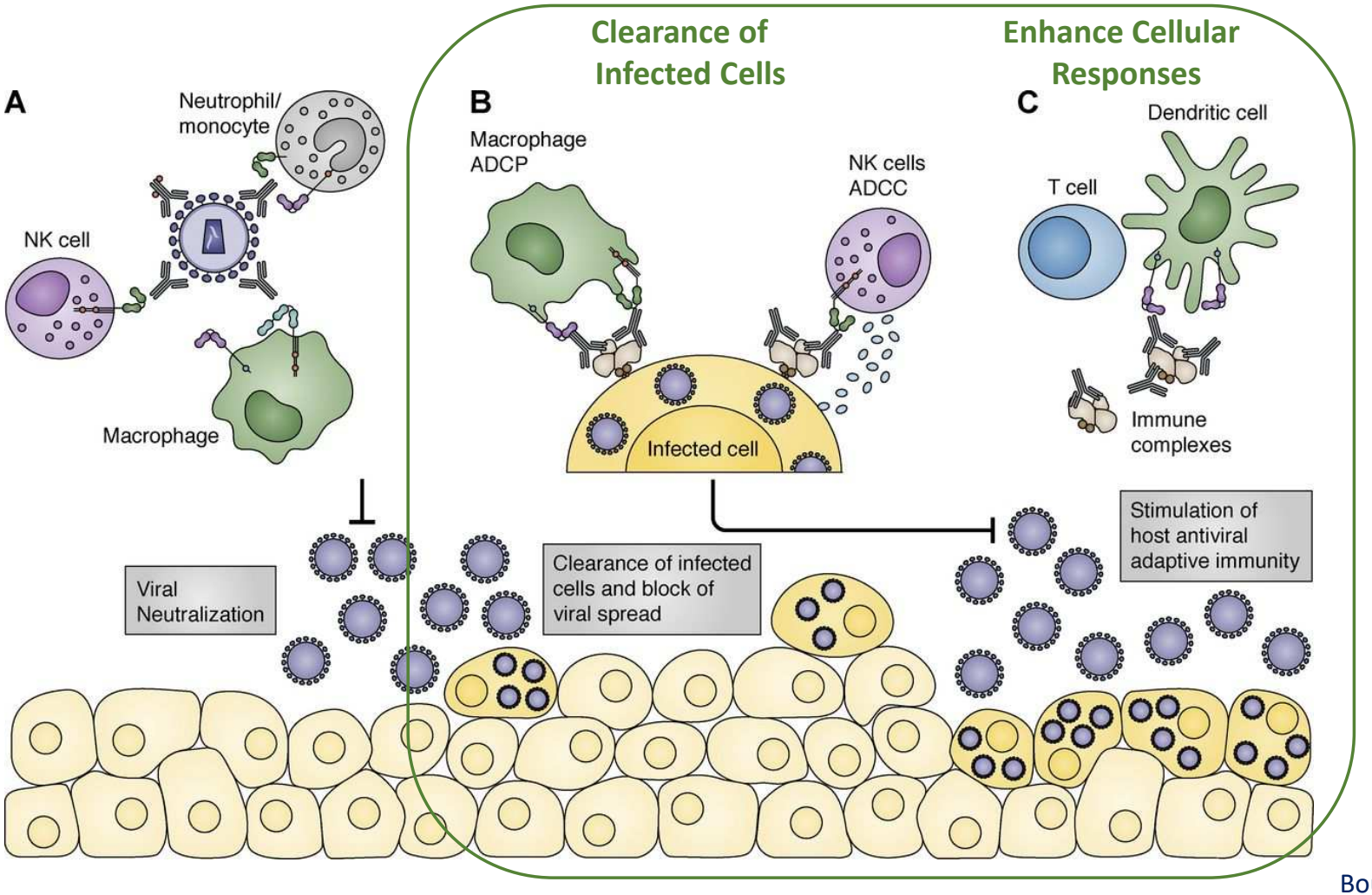


- Participants not screened for sensitivity
  - **13/17 (76%)** ppts maintained VL < 200 cp/ml through the dosing period of 20 weeks.
- **Median time to rebound was 28.5 weeks** (7- > 48 wks)

- **Participants initiated on ART during acute/early HIV**
- Participants not screened for sensitivity
  - 5/7 ppts maintained VL < 40 cp/ml for > 28wks
- **Median time to rebound was 33 weeks (7-43 wks)**

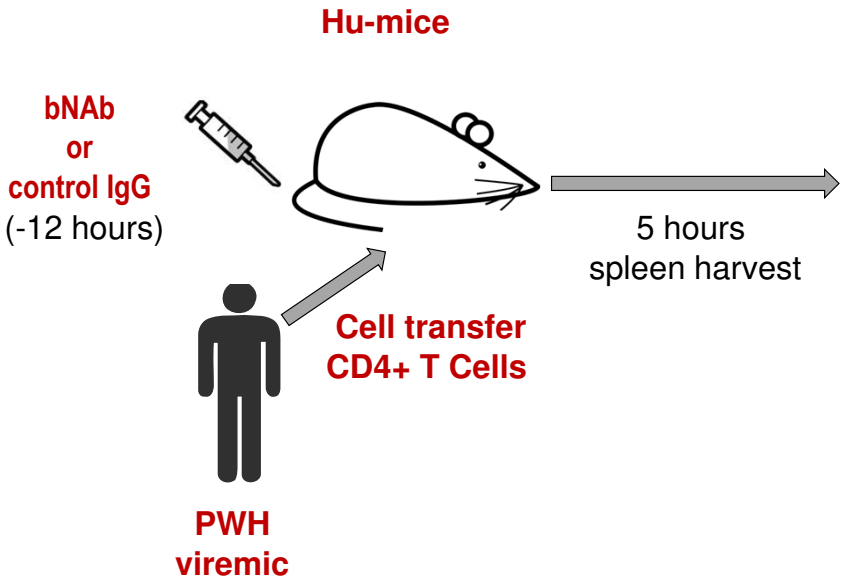
In addition to suppressing viremia, can bNAbs *perturb HIV-1 reservoirs* and *enhance immune responses*?

Antibodies differ from standard ART in their potential to directly eliminate HIV-infected cell and enhance host immune responses

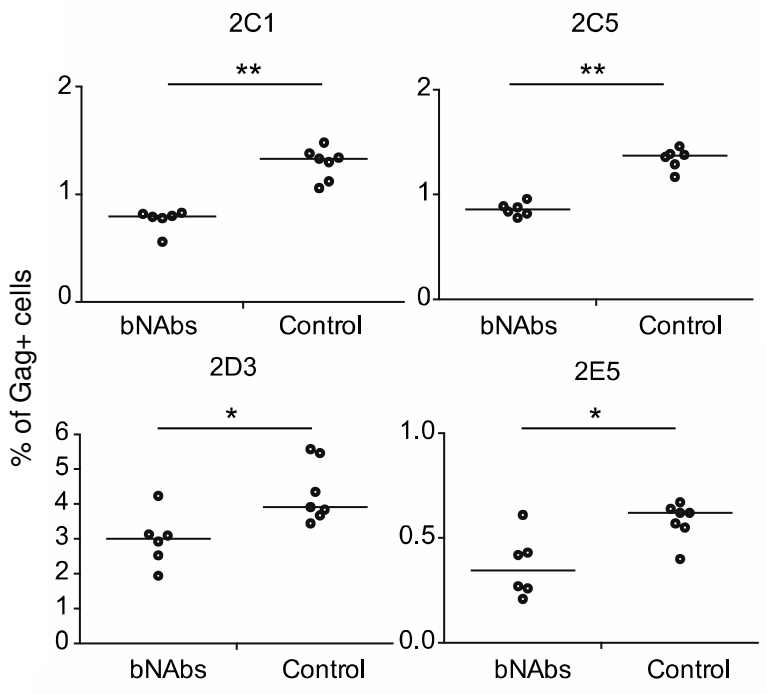


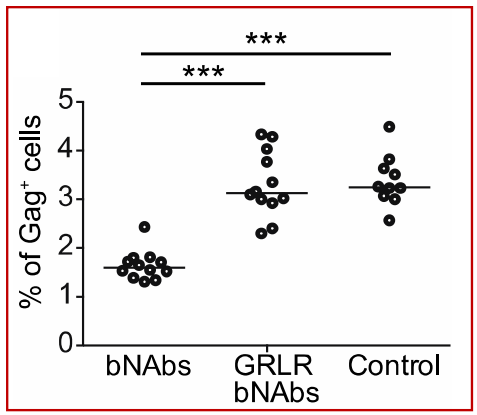
Bournazos et al., 2015

bNAbs accelerate clearance of HIV-infected cells in vivo



*cell suspensions and mice treated with ART to block spread.

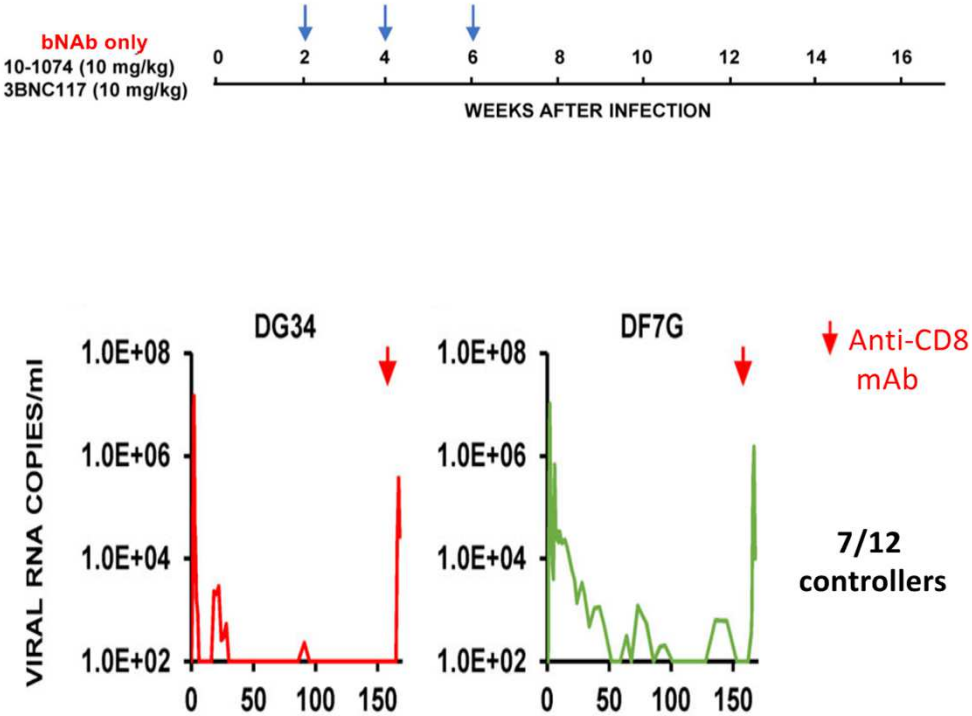




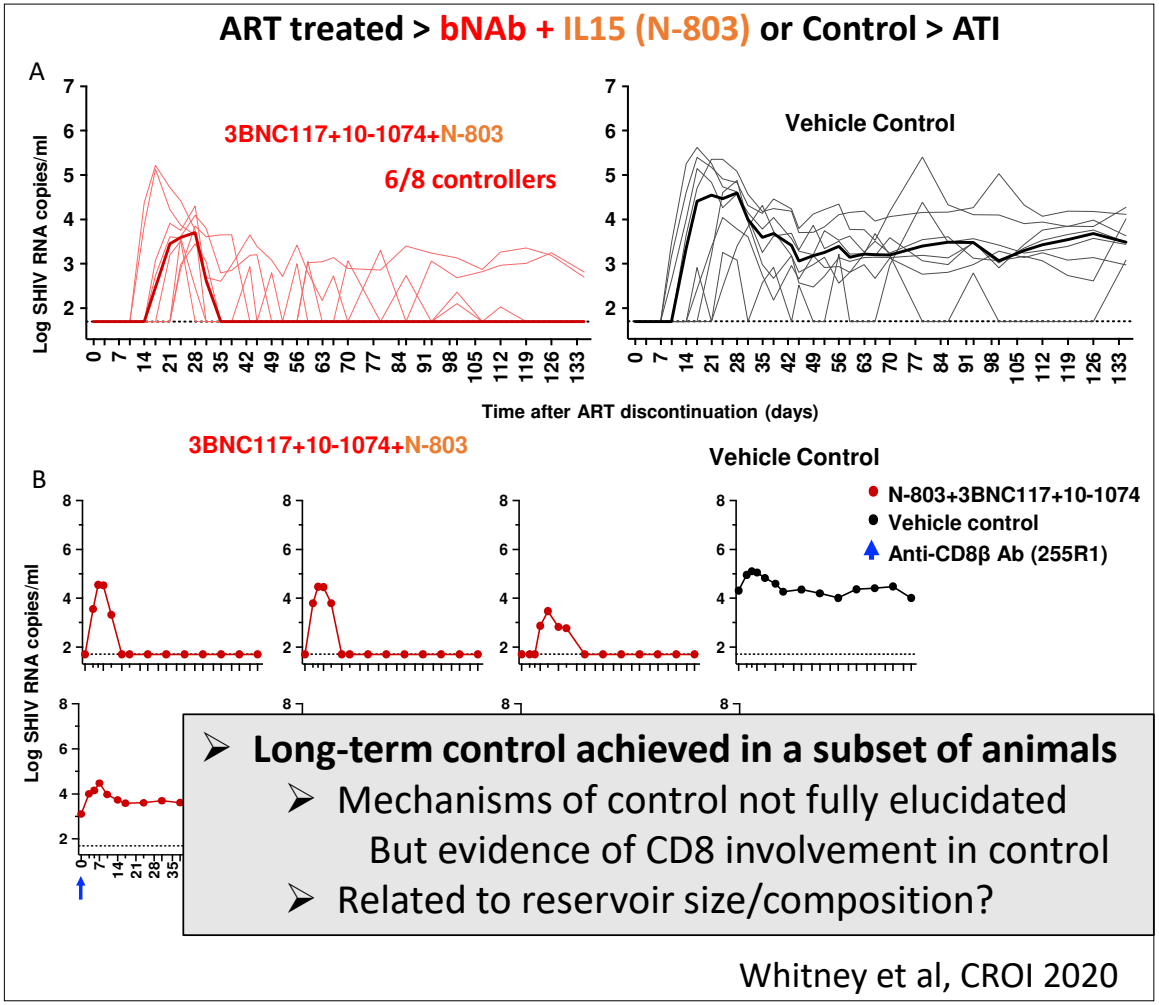
➢ FcgR engagement is required to facilitate clearance of HIV-1-infected cells

Lu et al., Science 2016

bNAb therapy leads to CD8-mediated control of SHIV-AD8$_{EO}$ infection in subset of non-human primates



Nishimura et al, JEM 2020

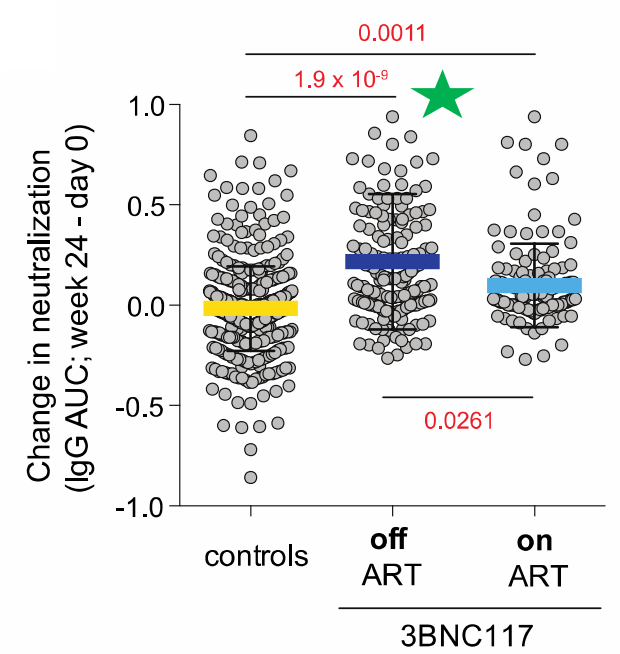


Whitney et al, CROI 2020

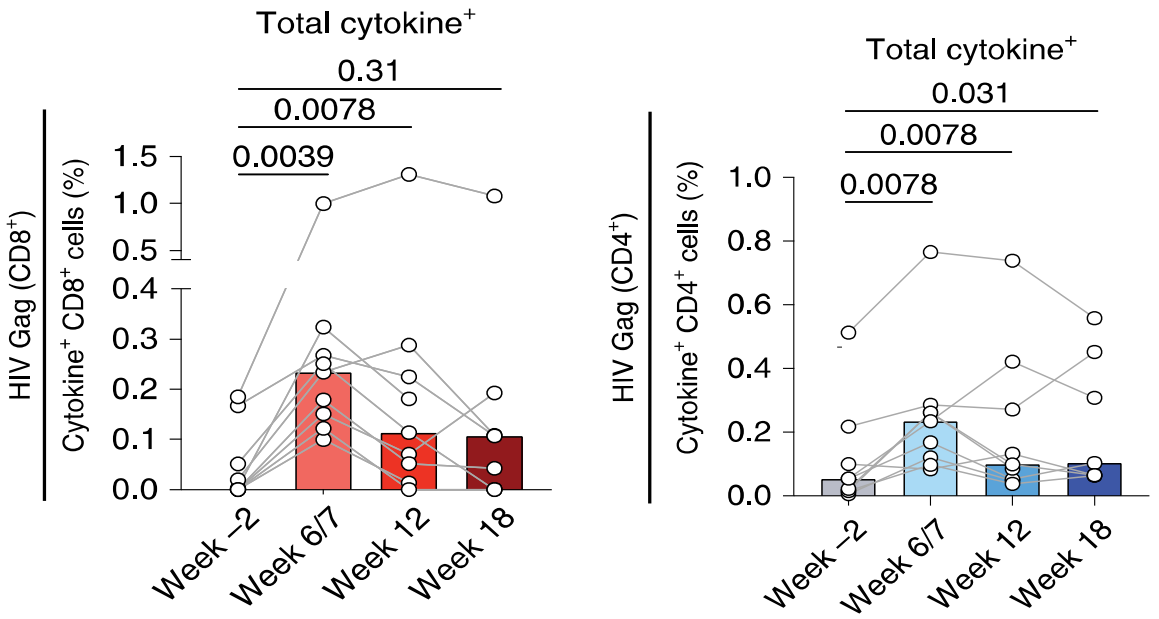
Can bNAbs *perturb HIV-1 reservoirs* and *enhance immune responses* in PLWH?

Enhancement of anti-HIV-1 humoral and cellular immune responses following bNAb therapy

Anti-HIV-1 humoral immune responses evolved following 3BNC117 during viremia



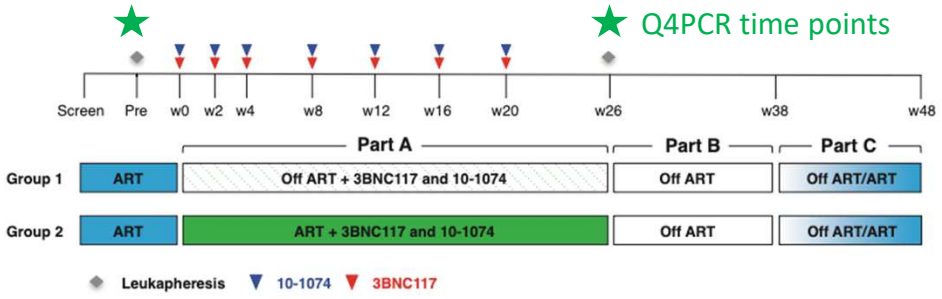
Gag-specific T cell responses were enhanced during bNAb-mediated viral suppression

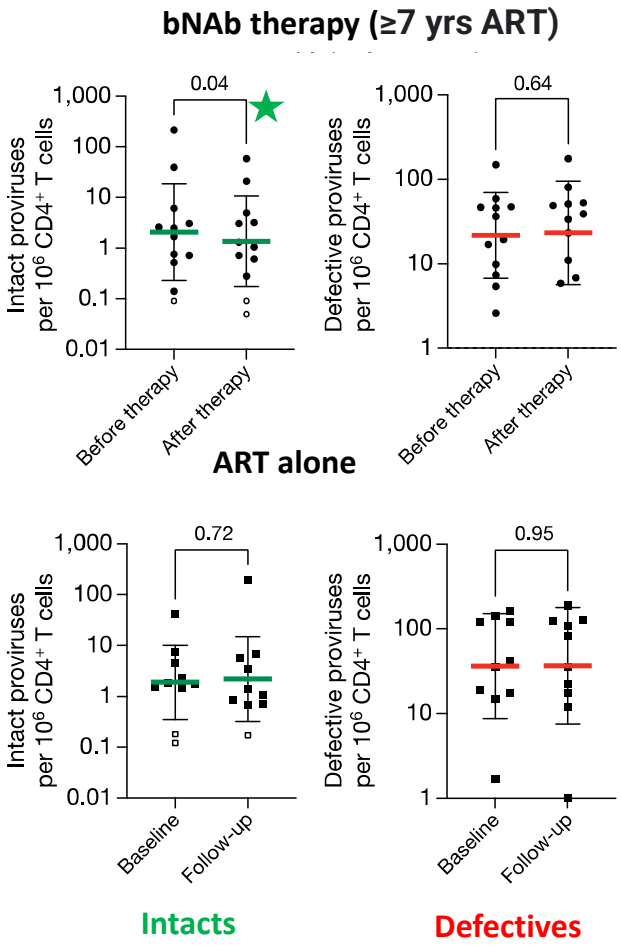


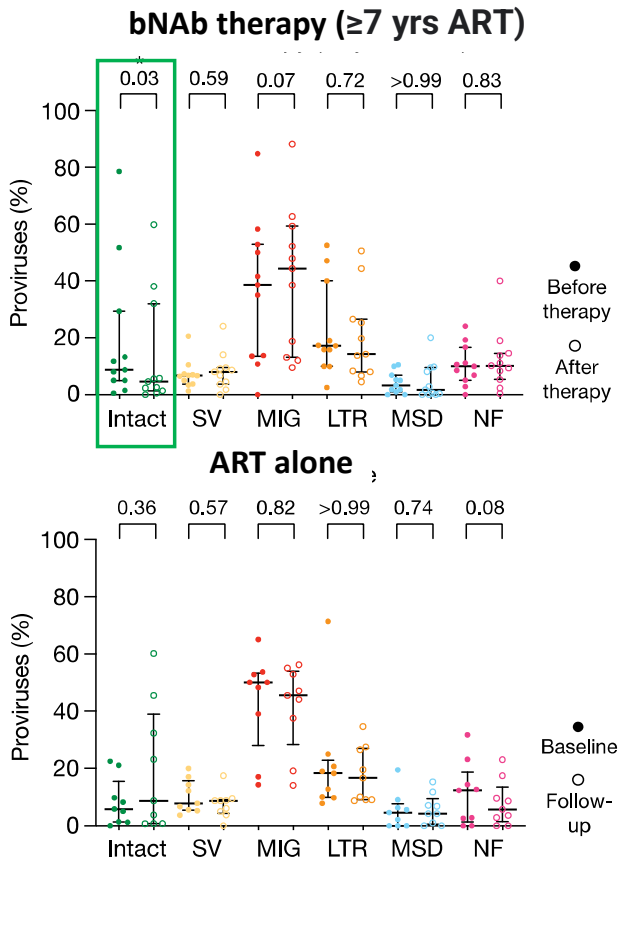
Schoofs T et al, Science 2016
Niessl et al, Nat Med 2020

Reservoir Assessments Following Repeated doses of 3BNC117 plus 10-1074

Gaebler et al.,
Nature 2022



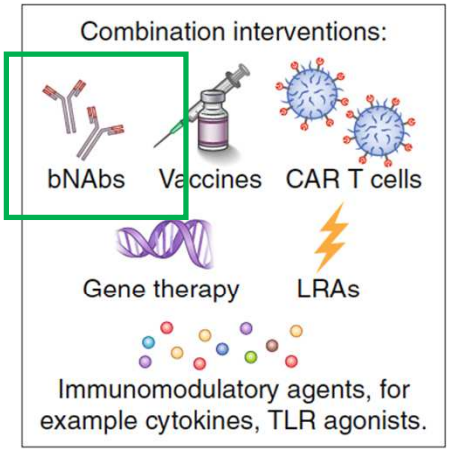




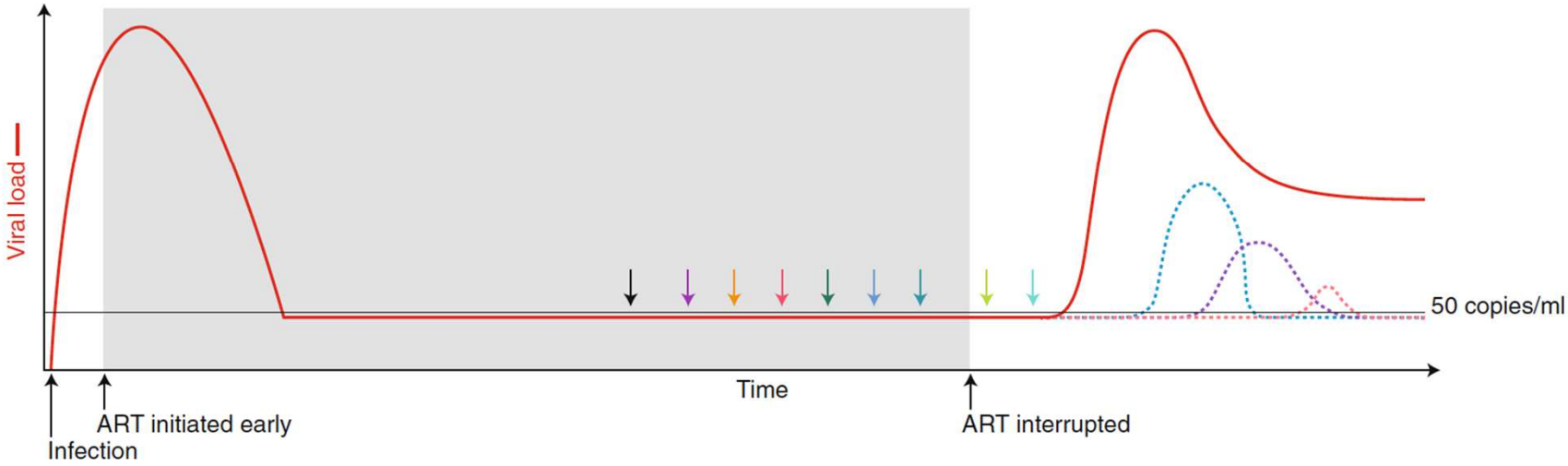
- **Moderate but significant changes** (baseline vs 26 wks) in both the absolute number and relative representation of **intact proviruses in the combined study groups (n=12).**

Combination Immunotherapy Strategies

During Early infection or at ART initiation:
Approaches to **Limit reservoir** establishment and preserve immune responses

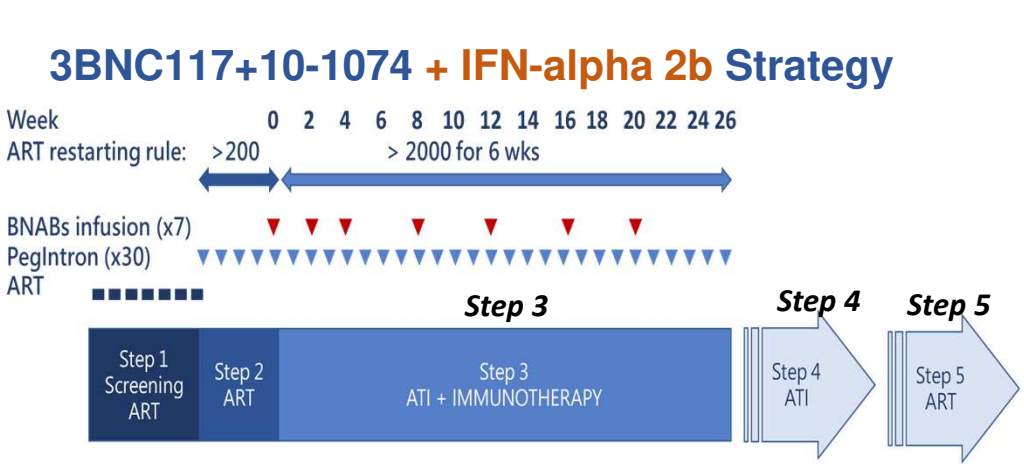


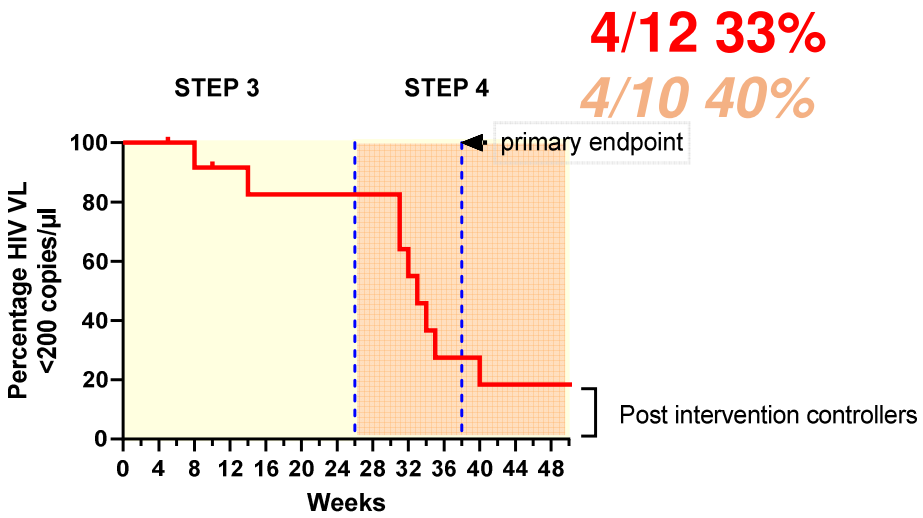
During ART suppression and/or ART interruption:
Approaches to **Reduce** and/or **Control** the reservoir



Deeks / IAS, Nat Med 2022

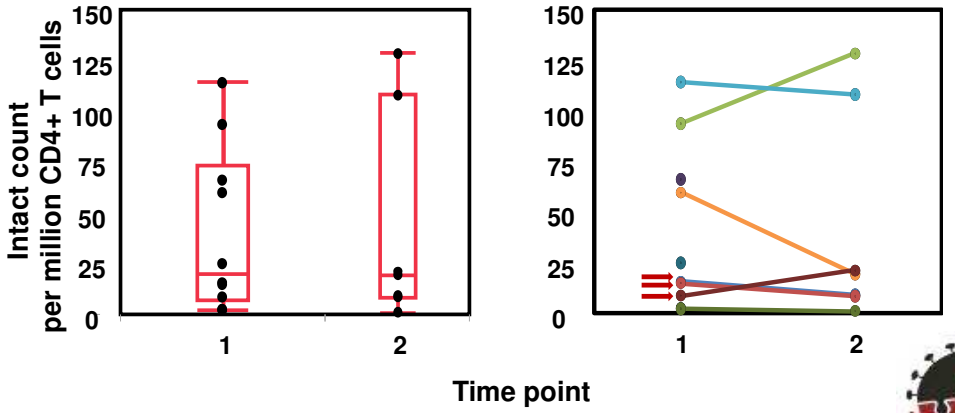
BEAT2 Trial: PEG-IFN-A2B + 3BNC117 & 10-1074





BEAT2 Study Key Features:

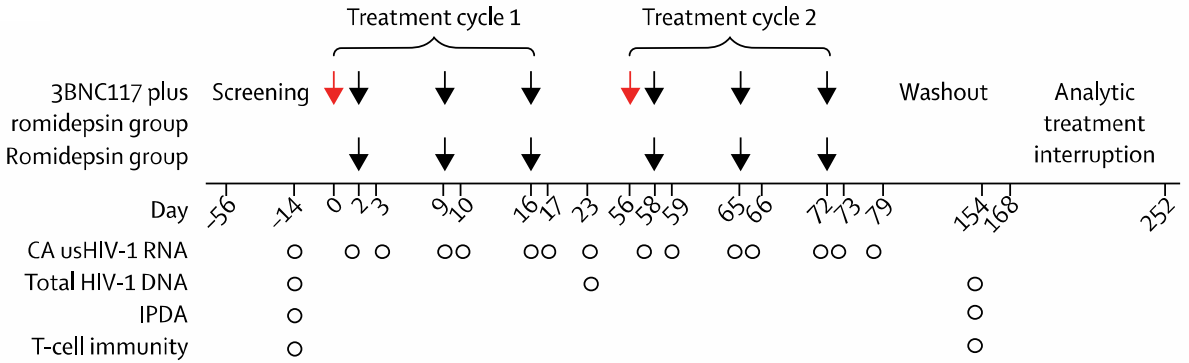
- Equal strategy to Gaebler et al, Nature'22
- Monogram sensitivity testing for entry
- Addition of Peg-IFN-alpha2b
- ART re-start (6 weeks >1000)



BEAT-HIV

Courtesy of Luis Montaner

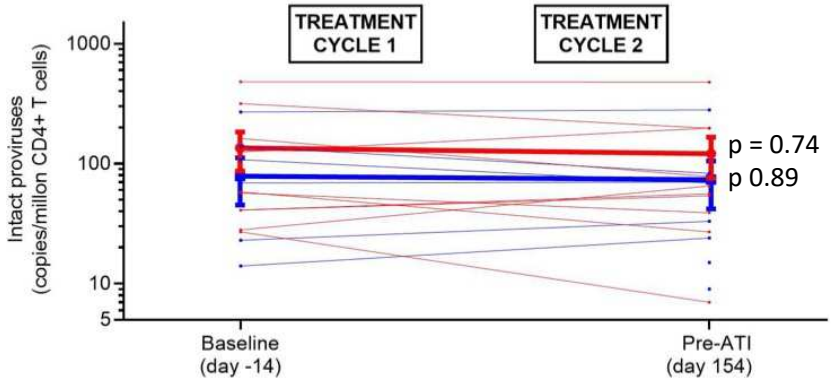
ROADMAP: Combination of 3BNC117 with Romidepsin during ART



Effect of HIV Transcription

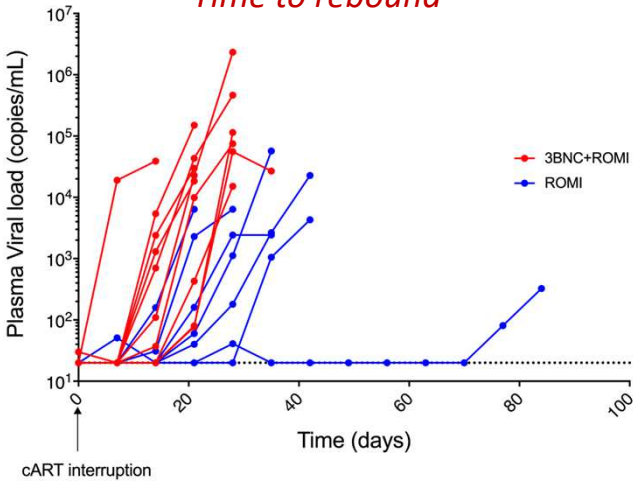
- CA-HIV-1 usRNA levels increased in both groups
- 15 out 19 ppts had detectable plasma HIV-1 RNA

Reservoir size



- No significant change in intact proviral DNA

Time to rebound

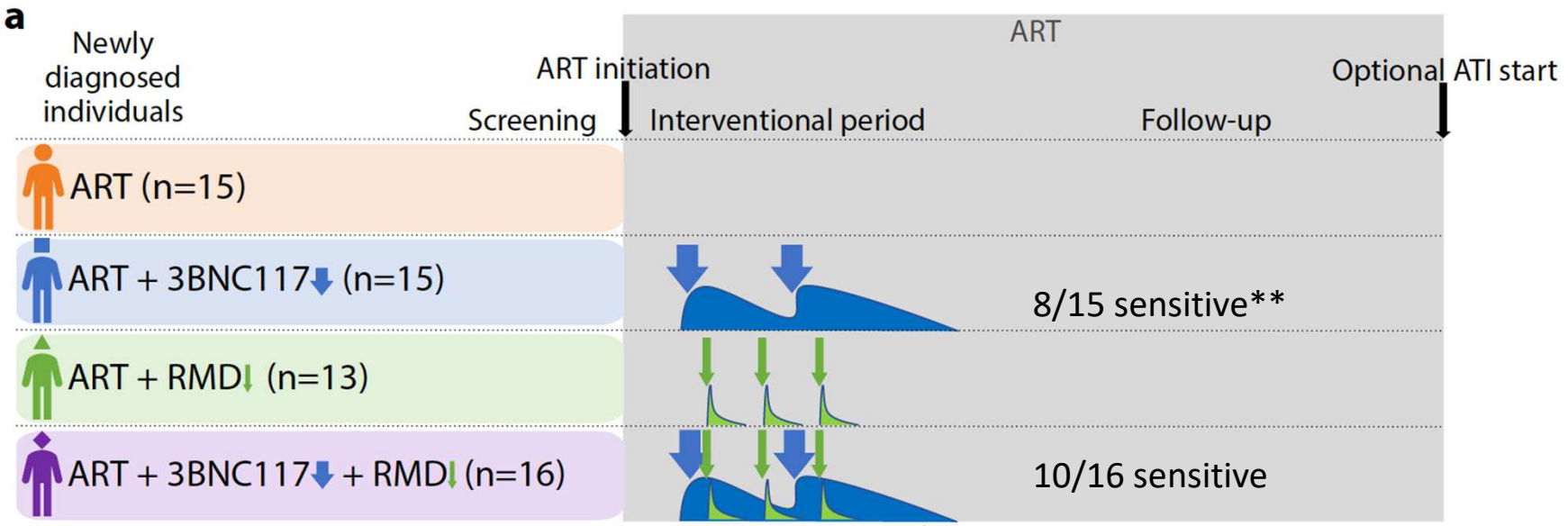


- 17.5 d for gp A and 28 d for gp B (p=0·02)

Supported by amfAR. In collaboration with Ole Sogaard and Florian Klein

Gruell et al, Lancet Microbe 2022

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



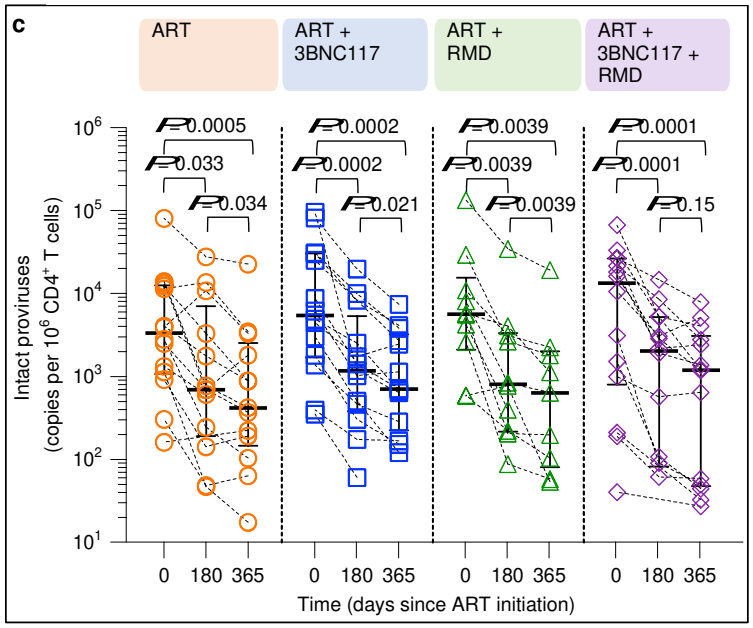
* 51% of participants in the trial harbored non-subtype B viruses

** Sensitivity by PhenoSense on pre-ART plasma viruses – IC_{90} < 1 mcg/ml

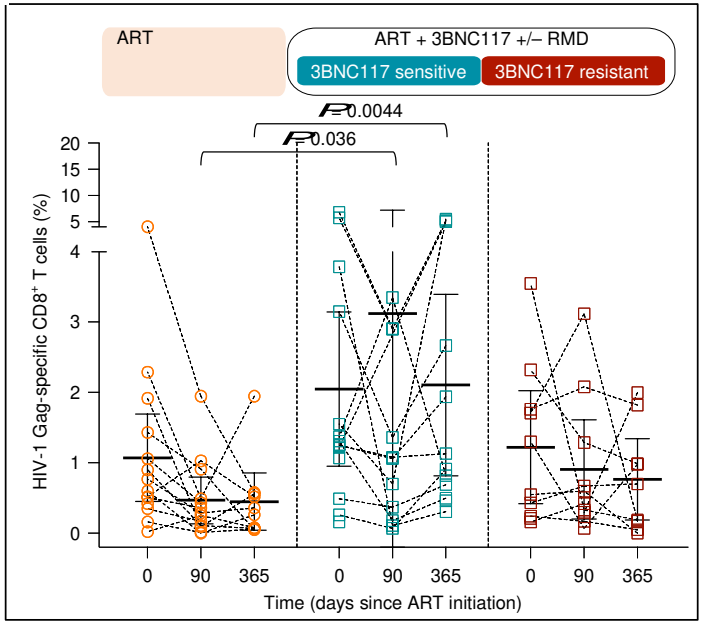
Gunst et al, Nat Med 2022
Rosás-Umbert et al, Nat Comm 2022

Increased T cell responses prior to ATI and delayed viral rebound among participants with 3BNC117 sensitive virus

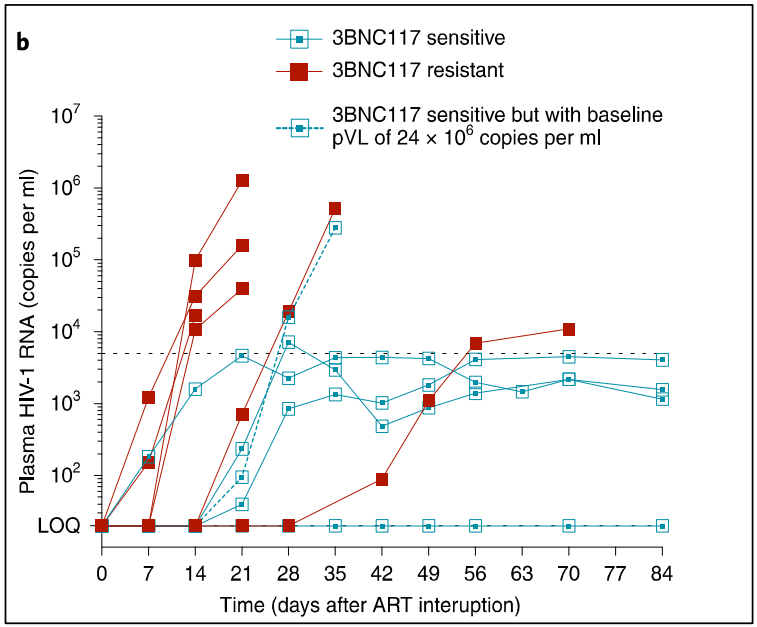
Intact Proviruses by 3dPCR Baseline to 365 days



HIV-1 Gag Specific CD8+ T cells



Time to loss of virologic control during 12 weeks of ATI



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

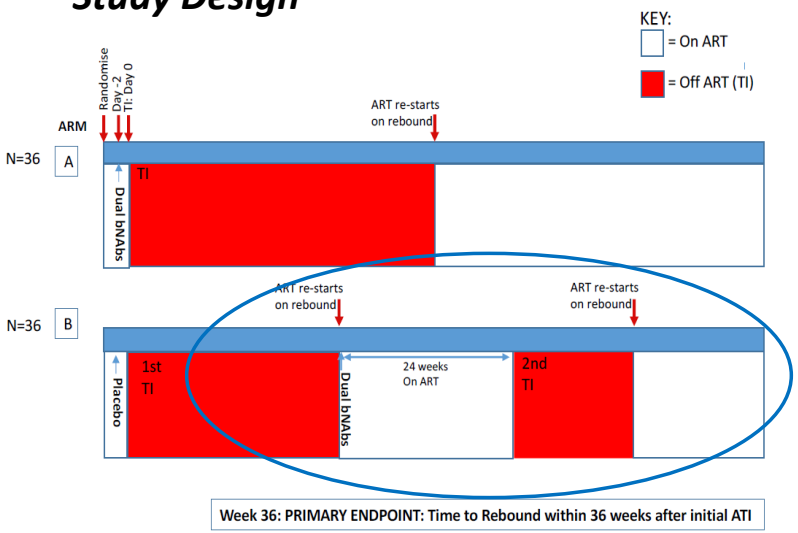
- Enhanced HIV gag-specific CD8 T cell responses among participants harboring 3BNC117 sensitive pre-ART viruses pre-ART viruses

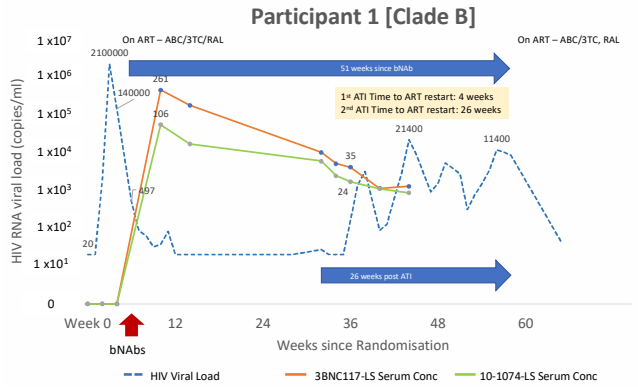
- Delayed time to viral rebound after ATI among participants harboring 3BNC117 sensitive pre-ART viruses

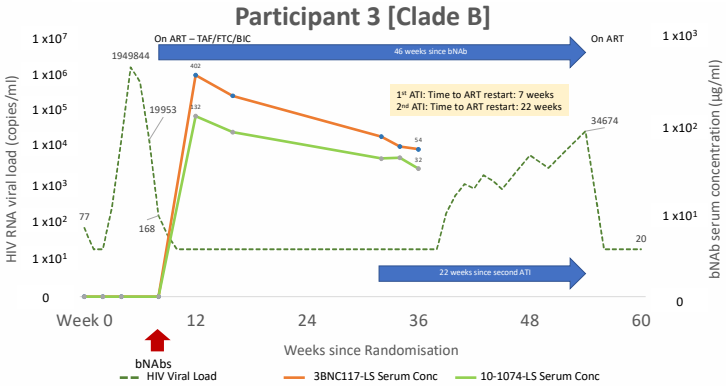
Gunst et al, Nat Med 2022
Rosás-Umbert et al, Nat Comm 2022

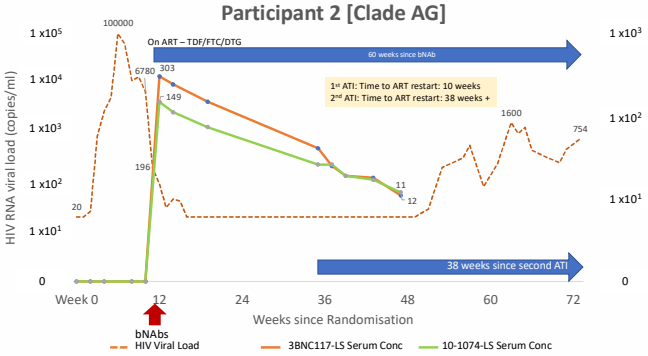
RIO Study: 3BNC117-LS+10-1074-LS during ATI and at ART re-start in PLWH treated during primary infection

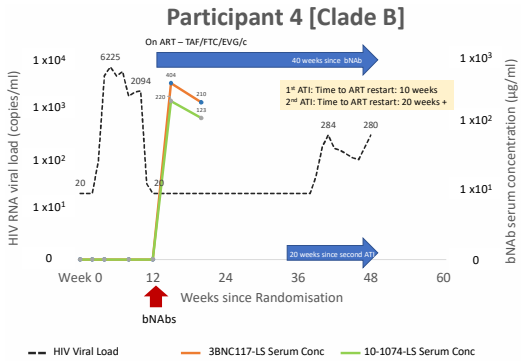
Study Design











➢ ***Stage 2 prelim results:***

All four participants lost viral control after the 2nd ATI, but rebound kinetics appears slower compared to the 1st ATI

Courtesy of Ming Lee, Sarah Fidler, John Frater

Funding: Bill & Melinda Gates foundation

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).
- ***Interventions at ART initiation may impact the course of HIV infection***
- However, **viral diversity is a challenge** to bNAb-based strategies.

Ongoing / Planned bNAb + Combination Immunotherapy Studies

Limit the Establishment

RHVIERA
3B-LS+1074-LS
Primary Infection
(Saez-Cirion)

A5388
VRC07523LS+PGT121-LS
Primary Infection
(ACTG – Crowell)

A5417
3B-LS+1074-LS
ART Naïve – SSAfrica
(ACTG – Crowell/Caskey)

Reduce and Control the Reservoir

RIO
3B-LS+1074-LS
ART at Primary Infx
bNAb ATI or ART restart
(Fidler/Frater)

MCA-1034
3B-LS+1074-LS
Chronic on ART
(Caskey /Sneller)

A5389
VRC07523LS+PGT121-LS
ART at Primary Infx
bNAb ATI or ART
(ACTG – Malvestutto)

BEAT HIV2
3BNC+1074+IFN
Chronic during ATI
(Tebas/Montaner)

TITAN
3BNC+1074+TLR9
Chronic during ATI
(Sogaard)

A5386
3BNC+1074+N803
Chronic on ART
(ACTG – Wilkin)

MCA-1031
3B-LS+1074-LS+N803
Chronic during ATI
(Caskey/Tebas/Wilkin)

FRESH
VRC07523LS+CAP256-LS /TLR7
ART at Primary Infx
(Gilead / Dong)

JAWS
DNA/MVA/TLR9
VRC07523LS+1074
Chronic/Primary on ART+ATI (Deeks)

NCT04983030 (BIDMC)
Ad26/MVA/VRC07-523LS+PDGM +PGT121 on ART
(Julg/Barouch)

A5374
ChAd/MVA/TLR7
3B-LS+1074-LS
ART at Primary Infx
(ACTG – Riddler)

In development
Enrolling
Completed/near completion

Acknowledgements

Study participants

Rockefeller University
Michel Nussenzweig
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Victor Ramos
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Cintia Bittar

Jill Horowitz
Katrina Millard
Martina Turroja
Melissa LaMar
Irina Shimeliovich

Imperial College
Sarah Fidler
Ming Lee

Oxford
John Frater

Weill Cornell Medicine
Brad Jones
Adam Ward
Dennis Copertino
Winiffer Conce Alberto
Tim Wilkin
Trip Gulick

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Natalie N. Kinloch

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Johannes Scheid
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Bruce Walker

Dartmouth
Margie Ackerman

Aarhus University
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Marie H. Pahus
Miriam Rosás-Umbert

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Henning Gruell

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Tae-Wook Chun
Mike Sneller
Tony Fauci

Duke University
Georgia Tomaras
Kelly Seaton
David Montefiori

BIDMC Harvard
Michael Seaman

National Institute of Allergy and Infectious Diseases

CFAR Einstein-Rockefeller-CUNY Center for AIDS Research

Bill & Melinda Gates foundation

hhmi Howard Hughes Medical Institute

Robertson Foundation

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Research Enterprise to Advance a Cure for HIV
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clinical fellow/early career investigator
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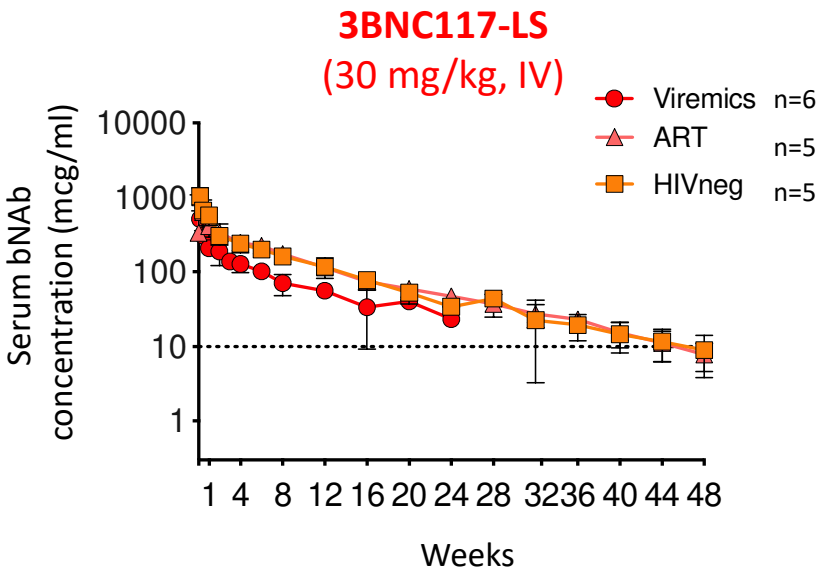
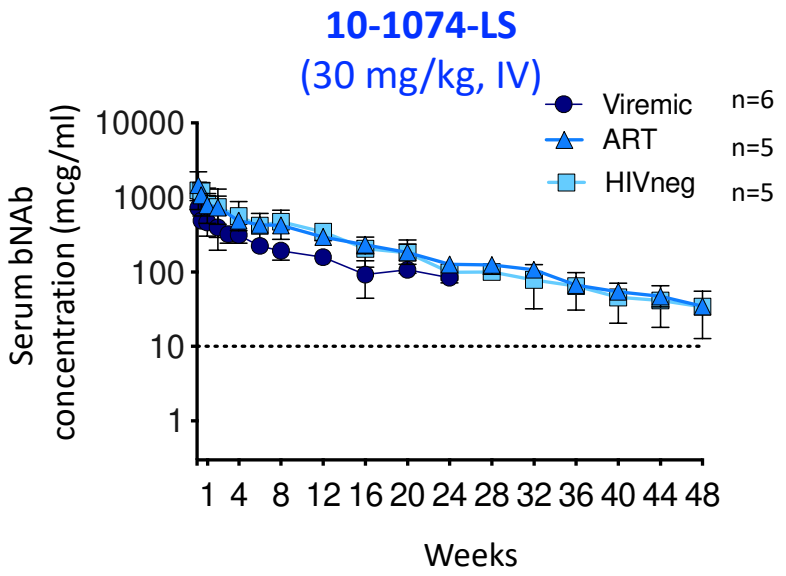
LS Variants: Serum Antibody Levels in Viremic Participants





- 3BNC117-LS has an approx. half-life of 60 days and 10-1074-LS has an approx. half-life of 80 days in healthy volunteers and during ART suppression
- Faster decay of both bNAbs in viremic participants – as seen with the parental antibodies

Kelly Seaton, Georgia Tomaras (Duke Univ)

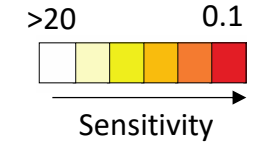
LS Variants: Antiviral Activity Relates to Baseline Sensitivity of Plasma Viruses

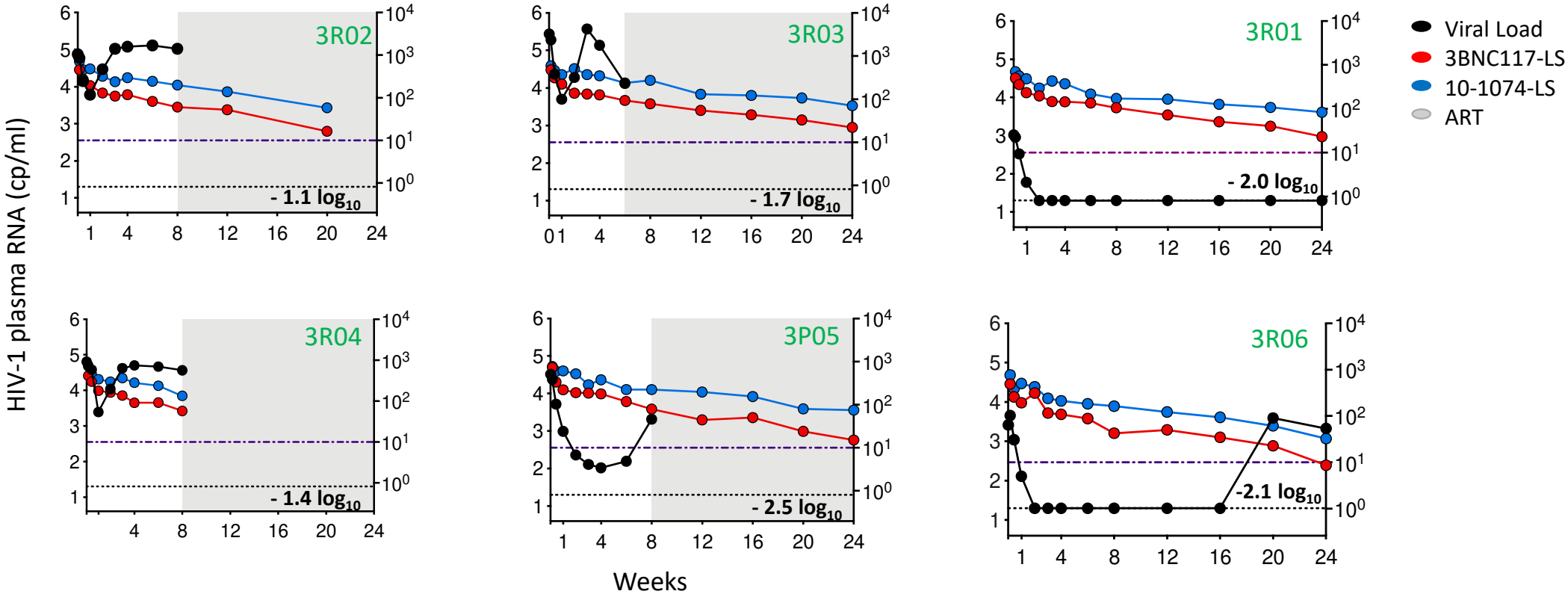
PhenoSense Baseline PLASMA

Study ID	3BNC117 IC90	10-1074 IC90
3R02	3.182	>50
3R04	3.615	>50

Study ID	3BNC117 IC90	10-1074 IC90
3R03	6.972	0.125
3P05	12.243	0.104

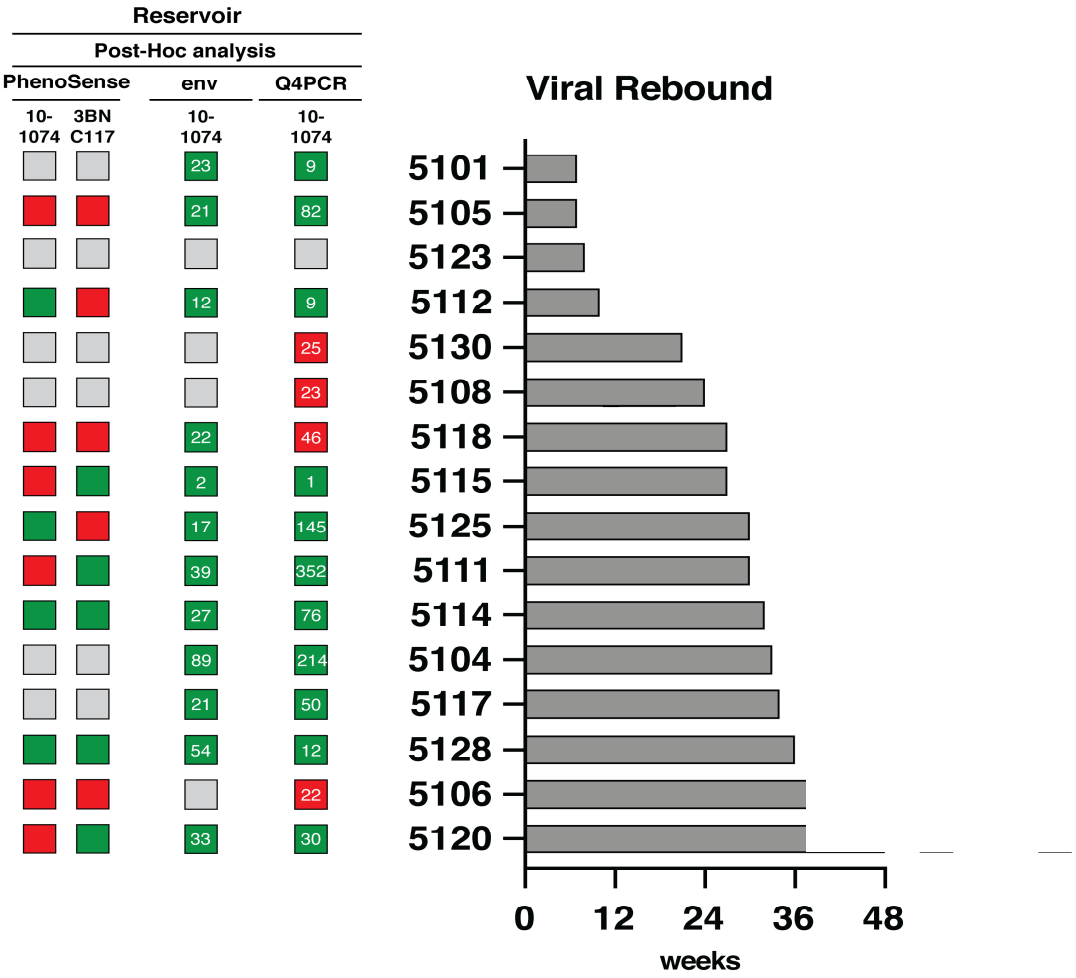
Study ID	3BNC117 IC90	10-1074 IC90
3R01	0.619	0.539
3R06	0.607	0.430





- Overall, **reduction** in plasma viremia of **~ 1.9 log_{10} cp/ml**.

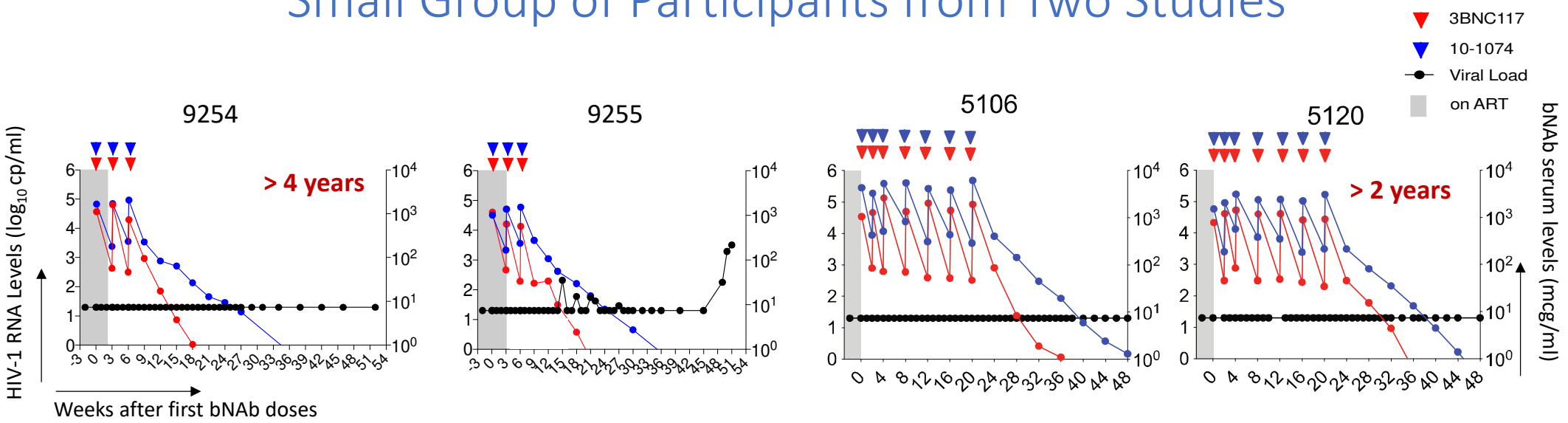
Assessment of Baseline bNAb Sensitivity: Phenotypic and Genotypic Methods



Christian Gaebler
Thiago Oliveira
Jackie Reeves (Monogram)

- Both genotypic and phenotypic sensitivity **analyses of proviruses would not** have reliably **predicted clinical outcome and time to viral rebound** in this cohort

Long-Term Viral Suppression after bNAbs in a Small Group of Participants from Two Studies



- Intact IUPM – 27.34
- ART initiated **4-5 mo of infection**
- On ART x 21 years.
- HLA-A*1 and A*29
  B*38 and B*44

- Intact IUPM – 6.51
- ART initiated ~ 7 mo after Dx
- On ART x 4 years.
- HLA-A*3 and A*25
  B*18 and B*44

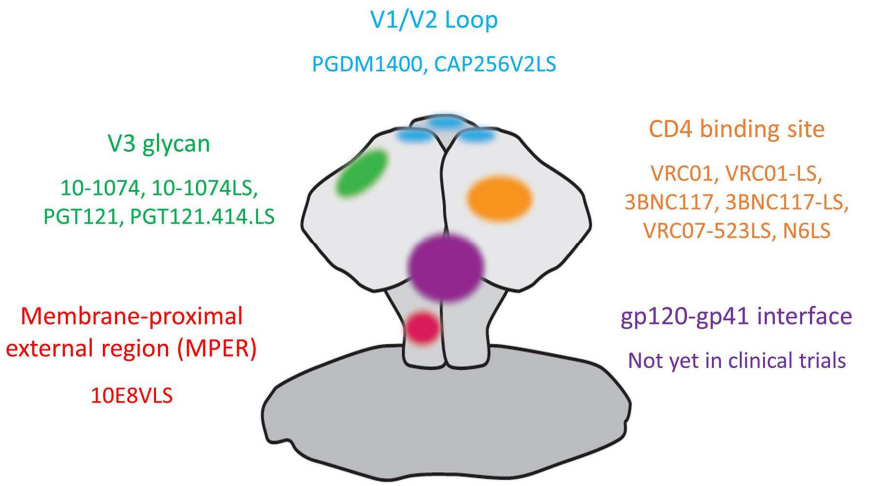
- Intact IUPM – 7.29
- ART initiated ~ 1 after Dx
- On ART x 6 years.
- HLA-A*3 and A*3
  B*38 and **B*57**

- Intact IUPM – **0.76**
- ART initiated **< 1 yr of infection**
- On ART x 19 years.
- HLA-A*2 and A*29
  B*15 and B*44

➢ ***Are there common features implicated in long-term viral suppression?***

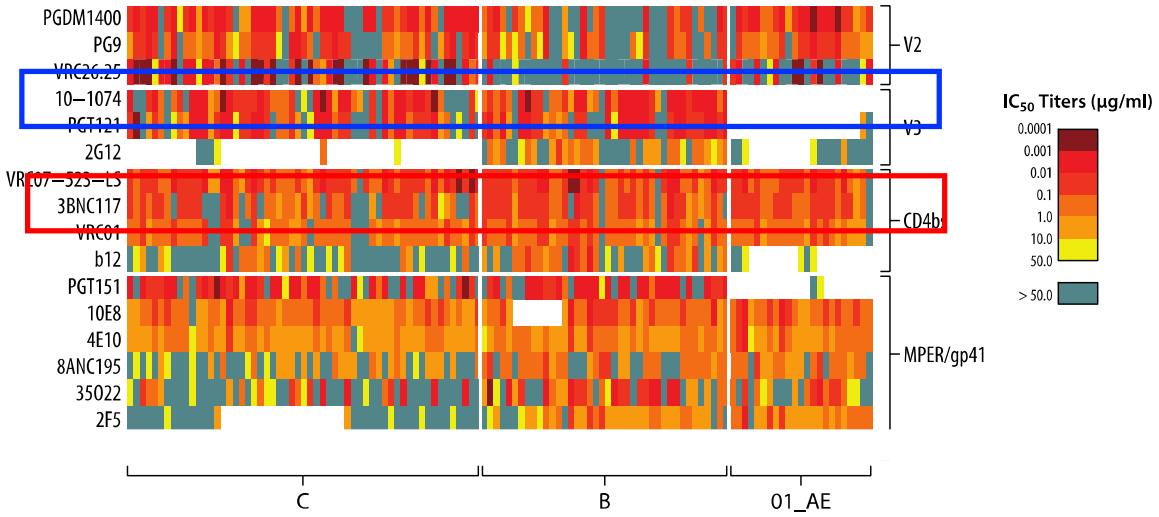
Anti-HIV-1 bNAbs Targeting Different Epitopes in Clinical Trials

Neutralization Targets



Hsu et al, Front Immunol 2021

bNAbs with Greater Breadth and Potency

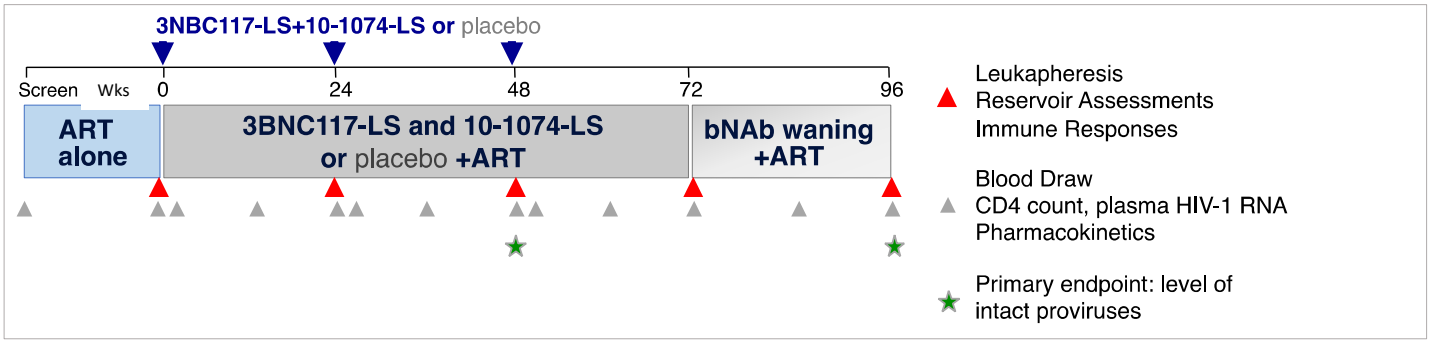


Karuna et al, Ann Rev Med 2020

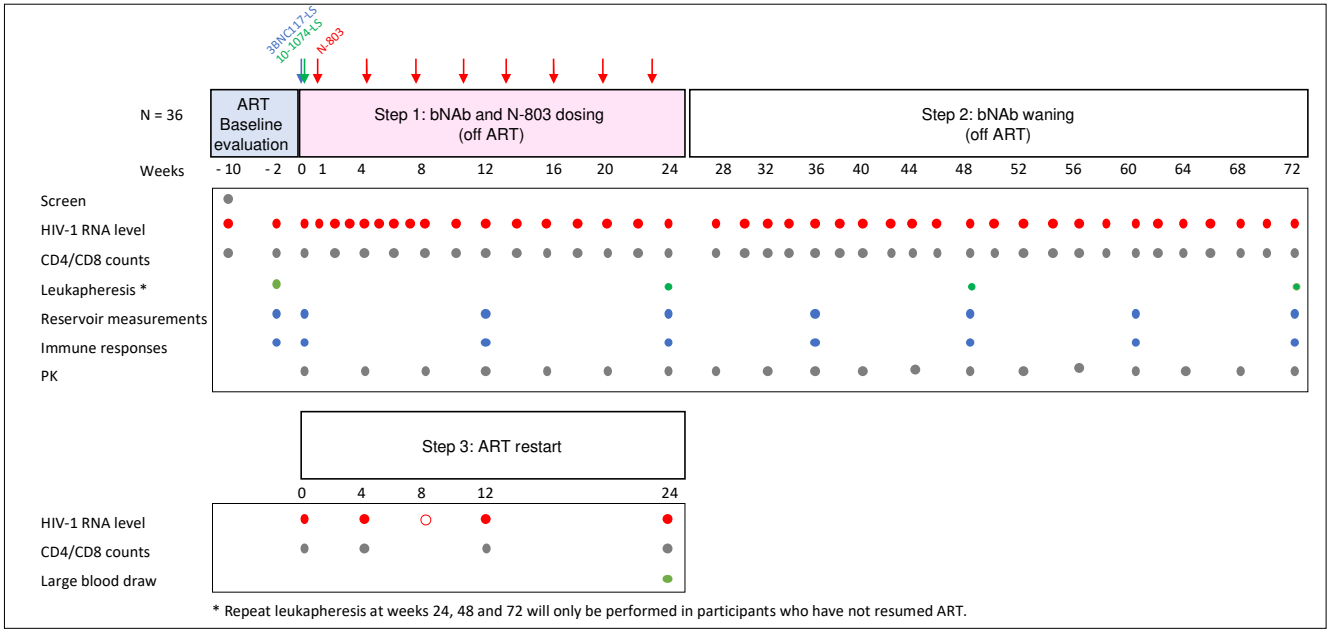
- Bi-specific & tri-specific
- AAV-delivery

Next steps:

Can prolonged exposure to bNAbs during ART suppression further impact the proviral reservoir?

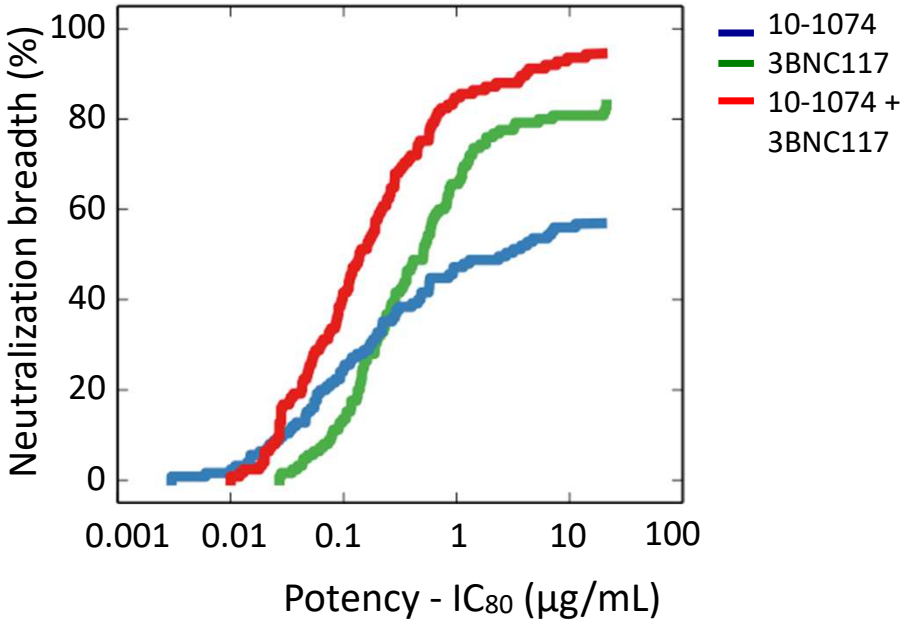


Can bNAbs with N-803 (LRA+immune modulation) during ATI impact the reservoir and immune responses?



3BNC117 (CD4bs) and 10-1074 (V3 loop): *In Vitro* Neutralizing Activity

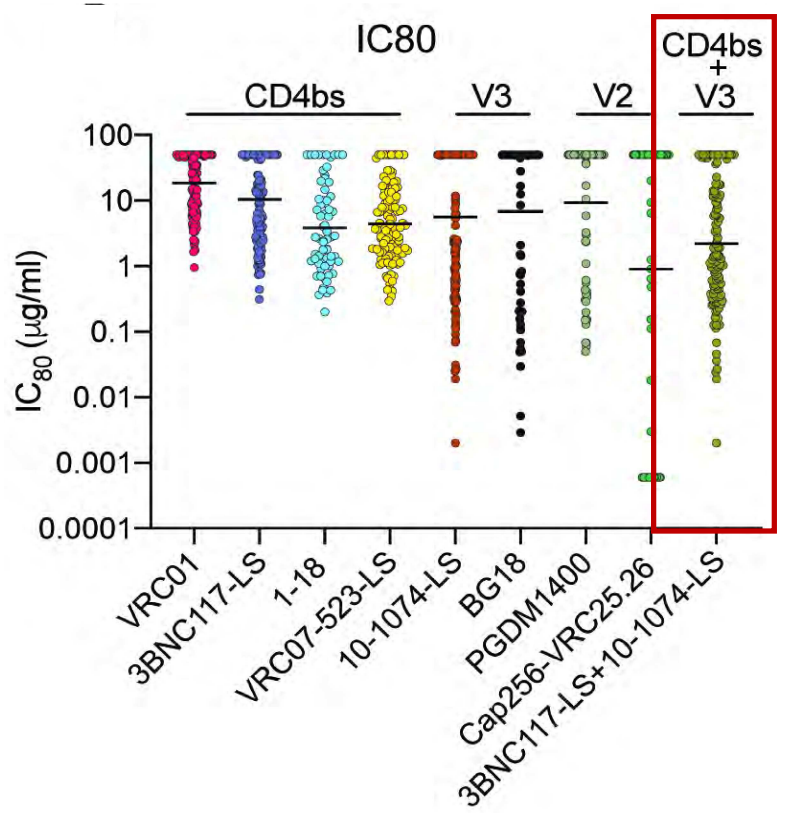
Pseudovirus Panel (Multi-Clade)



Coverage of **93%** - IC_{80} < 10 µg/ml
GeoMean **IC_{80} 0.15 µg/ml**

Kong et al, J Virol 2015

Primary Isolates (Clades A, C, D)



Coverage 84%

GeoMean IC_{80} 2.2 µg/ml

Lorenzi et al, J Virol 2020