

*Update on HIV-1 bNAbs for the
Prevention, Therapy, and Cure of HIV*

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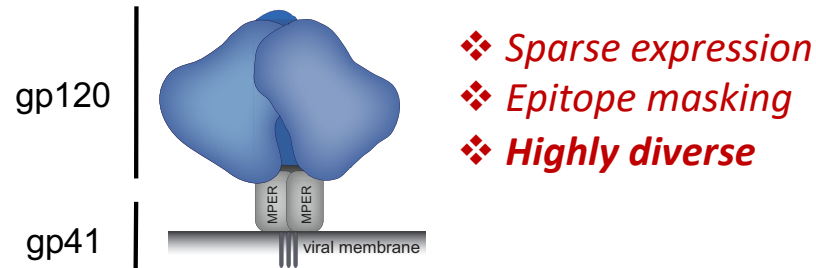
This activity is jointly provided by Physicians' Research Network and the Medical Society of the State of New York.

Conflict of Interest Statement

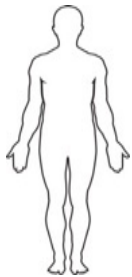
- Gilead Biosciences – Ad-Hoc SAB

Broadly Neutralizing Antibodies Develop during HIV Infection

HIV-1 Envelope



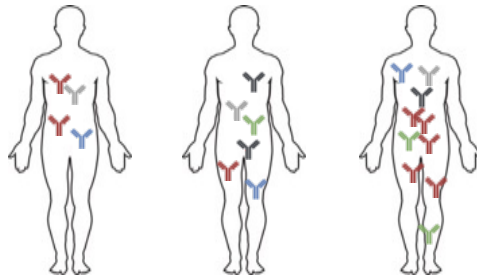
Transmission



Acute infection



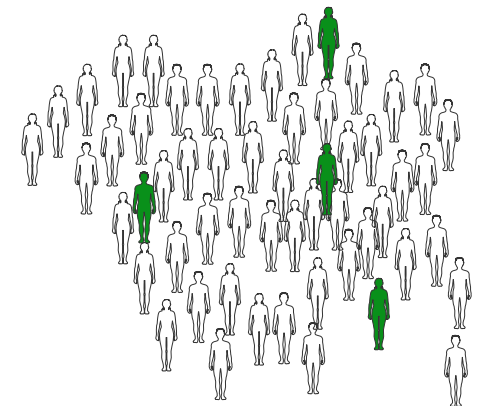
Chronic infection



10-20%
develop
bNAbs



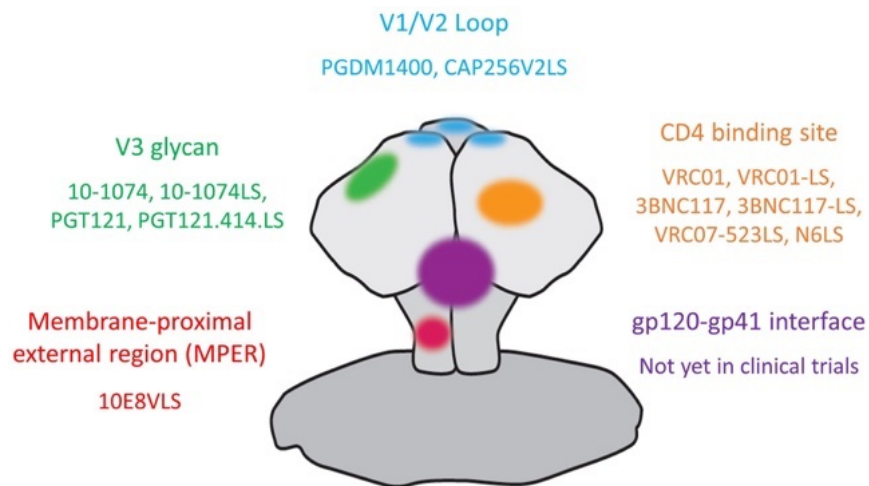
2-3 yrs



Can neutralizing antibodies have a role in HIV infection?

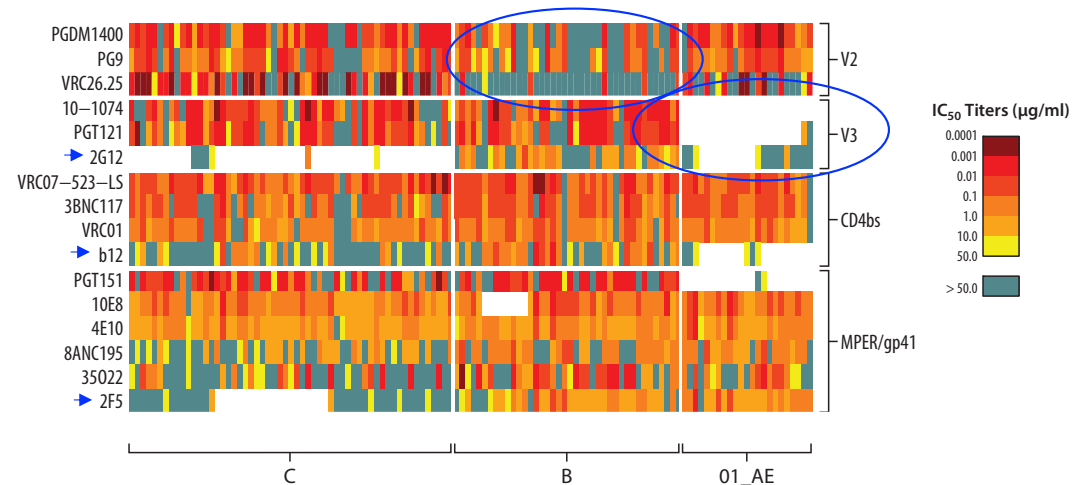
Anti-HIV-1 bNAbs Targeting Different Epitopes in Clinical Trials

Neutralization Targets



Hsu et al, Front Immunol 2021

bNAbs with Greater Breadth and Potency



Karuna et al, Ann Rev Med 2020

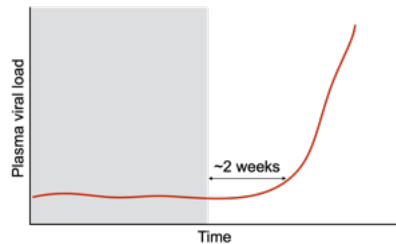
- ❖ Bi-specific & tri-specific
- ❖ AAV-delivery

➤ **At an individual level, greater *env* diversity is associated with high neutralization titers and breadth, *but also with resistance to certain bNAbs and autologous viruses.***

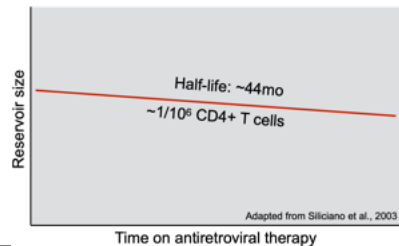
Anti-HIV Broadly Neutralizing Antibodies: Challenges and Potential

HIV – ongoing problems

- Incidence rates remain high
 - No effective vaccine
 - PrEP uptake is below targets
- **Treatment is lifelong**
 - Rapid rebound after ART cessation

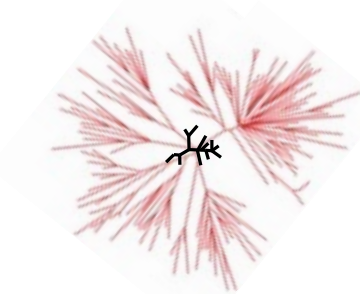


- Long-lived reservoir of infected cells



HIV bNAb challenges

- **Envelope** is sparsely expressed
 - Complex glycan shield
- Epitope masking
 - Complex glycan shield
- **Highly diverse**

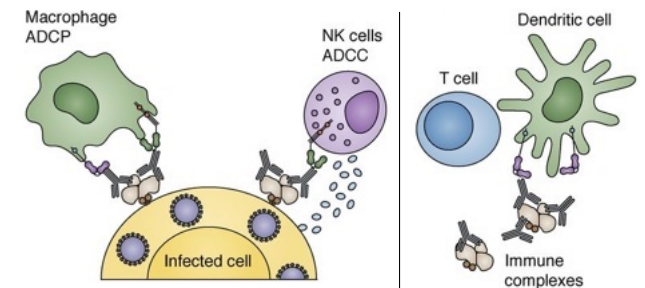


HIV-1 Env seq. variation
(Demo. Republic of the Congo)

Influenza A virus
(Global variation, 1996)
Korber et al., IAVI 2010

HIV bNAb potential roles

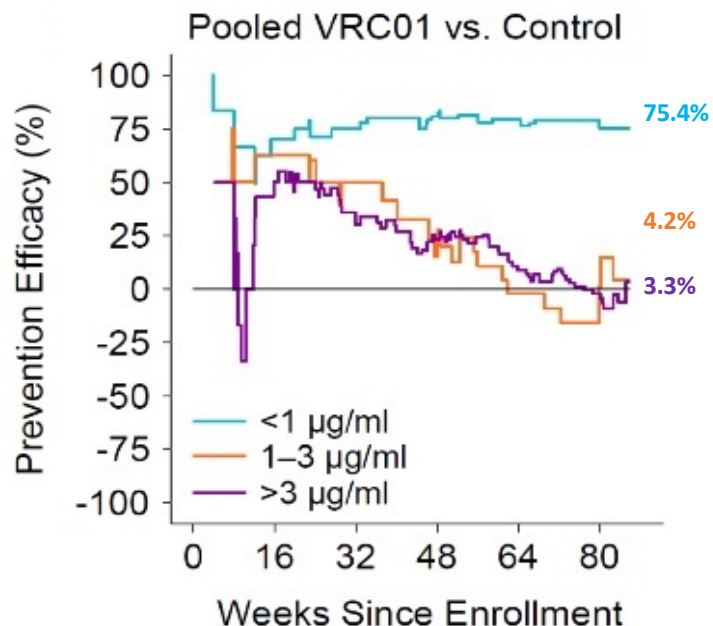
- **Therapy & Prevention**
 - Safety
 - Long-half lives
- **ART-free sustained virologic control - Fc-mediated effector functions**
 - Eliminate infected cells
 - Enhance immunity



Bournazos et al, 2015

HIV-1 bNAbs: Prevention

AMP Studies: VRC01 achieved prevention efficacy against neutralization sensitive viruses

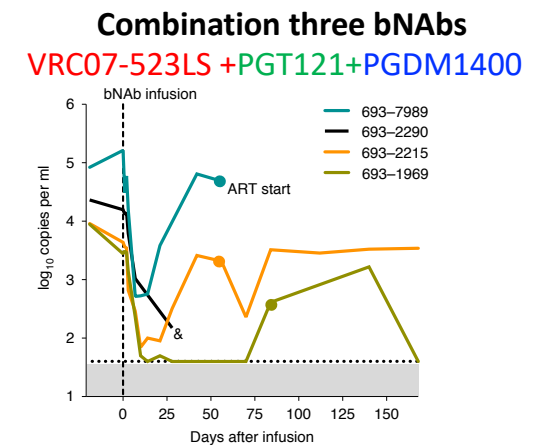
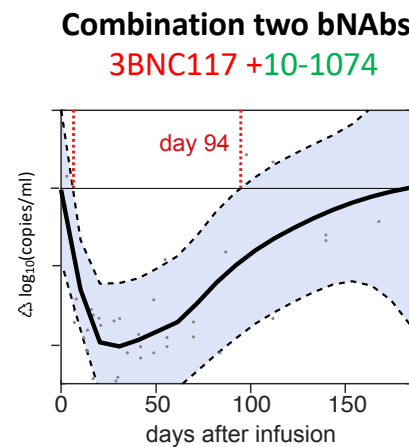
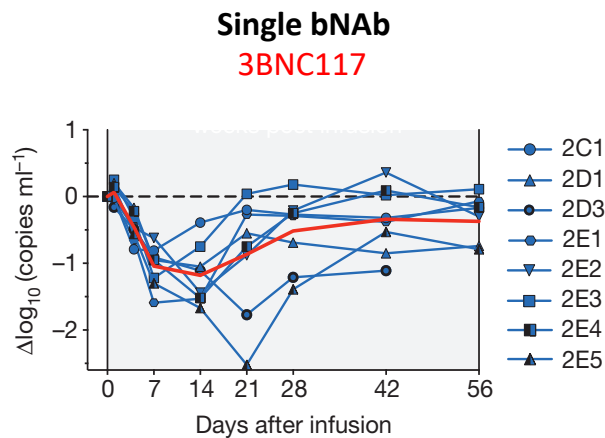


- **Prevention can be achieved by bAb administration**
 - **Regardless of gender and region-specific clade**
*However, it is **dependent on neutralization sensitivity of circulating strains (only 30% VRC01 sensitive) and required higher levels than anticipated***
- **In vitro neutralization assays can predict outcome**
But predictions based on TZM/bl assays against pseudoviruses were about 1 log “off” from required in vivo sensitivity against “real viruses”.
- **Prevention efficacy biomarker: predicted serum neutralization ID80 titer of 200**

Glass half full or half empty: Next steps after AMP results?

- Will combination of bNAbs provide greater protection?
 - How many bNAbs will be needed?
- What dose level and frequency will be needed to achieve protection titers?
- Is resistance to bNAbs evolving over time on a population level?

HIV-1 bNAbs: Therapy Effects on Plasma Viremia



- **Across studies: A subset of participants with baseline resistance**
- **Transient reduction in plasma viremia - nadir ~ 1.5 log₁₀ cp/ml.**
- **Selection of resistant viral strains occurred**
- **Viral suppression only achieved with low starting VLs**
 - Viral rebound observed without clear selection of resistance to VRC07-523LS or 3BNC117

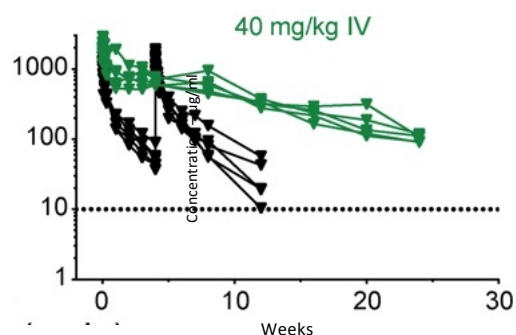
Caskey, Klein et al., 2015
Bar-On, et al 2018
Julg, et. al. 2022

HIV-1 bNAbs: Therapy

Engineered antibodies: Increased Bioavailability

LS mutations (**M428L/N434S**) enhance FcRn binding and prolong half-life

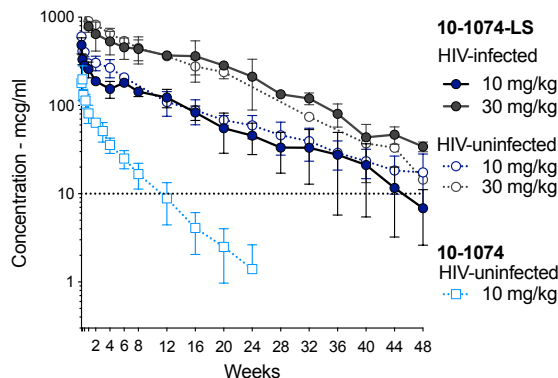
VRC01-LS



VRC01-LS $t_{1/2}$ 71 days
(vs. VRC01 $t_{1/2}$ of 15 d)

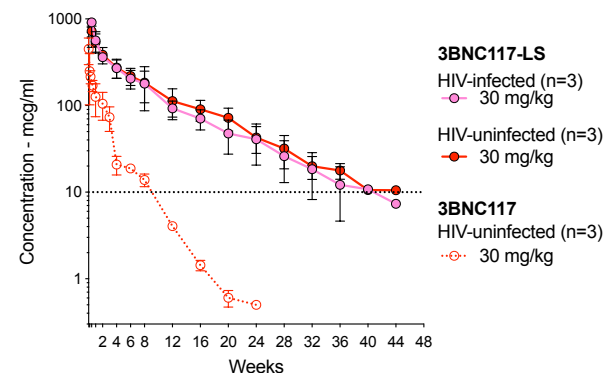
Gaudinski et al, 2018

10-1074-LS



10-1074-LS $t_{1/2}$ 80 days
(vs. 10-1074 $t_{1/2}$ of 24 d)

3BNC117-LS



3BNC117-LS $t_{1/2}$ 66 days
(vs. 3BNC117 $t_{1/2}$ of 17 d)

- Half-life of LS variants > 3 fold longer than parental mAbs
- Allows for twice/yr IV infusions, or quarterly SC doses

HIV-1 bNAbs: Therapy

Engineered antibodies: Increased Potency and/or Breadth

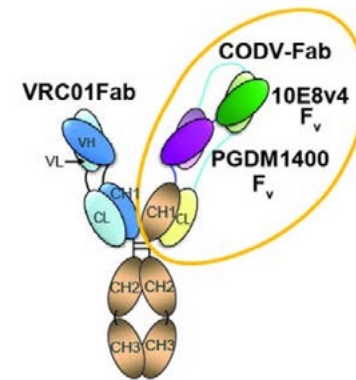
Bi-specific

iMab/10e8v2.0



Tri-specific

VRC01/10E8v4-PGDM1400-LS
(SAR441236)



Sobieszczyk, CROI 2022:

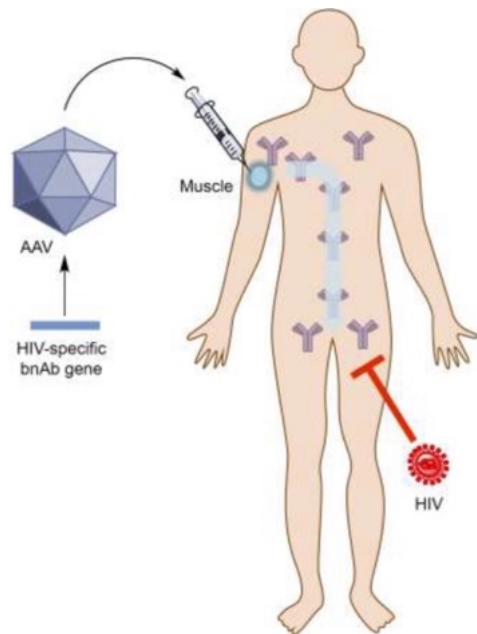
- Good safety profile
- Detected in serum – PK analysis ongoing
- **No neutralizing ADA** (except for 1 participant)
- **VL decline** of 1.5 log₁₀ cp/ml

A5377:

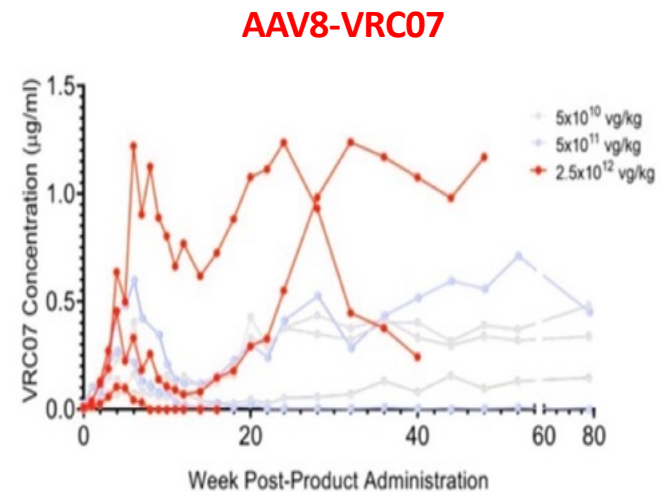
- Will complete follow up in November 2023
- No safety concerns to date

Delivery Systems: Sustained in vivo secretion of bNAbs

AAV Vectors



Yang et al, 2014



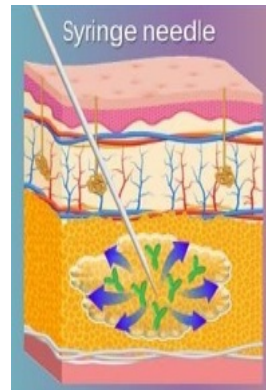
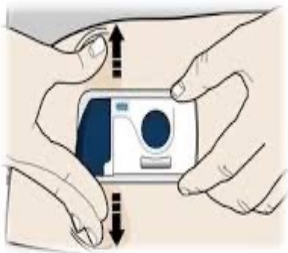
- **VRC 603**: 8 people received **AAV8-VRC07** (three doses)
- **2/3 at high dose had sustained production of VRC07.**
- ADA responses detected

Casazza et al, Nat Med 2022

Delivery Systems: SC delivery of high volumes

Approaches

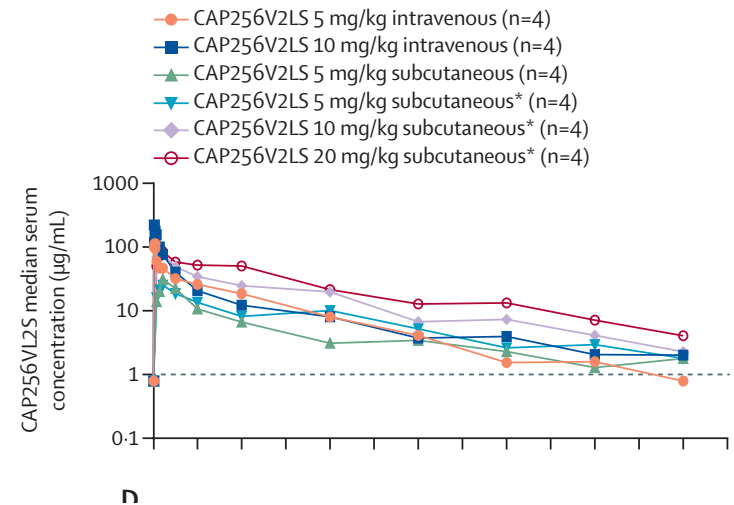
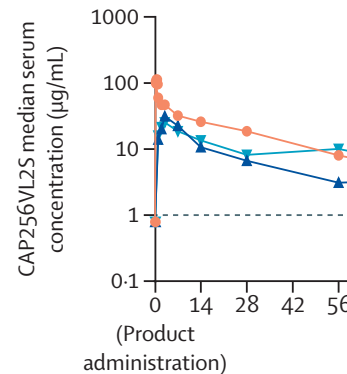
- High-concentration injectables
 - Form fluid suspensions
 - Minimize intermolecular interactions
- Delivery of larger volumes
 - Devices
 - **Modifying SC space - *hyaluronidase***



Safety and pharmacokinetics of escalating doses of neutralising monoclonal antibody CAP256V2LS administered with and without VRC07-523LS in HIV-negative women in South Africa (CAPRISA 012B): a phase 1, dose-escalation, randomised controlled trial

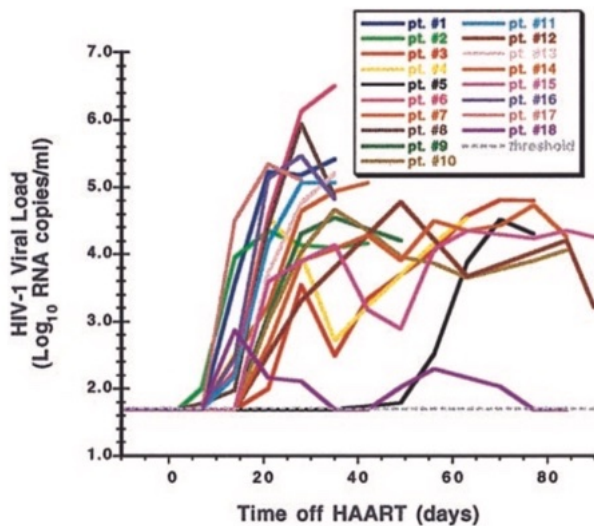
Sharana Mahomed, Nigel Garrett, Edmund V Capparelli, Farzana Osman, Nonhlanhla N Mkhize, Ishana Harkoo, Tanuja N Gengiah, Leila E Mansoor, Cheryl Baxter, Derseree Archary, Nonhlanhla Yende-Zuma, Natasha Samsunder, Kevin Carlton, Sandeep Narpala, Adrian B McDermott, Nicole A Doria-Rose, Penny L Moore, Lynn Morris, Quarraisha Abdool Karim, John R Mascola, Salim S Abdool Karim

- CAP256V2LS 5 mg/kg intravenous (n=4)
- CAP256V2LS 5 mg/kg subcutaneous (n=4)
- CAP256V2LS 5 mg/kg subcutaneous* (n=4)

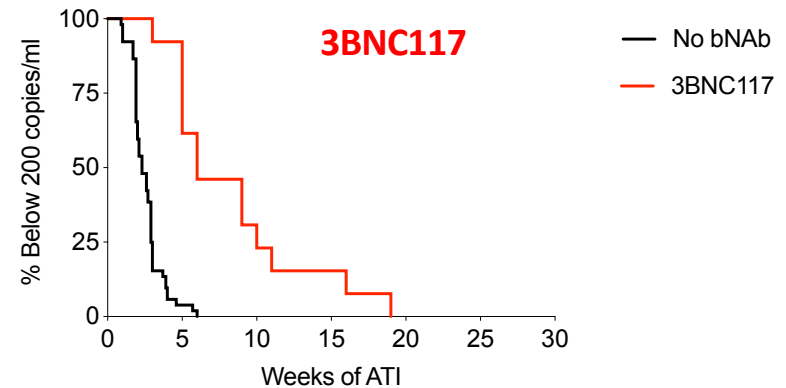
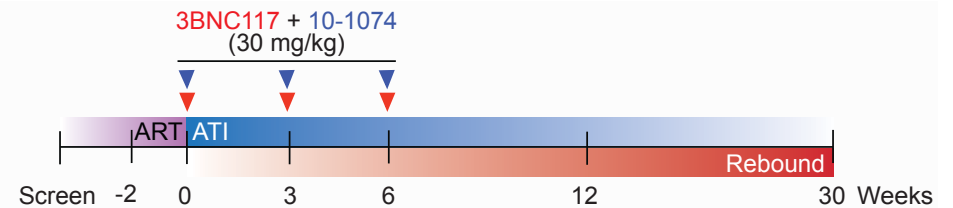


HIV-1 bNABs: Therapy

Can bNABs maintain viral suppression in the absence of ART?

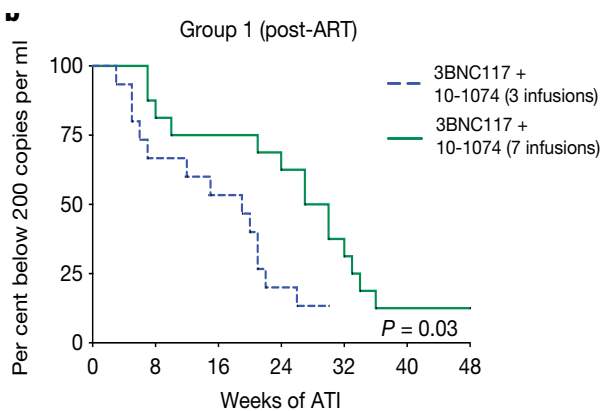
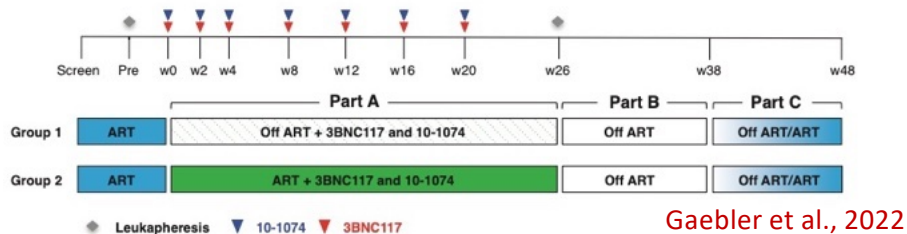


Davey et al. *PNAS* 1999

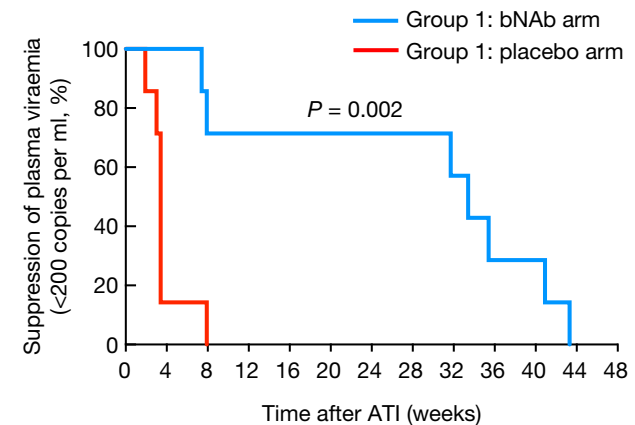
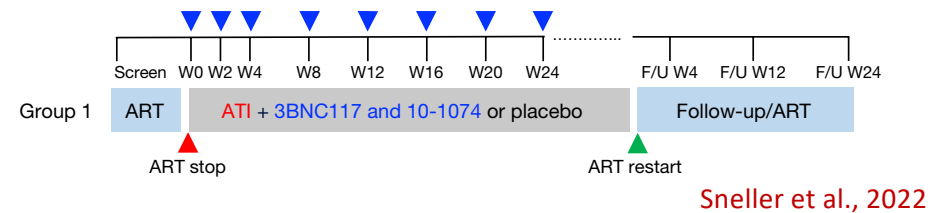


- **Average time to rebound: 8.4 wks**
 - Rebound was monogenic
 - Selection of resistance

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



- 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)**

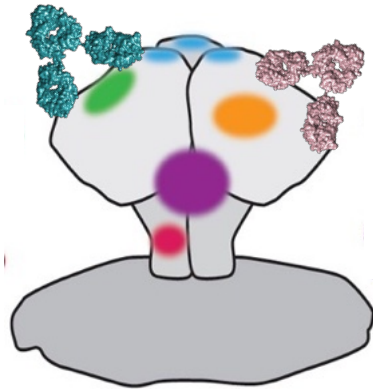
Other “Switch” Studies: LS-bNAbs + LA-ARV

- Capsid Inhibitor

- Lenacapavir

- bNAbs

10-1074-LS + 3BNC117-LS



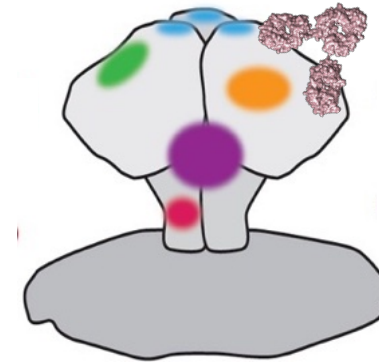
NCT04811040

- Integrase Inhibitor

- Cabotegravir

- bNAbs

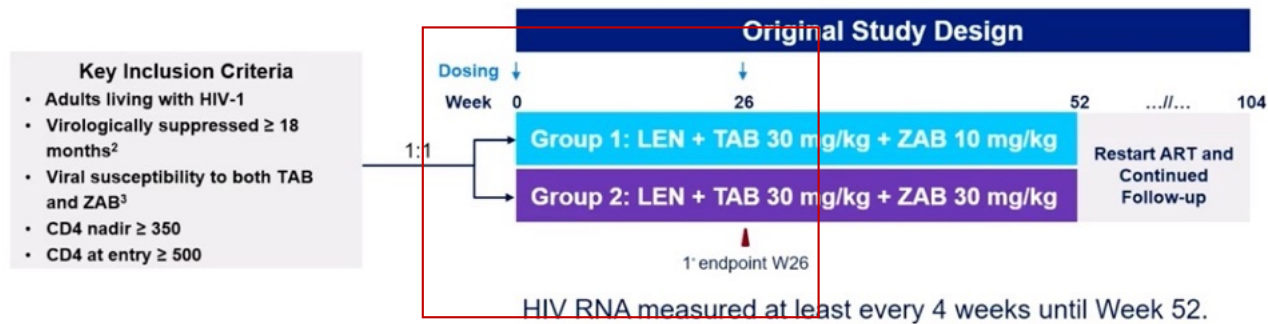
VRC07-523LS



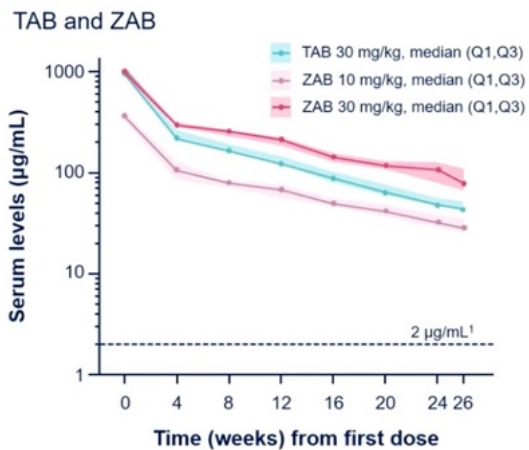
A5357 / NCT03739996

Lenacapavir with bNABs GS-5423 (3BNC117-LS) AND GS-2872 (10-1074-LS) dosed every 6 months in people with HIV*

➤ Randomized, blinded phase 1b study assessing safety and efficacy of a long-acting regimen (NCT04811040)

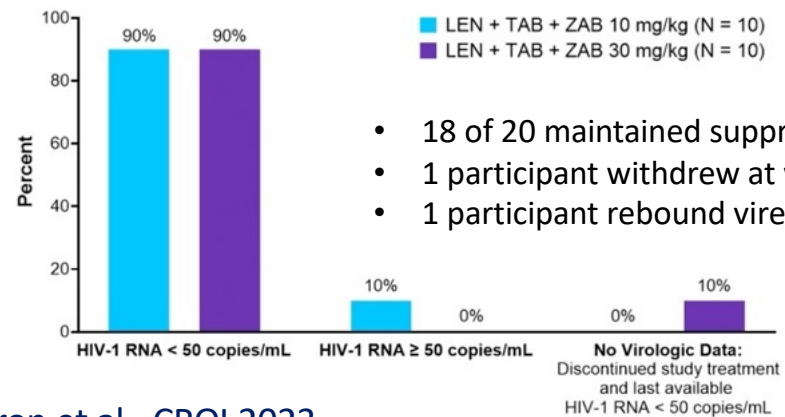


PK: Therapeutic Serum Levels Maintained > 26 wks



Antiviral activity:

Long acting regimen maintained viral suppression

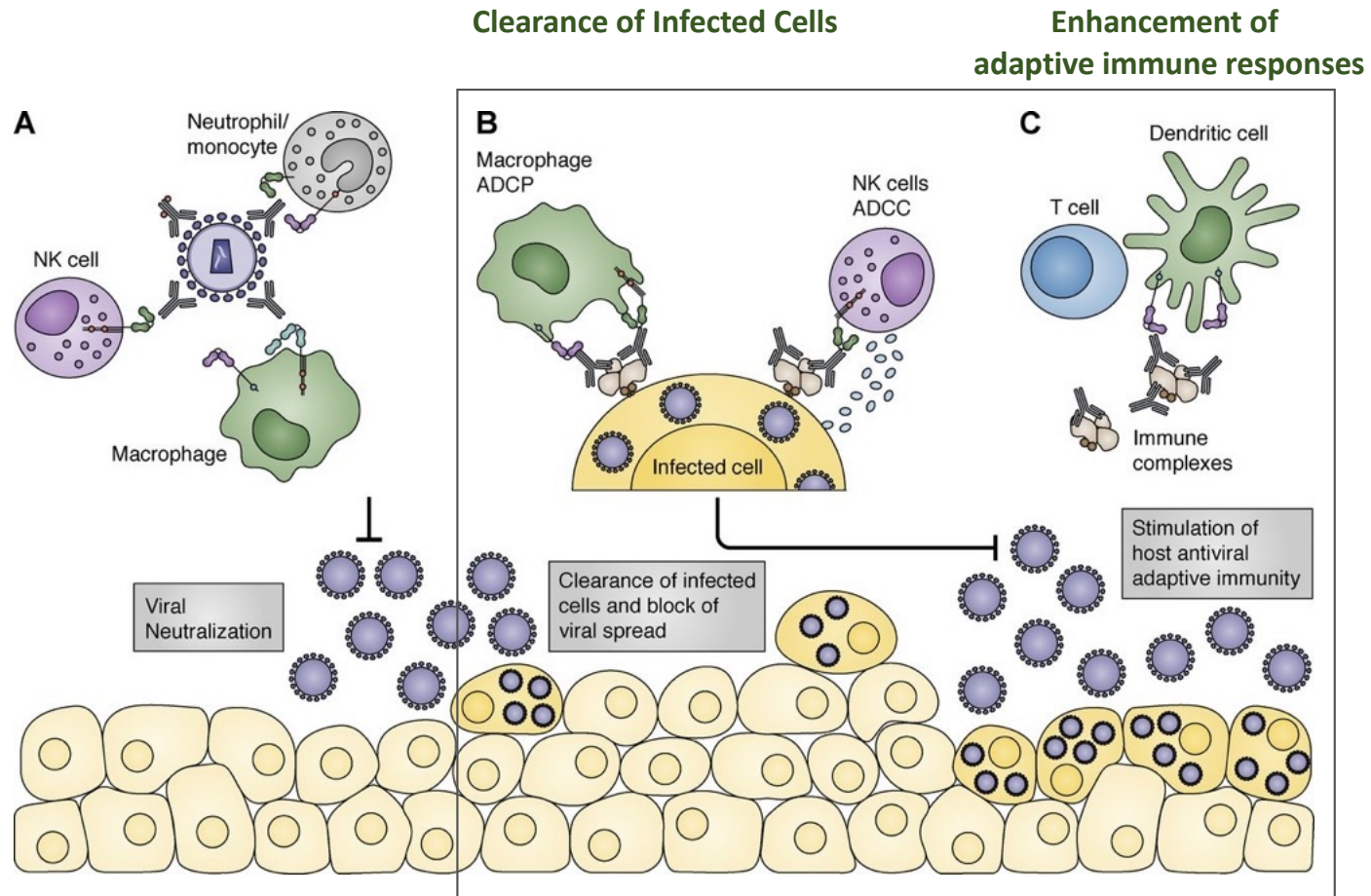


* Adapted from Eron et al., CROI 2023

Anti-HIV-1 bNAbs Clinical Studies – Summary I

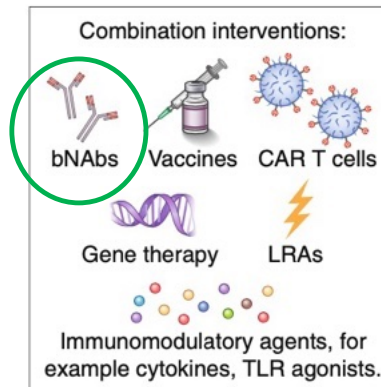
- Evidence that combination **bNAbs can maintain viral suppression**
- However, **viral reservoir diversity is a challenge** to bNAb-based strategies
 - Improved sensitivity testing methods are being developed
- Potential advantages:
 - safety profile
 - no selection of ARV resistance
 - bi-annual dosing with long-acting bNAbs (IV infusions)
- Future: Combinations of LA-ARV and LA-bNAbs
 - Other bNAb combinations, including 3 bNAbs
 - Bi- and Tri-specific molecules
 - Newer bNAbs with greater breadth and diff. mechanism of resistance

Antibodies differ from ARVs: Fc Effector Functions

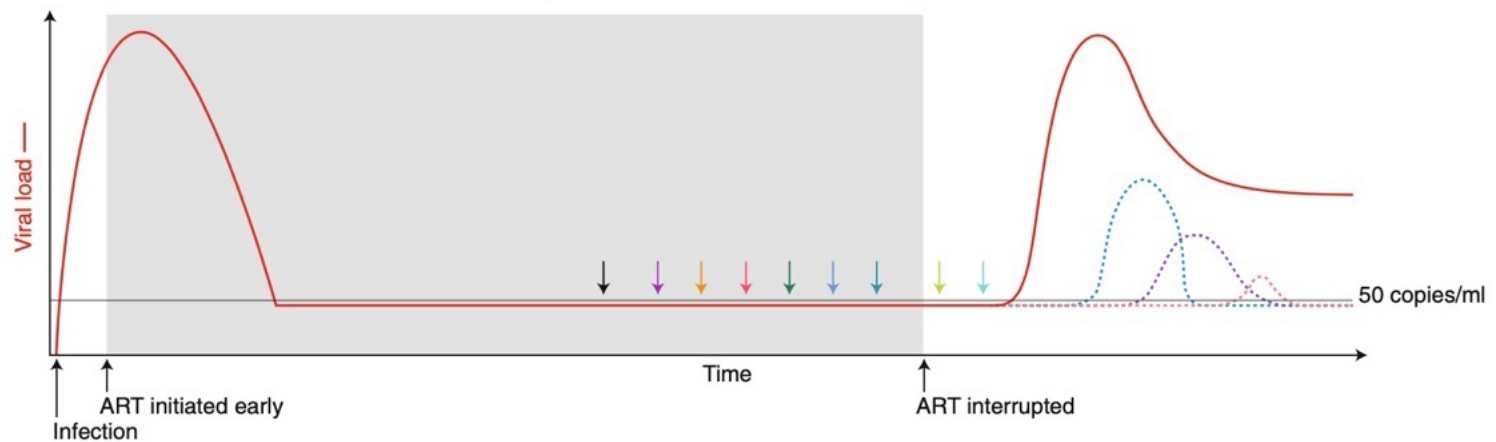


Combination Immunotherapy Strategies

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

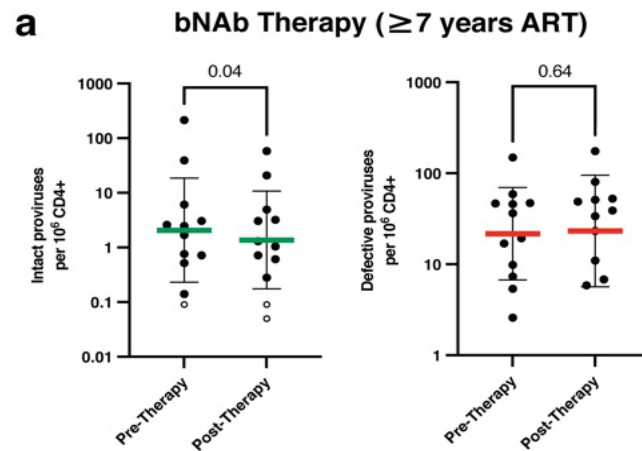


During ART suppression and/or ART interruption: Approaches to **Reduce** and/or **Control** the reservoir



Do bNAbs affect the viral reservoir and host immune responses?

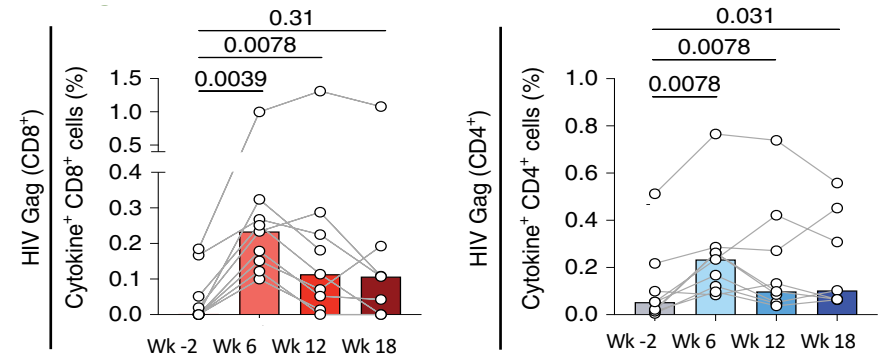
Effects on Intact Proviruses



- Moderate but significant changes in intact proviruses during bNAb therapy x 5 months.
- No change in defective proviruses

Gaebler et al, 2022

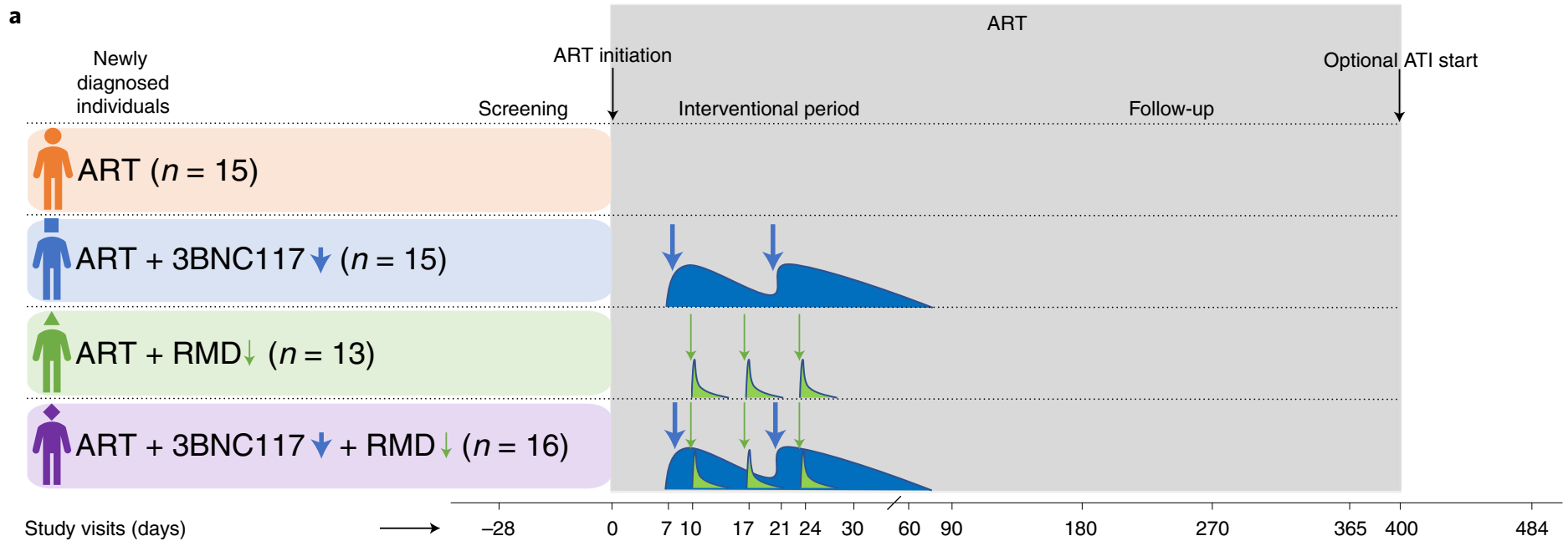
Effects on T Cell Immune Responses



- HIV-1 Gag-specific T cell responses were enhanced during bNAb- vs. ART-mediated viral suppression

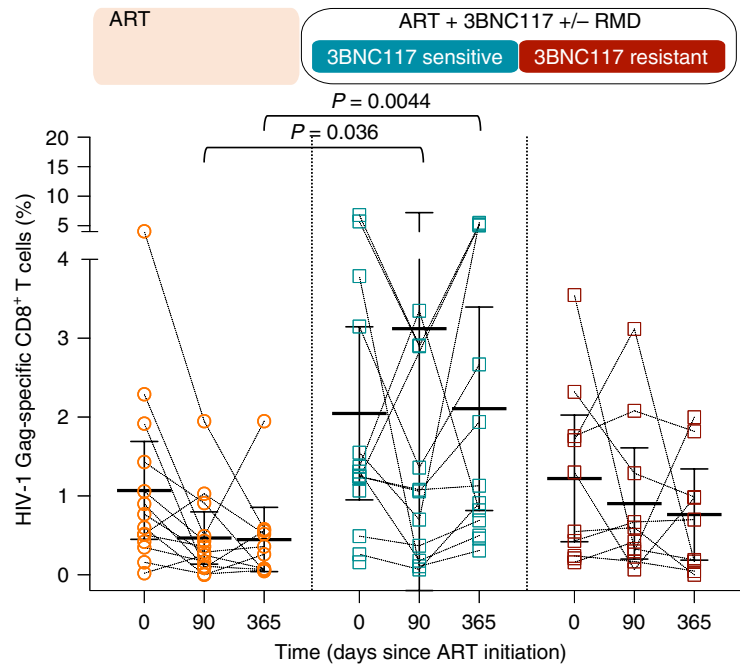
Niessl et al, 2020

eCLEAR Study: 3BNC117 +/- romidepsin (LRA) at ART initiation

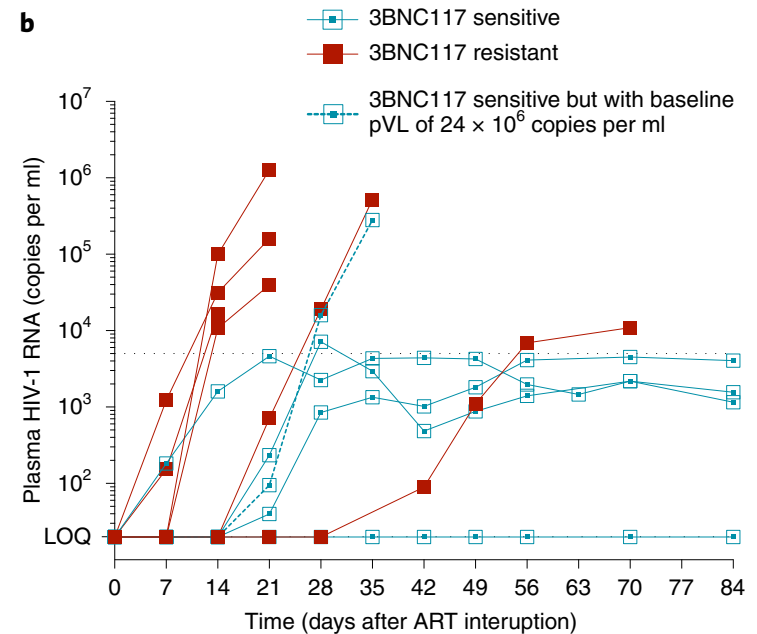


Increased T cell responses prior to ATI and delayed viral rebound among participants with 3BNC117 sensitive virus

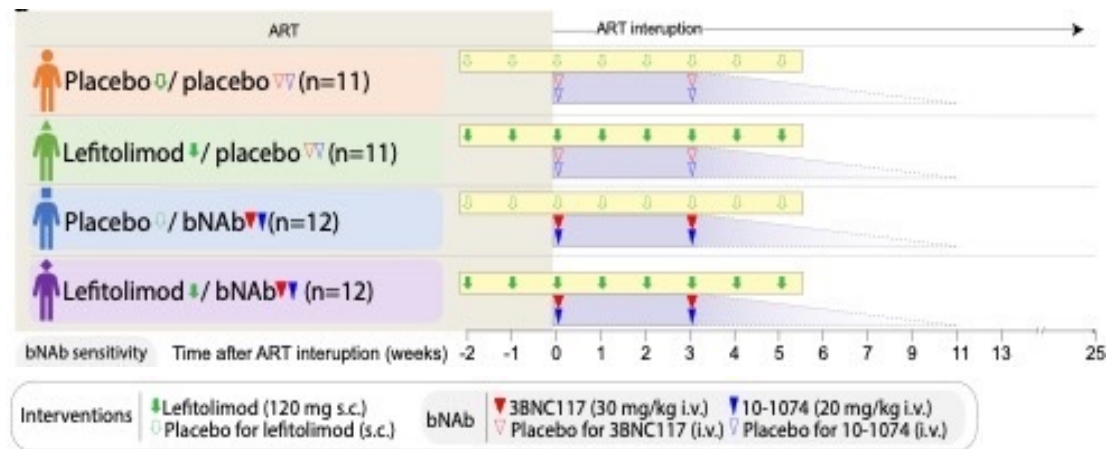
Enhanced HIV gag-specific CD8⁺ T cell responses among participants harboring 3BNC117 sensitive pre-ART viruses



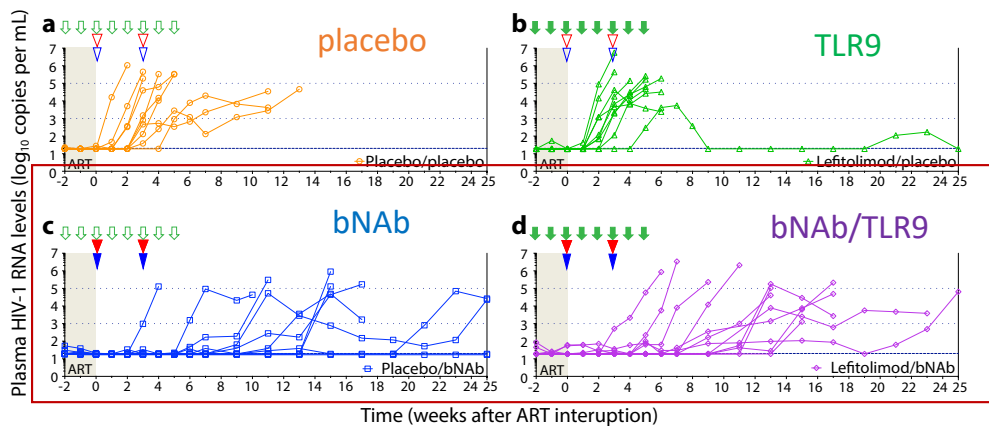
Delayed time to viral rebound after ATI among participants harboring 3BNC117 sensitive pre-ART viruses



TITAN study: 3BNC117+10-1074 +/- TLR9 agonist during ATI



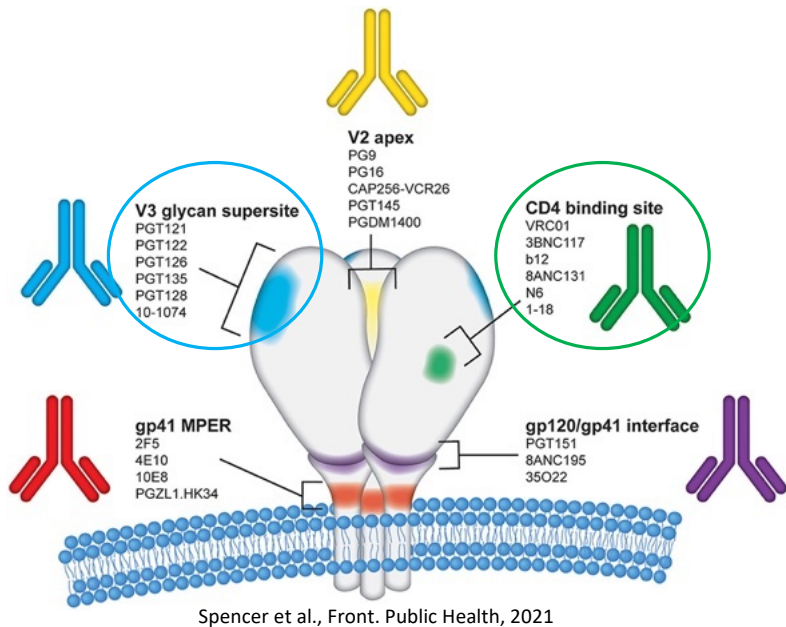
bNAb groups had longer period of viral suppression



- Median time to loss of control during ATI was 14 (bNAb/TLR9) and 17 weeks (bNAb)
- 4/11 participants in bNAb only group did not meet ART restart criteria in 25wks
- Trends towards increased Gag-specific CD8 T cells in bNAb recipients during viral suppression
- **No clear additional beneficial effect of combining lefitolimod with bNAb**

Clinical Trials of bNAbs in Children

- Adjunct to ART for **perinatal infection**
- **Prevention** of breast-milk transmission
- **Potential for ART-free remission** with very early ART.



IMPAACT P1112: Safety and dose finding studies (VRC01, VRC01-LS, VRC07-523LS) in newborns exposed to HIV
(Cunningham C et al. JID 2020; McFarland E. et al. JID 2021)

IMPAACT 2008: Early treatment of Infants with and without bNAbs (VRC01) to reduce reservoirs
(AIDS 2022; Khaitan A et al. for the IMPAACT 2008 team)

Tatelo Study: Efficacy of (combination VRC01-LS and 10-1074) maintaining 24 weeks of viral suppression during ATI in very early treated children

- 11 (44%) maintained HIV RNA <40 copies/mL through 24 weeks of bNAb-only treatment

(Shapiro R et al., Sci Transl Med 2023)

IMPAACT P1115 : Very early ART +/- VRC01 for remission; plan to switch to VRC07-523 LS

➤ Progress to date provides a framework for building future trials across the age-spectrum

Courtesy of Debbie Persaud (Johns Hopkins)



Summary II

- In non-human primate studies, promising results with different immunologic approaches: bNAbs, vaccines, TLR agonists and cytokines
- In clinical studies:
 - Early data suggest that **bNAbs may impact the intact proviral reservoir and modify anti-HIV immune responses**
 - **Interventions at ART initiation may impact the course of HIV infection**
- Future: Promising new molecules and delivery systems in development
Multiple ongoing/planned studies over next 2 yrs - including combination immunotherapy strategies

Acknowledgements

Study participants

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Brad Jones Trip Gulick

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Harris Goldstein

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Michael Seaman

Dartmouth

Margie Ackerman

IAVI

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Angela Lombardo

Harriet Park

Duke University

Georgia Tomaras

Kelly Seaton

David Montefiori



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