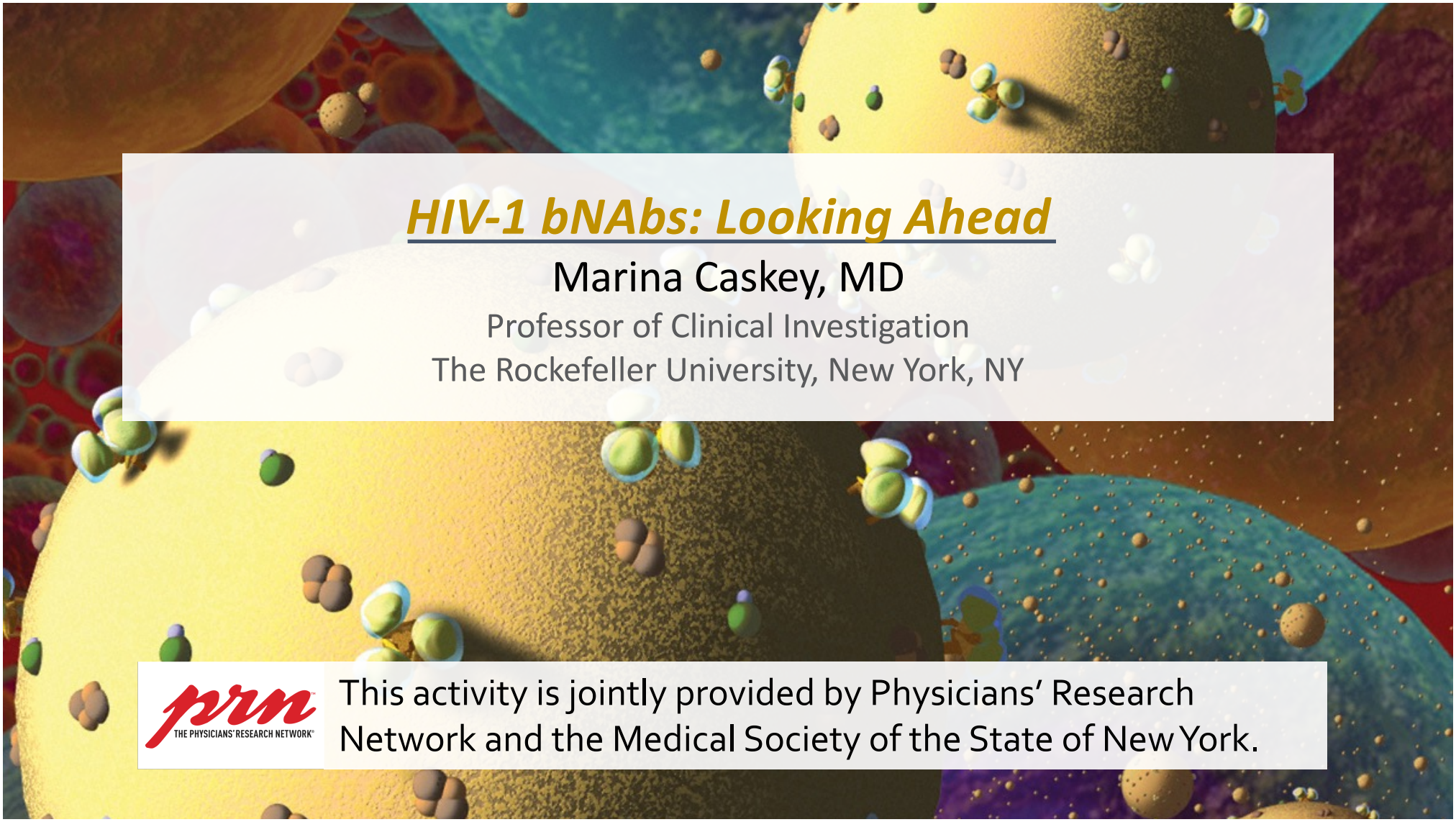


HIV-1 bNAbs: Looking Ahead

Marina Caskey, MD
Professor of Clinical Investigation
The Rockefeller University, New York, NY

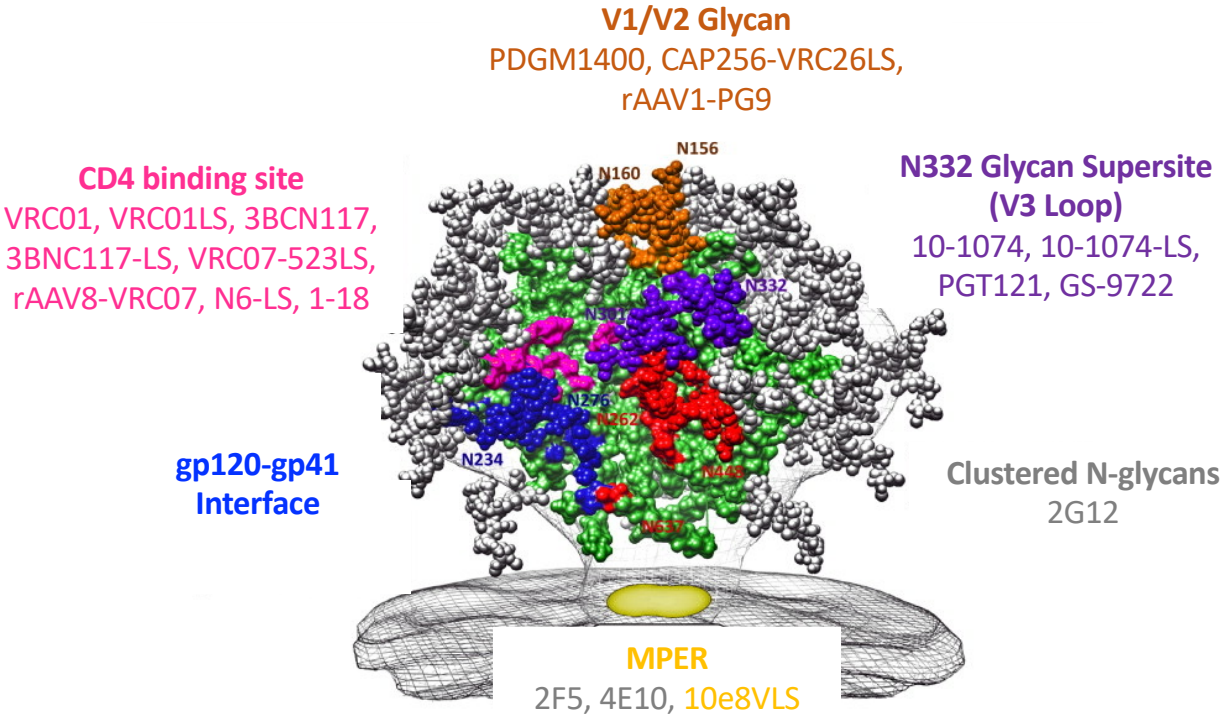
This activity is jointly provided by Physicians' Research Network and the Medical Society of the State of New York.

Outline

- Potential roles of HIV-1 bNAbs
- HIV-1 bNAbs clinical data: *Prevention, Therapy, Cure*
- Advances: promising preclinical data, new technologies & delivery systems

Single B cell cloning methods allowed the identification of many bNAbs targeting different epitopes

HIV bNAbs in Clinical Development



Adapted from Mouquet *et al.*, Trends Immunol 2014

Potential roles of bNAbs in HIV-1 infection

Treatment or prevention:
Long-acting alternative to ART

→

Safety: As a class, mAbs are **considered safe**

Adherence: mAbs **have long half-lives**, that can be prolonged to > 2 months

Provide immediate protection

Treatment-free remission:
Immune-mediated control of viral replication

→

mAbs might **"boost"** or "improve" existing **immune responses**

mAbs have potential to **directly eliminate infected cells** and therefore interfere with the HIV latent reservoir

Clinical Experience: Safety & Pharmacokinetics

- **Safety:** 15 "new generation" bNAbs tested in clinical studies to date (including bi- and tri-specific antibodies)
  - Well tolerated: AMP studies : repeated VRC01 >30,000 doses to > 3,000 participant
    - Infrequent infusion related reactions (most mild).

    ***Takuva** et al*, CROI 2021

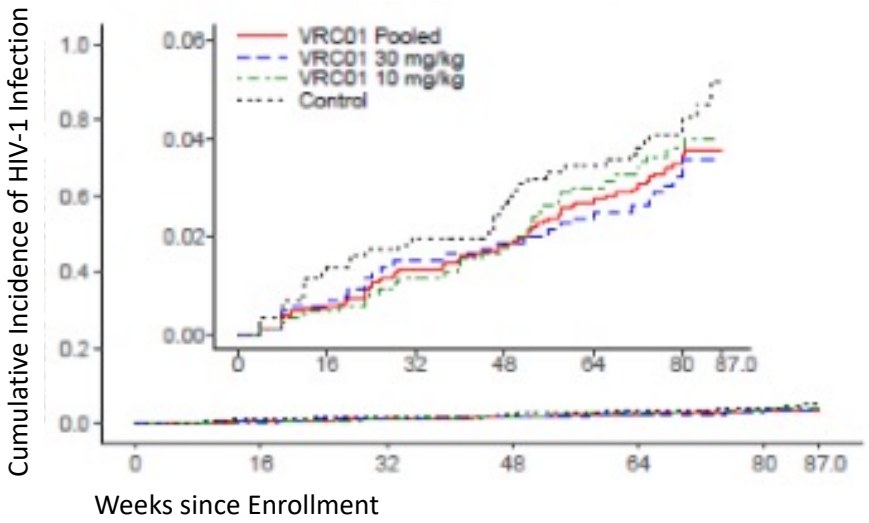
    Pediatric studies: VRC01LS+10-1074 in Children on ART

    ***Capparelli** et al*, CROI 2021
  - 10e8.VLS - Grade 3 local reactogenicity, study suspended
- **PK**: Half-lives of naturally occurring bNAbs range between 2-3 weeks
  - Half-life can be extended by ~ 3-fold

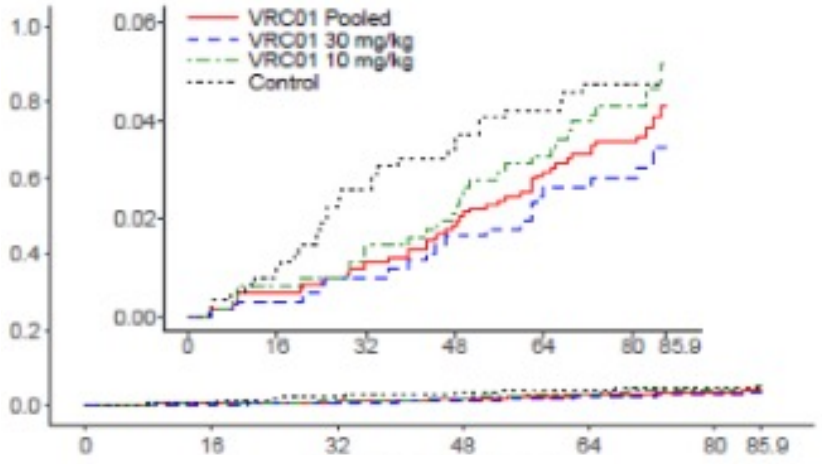
HIV-1 bNAbs: Prevention

Antibody Mediated Prevention (AMP) Studies: *VRC01 showed overall prevention efficacy of only 18.1%*

HVTN 704/HPTN 085

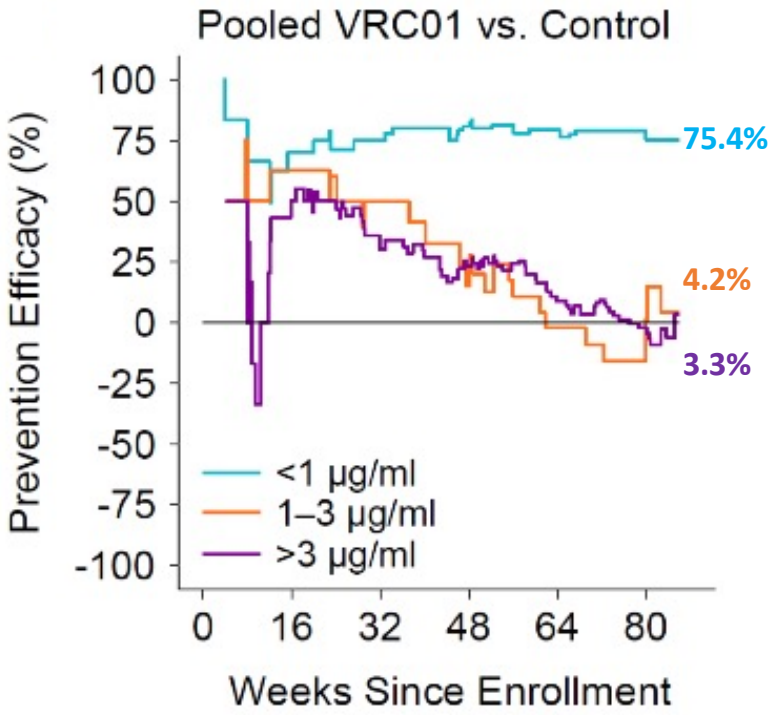


HVTN 703/HPTN 081



Corey L, NEJM 2021

VRC01 achieved *prevention efficacy* against *neutralization sensitive* viruses



- Prevention can be achieved by bNAb administration
  However, it is dependent on neutralization sensitivity of circulating strains ***(only 30% VRC01 sensitive)***
- *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".

➢ Viruses from placebo arm tested for other bNAbs – triple combination can achieve coverage of 90%

Corey L, NEJM 2021

Antibody Mediated HIV Prevention: Looking Ahead

Challenges:

- **Antibody resistance** among circulating strains is a major challenge
- Combination of potent antibodies will be needed
  - Will 2 or 3 long-acting antibodies be sufficient?
- Manufacturing challenges / high cost - SARS CoV-2 has shown these may be addressed
- **LA-cabotegravir has shown efficacy** and others are moving into efficacy studies
  - Long-term safety? Risk of resistance emerging to standard therapy?

Opportunities:

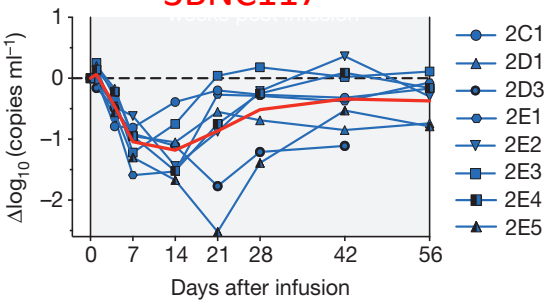
- Antibodies may provide a safe/viable alternative for long-term prevention:
  e.g. SC/IM delivery or yearly IV infusions (?)
- May have a niche in special settings: e.g. PMTCT

HIV-1 bNAbs: Therapy

Effects on Plasma Viremia

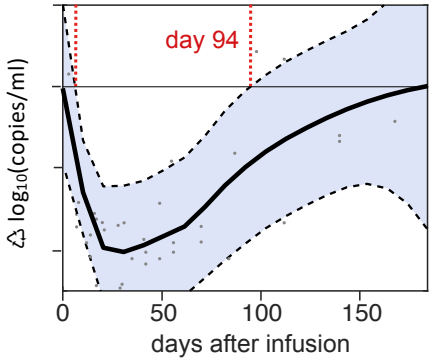
Single bNAb

3BNC117



Combination two bNAbs

3BNC117 +10-1074



Caskey, Klein et al., Nature 2015

Bar-On, Nat Med et al. 2018

- **Across studies: A subset of participants with baseline bNAb resistance**
- **Reduction in plasma viremia** of ~ 1.5 $\log_{10}$ cp/ml.
- **Viral suppression only** achieved **with low starting VLs**
- **Selection of resistant viral strains with monotherapy.**
  - Prolonged viral suppression observed in PGT-121 in 2 participants with low VLs (< 1,000 cp/ml) (Stephenson, CROI 2019)

Also tested/planned: VRC01, VRC01LS, N6LS, 10-1074, PGT121, PDGM-1400, CAP256V2LS

HIV-1 bNAbs: Therapy

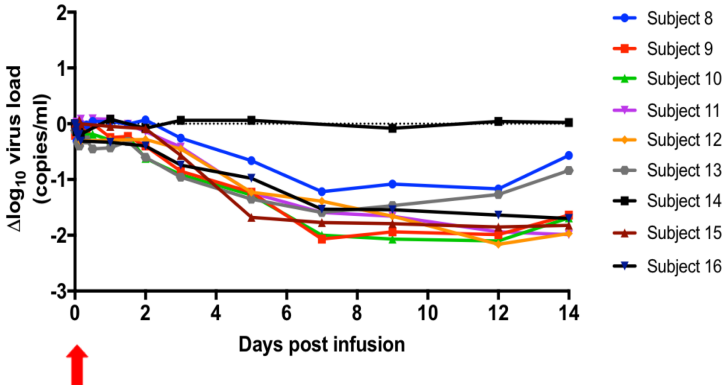
Engineered antibodies: Increased Potency and/or Breadth

Binding to different epitopes

Mono-specific

VRC07-523LS: CD4bs bNAb with superior breadth & potency

Chen, IAS 2019



Bi-specific

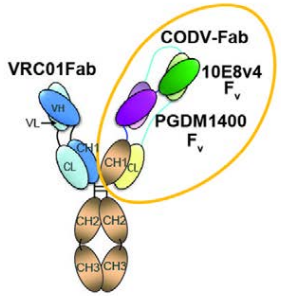
iMab/10e8v2.0

Sobieszczyk, R4P 2021:

- Good safety profile
- Detected in serum – PK analysis ongoing
- ***No neutralizing ADA*** (except for 1 participant)
- ***VL decline*** of 1.5 log_{10} cp/ml

Tri-specific

VRC01/10E8v4-PGDM1400-LS
(SAR441236)



A5377:

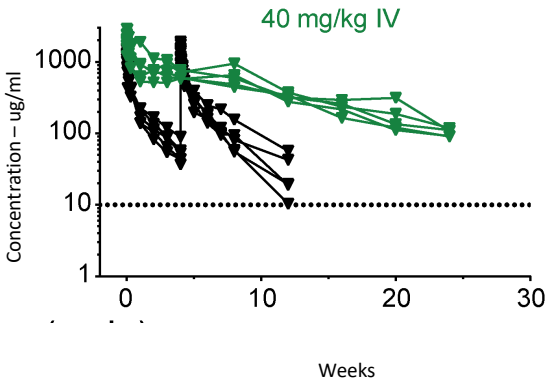
- Enrollment ongoing
- No safety concerns to date

HIV-1 bNAbs: Therapy

Engineered antibodies: Increased Bioavailability

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

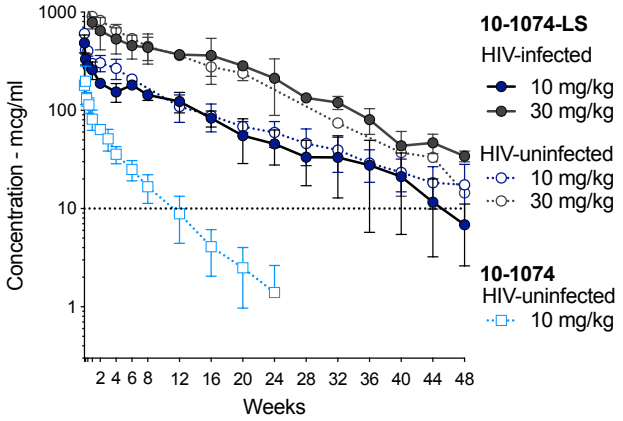
VRC01-LS



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

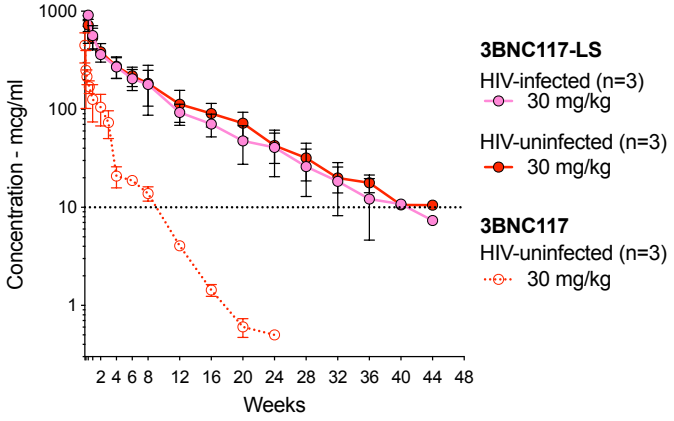
Gaudinski et al, PlosOne 2018

10-1074-LS



10-1074-LS $t_{1/2}$ 73.5 days
(vs. 10-1074 $t_{1/2}$ of 24 d)

3BNC117-LS



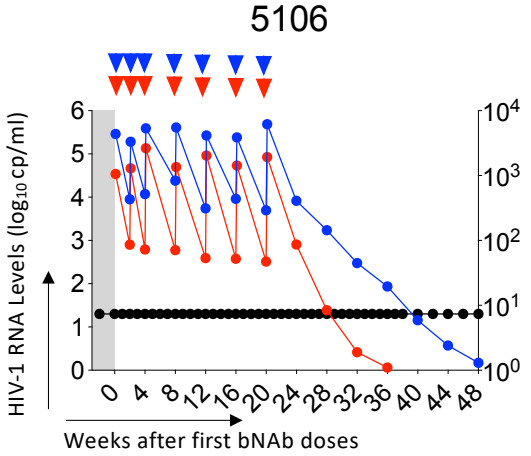
3BNC117-LS $t_{1/2}$ 61.3 days
(vs. 3BNC117 $t_{1/2}$ of 17.6 d)

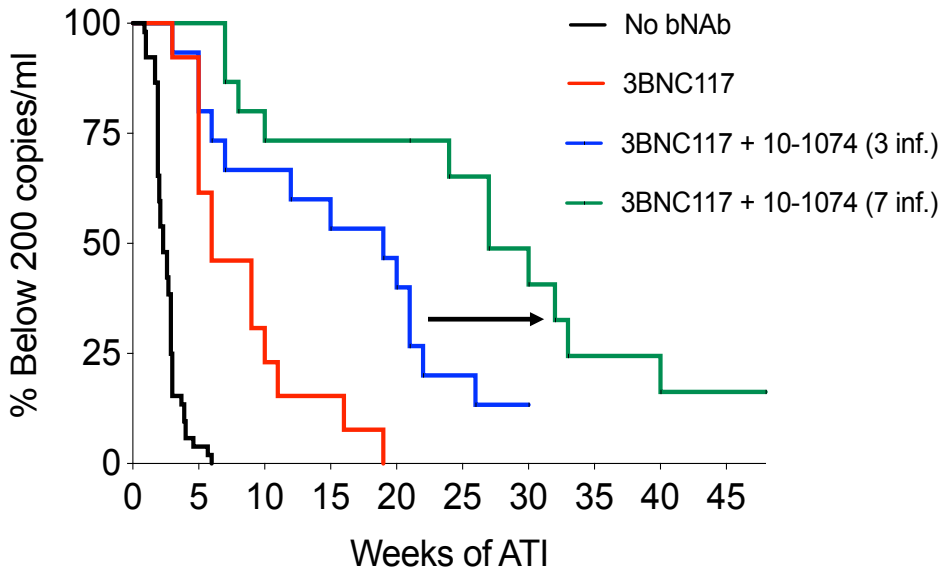
- Half-life of LS variants > 3 fold longer than parental mAbs
- Allows for quarterly SC or yearly IV administration

Combination of two bNAbs: maintains viral suppression in the absence of ART

Preliminary ongoing study

3BNC117+ 10-1074– infusions over 20 weeks in the absence of ART



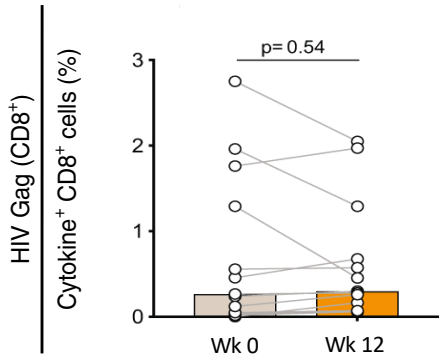


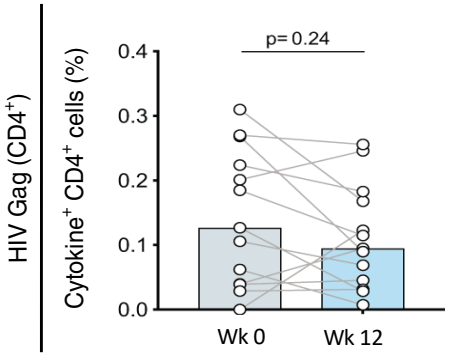
- ***~ 75% (13 out 17 participants) maintained viral suppression for > 20 wks post ATI***
  - 2 maintained suppression for at least 12 months
- Early rebounds associated with resistance to at least 1 of the bNAbs.

Scheid et al, Nature 2016
Mendoza et al, Nature 2018

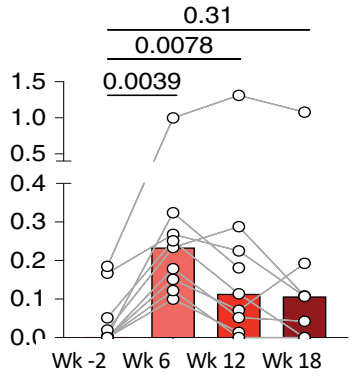
During combination bNAb therapy
Gag-specific T cell responses were enhanced

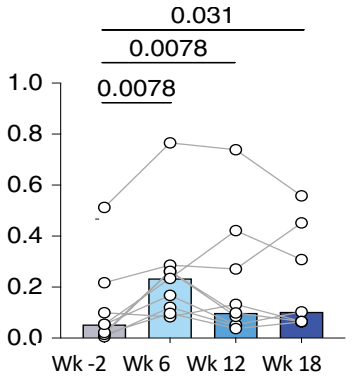
During ART-mediated viral suppression





During bNAb-mediated viral suppression





Niessl et al, Nat Med 2020

HIV bNAbs: Clinical Findings to Date

- bNAbs are generally **safe** in humans and have **half-lives of 2 and 3 wks**.
  - LS mutations prolong half-lives by > 3-fold.
- Proof-of-principle that **antibody-mediated protection can be achieved** against sensitive viruses
  - *But also highlights need for improved breadth and potency*
- In viremic individuals, single bNAb infusions lead to **significant decline is plasma viremia (~ 1.5 log copies/ml)**. Resistant strains are selected.
- **A combination of two bNAbs lowers viremia and maintains viral suppression** for **longer period** of time than monotherapy.
  - *De novo* resistance to both antibodies did not occur.
- Short-term bNAb studies so far did not show significant **changes in latent reservoir size**.
- Studies suggest that humoral & T cell responses can be enhanced during bNAb therapy.

HIV-1 bNAbs: Cure or Remission

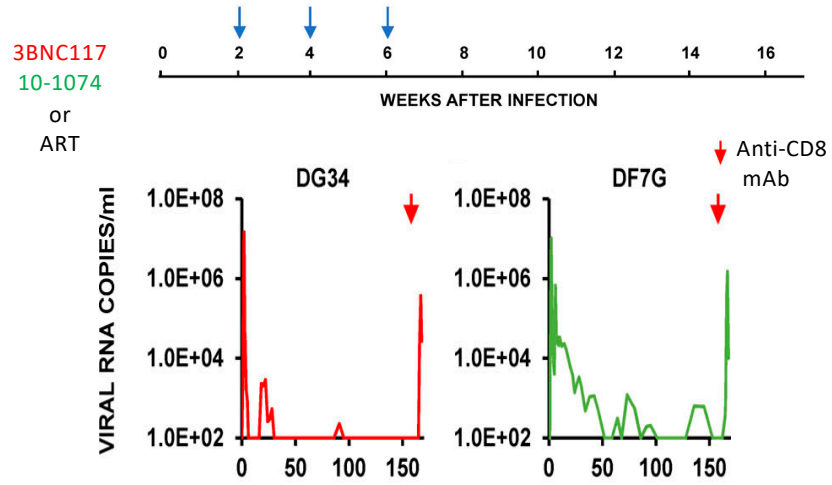
By **direct antiviral activity** and **Fc-mediated mechanisms**
bNAbs have the potential to:

Limit the establishment	***Reduce***		***Control***
Early ART	Resistance to infection	Depletion of infected cells	Enhance immunity
	Block/lock viral replication	Induce viral replication	

- *bNAb activity depends on binding to antigen*
  - Can $CD8^+$ T cell modulation be achieved in the presence of ART?
  - Will control require additional immune modulation and antigen expression: vaccines, TLR agonists or cytokines, as in cancer therapies?

bNAb Studies in NHP Lead to Long-term Viral Control in a Subset of Animals

➢ ***Early bNAb therapy*** *leads to CD8 mediated control of SHIV-AD8-E infection in NHP*



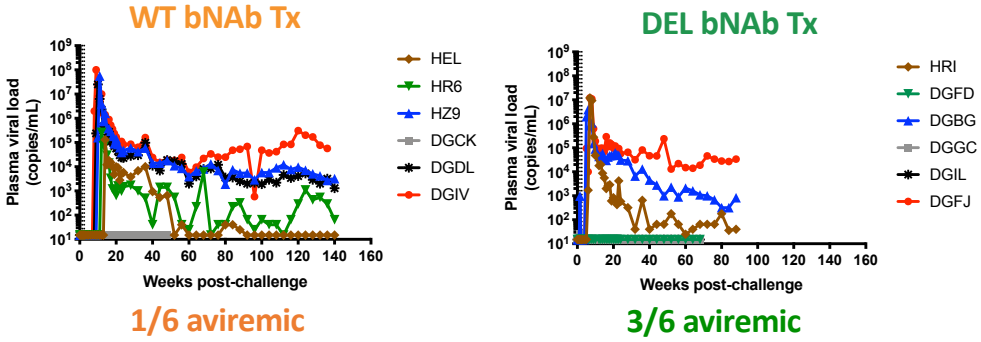
7/12 controllers

❖ **Accumulation of follicular CXCR5+ CD8+ T** cells in LNs

Nishimura et al, JEM 2020

➢ ***Early therapy with Fc-engineered bNAbs*** control viremia

SHIV-AD8-EO IR challenge
> VRC07-523LS + PGT121
> VRC07-523LS/DEL + PGT121/DEL
> No tx



1/6 aviremic **3/6 aviremic**

❖ **Fc-modified bNAb-treated monkeys** developed a distinct **LN transcriptomic profile**

Dias J. et al CROI 2021

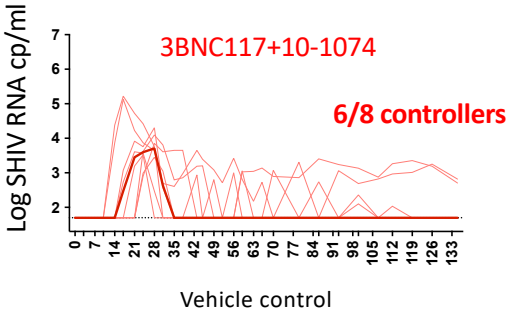
bNAbs in acute infection: clinical trials planned/underway

Name	Intervention	Population	Status	ATI
RV398 (MHRP - Ake)	- VRC01 > ART - VRC01 + ART	Acute infection	Enrolled / analysis ongoing	no
A5388 (ACTG – Crowell/Hsu)	- VRC07-523LS + PGT121BIJ414LS + ART	Acute infection	Planned 2021	yes
RHVIERA (Pasteur – Saez-Cirion)	- 3BNC117-LS + 10-1074-LS + ART	Acute infection	Planned 2021	yes

Combination Immunotherapy to increase antigen expression and modulate innate and adaptive responses

bNAb + IL15 (N-803)

SHIV-AD8 - ART at ~ 7 weeks

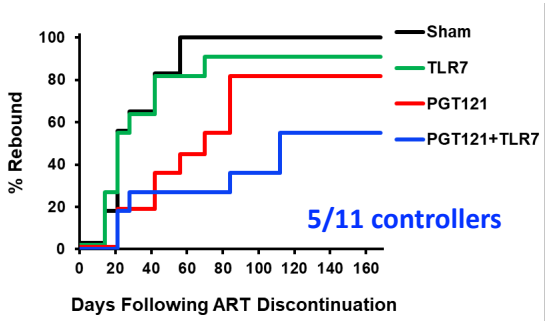


- NK and T cell activation
- CD8 depletion led to rebound

Whitney J, CROI 2020

bNAb + TLR7

SHIV-162.P3 – ART at 1 wk

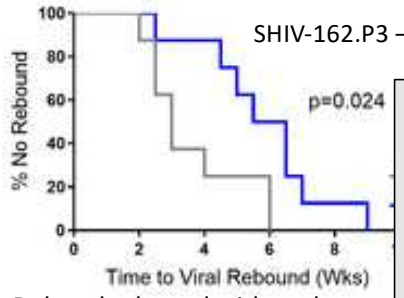


- NK and T cell activation
- No HIV-1 DNA and T cell responses in LNs

Borducchi E et al, Nature 2018

(*Nkolola J et al, CROI 2020 (Chronic Infection)

SHIV-162.P3 – ART at 2 wks

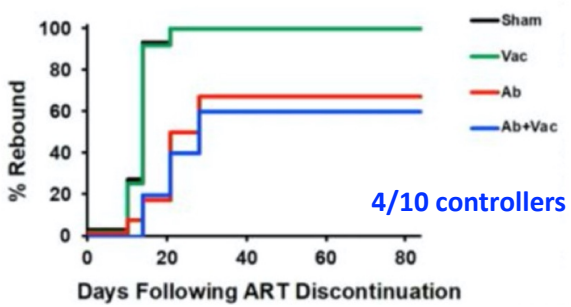


- Delayed rebound without long-te

Hsu D, Plos Pathogens *in press*

Vaccine + bNAb + TLR7

SHIV-162.P3 – ART at 1 wk



- CD4 activation and vaccine T and B cell responses
- VL setpoint and Gag+ responses correlated with control

Barouch D, CROI 2020

- Immune effects (NK cells, T cells) were observed
- **Long-term control achieved in a subset of animals**
  - Mechanisms of control not fully elucidated
    But evidence of CD8 involvement in control
  - Related to reservoir size/composition?

Combination immunotherapy: clinical trials planned/underway

Name	Intervention		Population	Status	ATI
ROADMAP (Sogaard/Caskey/Fatkenheuer)	3BNC117	Romidepsin	Chronic	CROI2020	yes
eCLEAR (Sogaard/Fidler)	3BNC117	Romidepsin	Early infection (viremic)	Late follow up	yes
A5386 (ACTG –Wilkin/Caskey/Jones)	VRC07-523LS 10-1074	N-803	Chronic	Planned 2021	yes
U01 – RU/Penn/Cornell (Caskey/Wilkin/Tebas)	3BNC117-LS 10-1074-LS	N-803	Chronic	Planned 2021	yes
BEAT HIV2 (Monaner/Tebas)	3BNC117 10-1074	Type I IFN	Chronic	Ongoing	yes
TITAN (Sogaard/Lewin)	3BNC117 10-1074	TLR9	Chronic	Ongoing	yes
amfAR/UCSF (Deeks)	VRC07-523LS 10-1074	DNA/MVA TLR9	Treated during acute infection	Ongoing	yes
A5374 (ACTG – Riddler/Gay/Mellors)	3BNC117-LS* 10-1074-LS*	ChAd/MVA TLR7	Treated during acute infection	Planned 2021	yes

HIV-1 bNAbs Advances

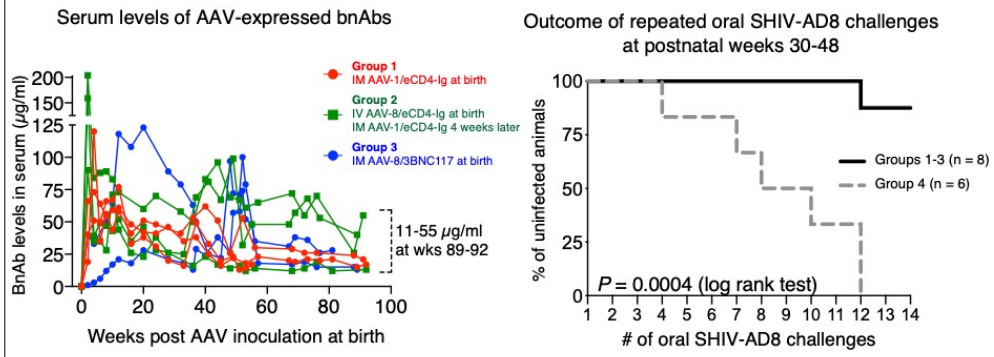
- *New naturally occurring and engineered antibodies* with greater breadth and potency:
  - **1-18** : a new CD4bs bNAb (Schommers et al., Cell 2020)
  - **BISC-1A***:* V2-V3 Loop bi-specific (Davis-Gardner et al., mBio 2020

- *Delivery systems* – long-term (in vivo) secretion of bNAbs
  - AAV Vectors
  - DNA Gene Transfer
  - B Cell Engineering

Sustained production of bNAbs by your own cells
AAV Vectors

Neonatal Delivery of AAV/bNAb Vectors in NHP

AAV8-eCD4-Ig or AAV8-3BNC117

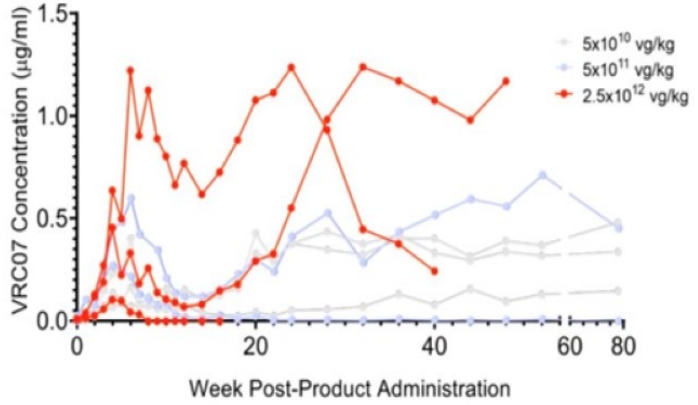


- **Results in persistent bNAb serum concentrations for >89 wks**
- **Protection infant rhesus macaques against repeated oral SHIV infection**

Martins M, CROI 2021

AAV/bNAb Delivery in Humans

AAV8-VRC07



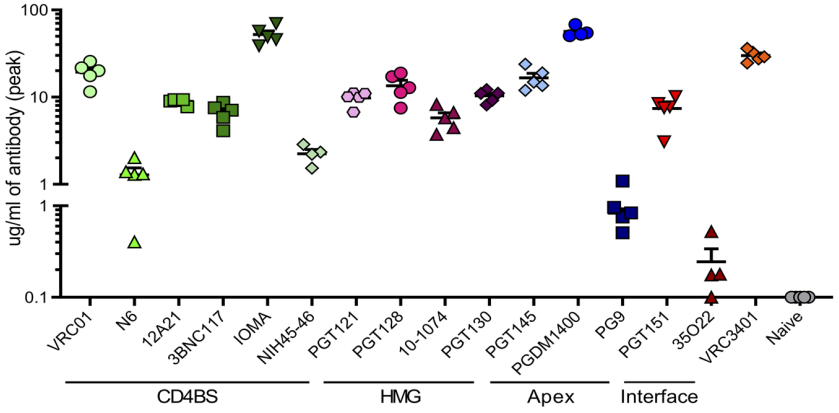
- **VRC 603**: 8 people received **AAV8-VRC07** (three doses)
- **2/3 at high dose had sustained production of VRC07.**
- ADA responses detected

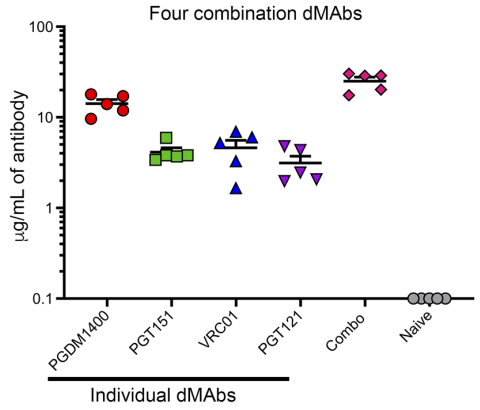
Casazza et al., CROI 2020 (LB 41)

Casazza et al. CROI 2021

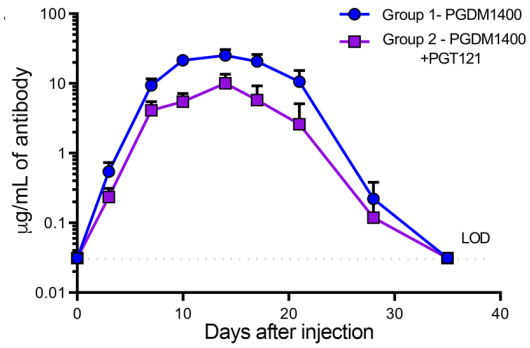
Sustained production of bNAbs by your own cells
DNA Gene Transfer

Delivery of multiple dmAb in immunodeficient mice





Delivery of dmAbs in NHP



- Successful **expression of multiple mAbs**
- Maintain binding and neutralizing activity
- In NHP, achieved serum levels of 5 and up to 30 mcg/mL

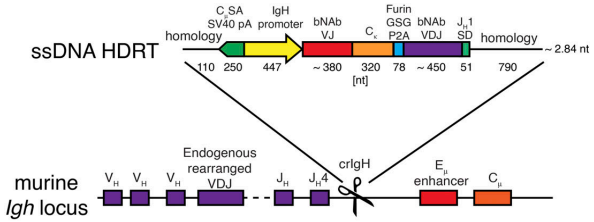
Wise et al., JCI 2020

Reprogramming B cells to produce bNAbs

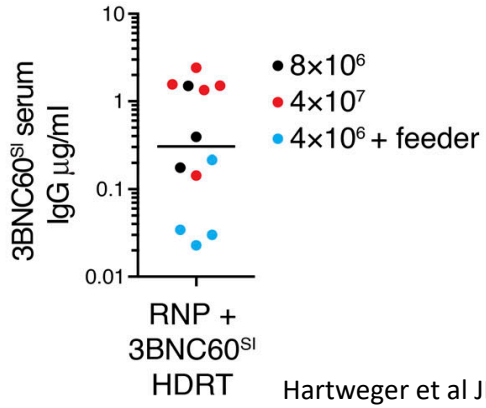
Engineered B cells by CRISPR/Cas9 **secrete functional bNAb** following immunization in mice

Engineered B cells by CRISPR/Cas9 enable **immunological memory** and undergo **clonal expansion *in vivo***

Targeting strategy

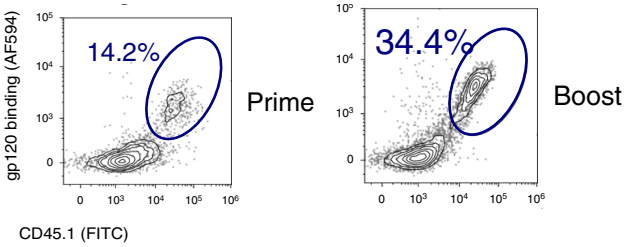


Antibody secretion in mice

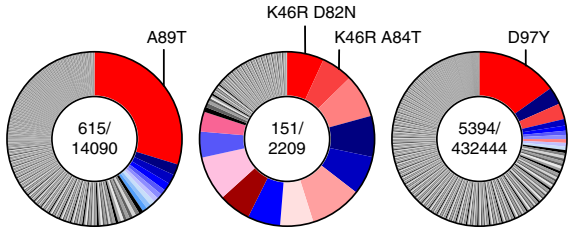


Hartweger et al JEM 2019

Engineered B Cells Expand in Vivo



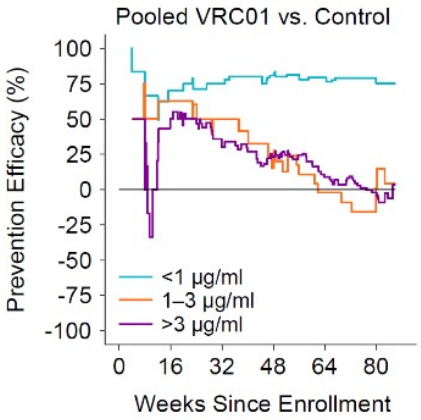
B cell clones after immunization



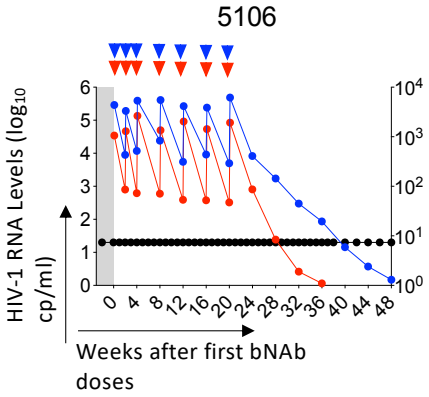
Nahmed et al Nat Commun 2020

State of bNAbs – Future Directions

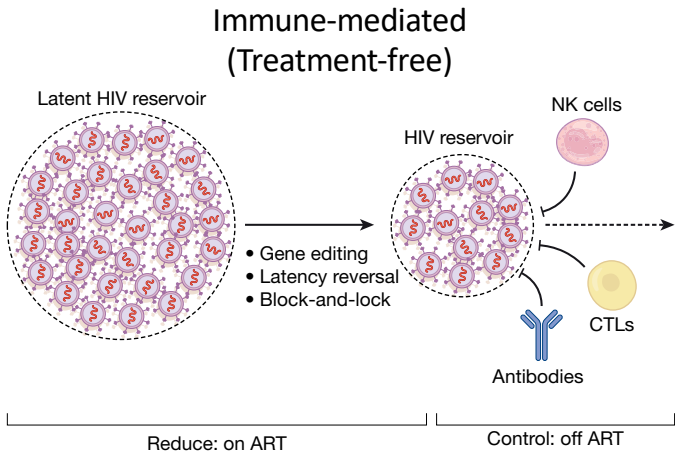
Prevention



Therapy



Long-Term Control



Ndungu McCune, Deeks, Nature 2019

- Proof-of-concept for antibody-mediated prevention
- Emerging evidence that bNAbs can maintain viral suppression
- Potential advantages: safety & no selection for ARV resistance
- Challenges: pre-existing resistance & cost
- Future: promising new molecules and delivery systems

- An aspirational goal - *likely to require combinations*
- Promising results in non-human primates
- Multiple ongoing/planned studies over next 2 yrs
- Early promising data with long-term delivery

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