Anti-HIV-1 bNAbs: Potential Clinical Applications

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Learning Objectives

After attending this presentation, learners will be able to:

- List potential indications of HIV-1 bNAbs
- Describe the engineering process of bNAbs and the delivery system in early clinical trials
- Describe the status of bNAb clinical trials in people with HIV (PWH)

Slide 3 of X

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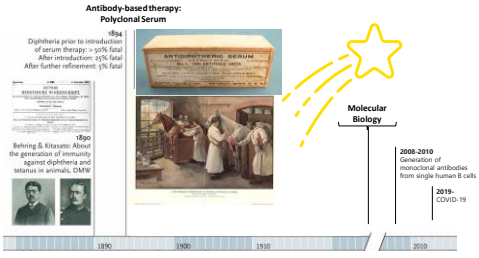
Passive immunization is effective against infectious diseases



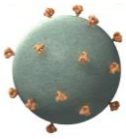
Slide 4

Modified from Kaufmann SHE. mBio 2017.

4

HIV & SARS-CoV-2:
Experience in both fields propel development of immunotherapy

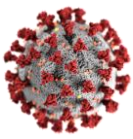
HIV *



Discovery: Cloning methods
Characterization: activity, specificity
Engineering:
Fc modifications for half-life and function

Safety: Diverse populations
Efficacy: Prevention & Therapy
Implementation: Fast development
Possibility of fast deployment

SARS-CoV2



* Key differences in HIV: Extreme viral diversity & latency – natural immunity does not cure infection

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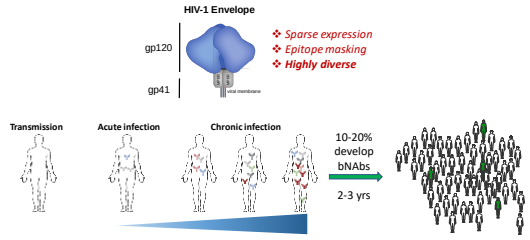
Broadly Neutralizing Antibodies Develop during HIV Infection



Can neutralizing antibodies have a role in HIV infection?

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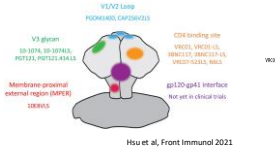
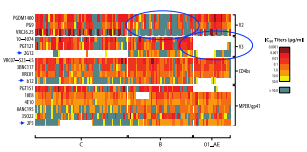
Anti-HIV-1 bNAbs Targeting Different Epitopes in Clinical Trials

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.***

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Potential Roles of bNAbs in HIV-1 Infection

Treatment & Prevention: Long-acting alternative to ART →

Safety: As a class, mAbs are **considered safe**
No risk of selecting **ARV resistance**

Adherence: mAbs **have long half-lives**, that can be prolonged to 2-3 months

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

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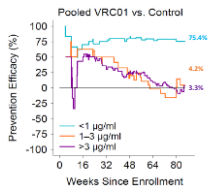
HIV-1 bNAbs: Prevention

AMP studies: VRC01 achieved prevention efficacy against neutralization sensitive viruses



- **Prevention can be achieved by bNAb 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*

Corey et al, NEJM 2021
Gilbert et al, Nat Med 2022

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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?

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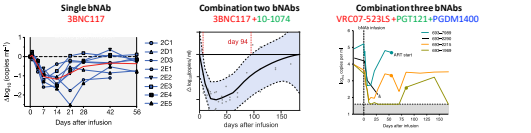
HIV-1 bNAbs: Therapy

Effects on Plasma Viremia

Single bNAb
3BNC117

Combination two bNAbs
3BNC117+10-1074

Combination three bNAbs
VRC07-523LS+PGT121+PGDM1400



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

- **Across studies: A subset of participants with baseline resistance**
- **Transient reduction in plasma viremia** - nadir ~ 1.5 $\log_{10}$ 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

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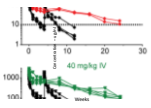
HIV-1 bNAbs: Therapy

Engineered Antibodies: Increased Bioavailability

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

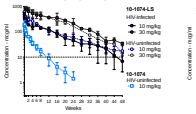
VRC01-LS



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

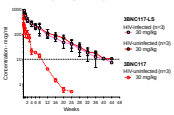
Gaudinski et al, 2018

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

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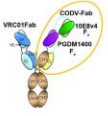
HIV-1 bNAbs: Therapy

Engineered Antibodies: Increased Potency and/or Breadth

Bi-specific
iMab/10e8v2.0

Sobieszczyk, CROI 2022:
- 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

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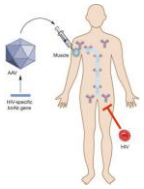
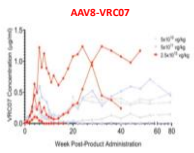
Delivery Systems: Sustained in vivo secretion of bNAbs

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

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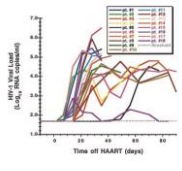
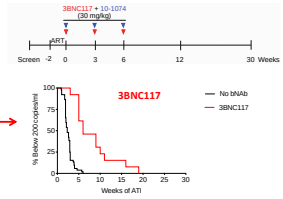
HIV-1 bNAbs: Therapy

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

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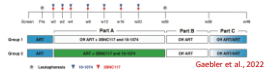
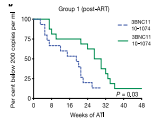
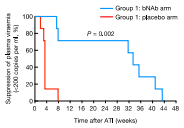
Repeated doses of two bNAbs can maintain suppression of sensitive viruses in the absence of ART



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)**

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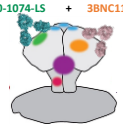
Ongoing "Switch" Studies: LS-bNAbs + LA-ARV

- Capsid Inhibitor
  - Lenacapavir
- bNAbs

10-1074-LS + 3BNC117-LS



NCT04811040

- Integrase Inhibitor
  - Cabotegravir
- bNAbs

VRC07-523LS

A5357 / NCT03739996

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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

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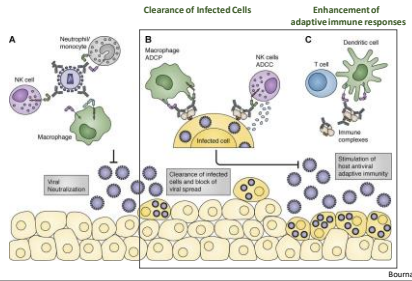
Antibodies Differ from ARVs: Fc Effector Functions



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Bournazos et al., JEM 2015

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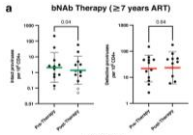
Do bNAbs affect the viral reservoir and host immune responses?

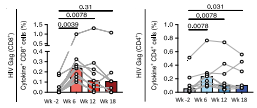
Effects on Intact Proviruses



- **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

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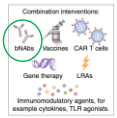
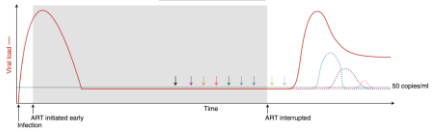
Combination Immunotherapy Strategies

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, 2022

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bNAbs – HIV Cure Strategies:

- *Promising results in non-human primate studies*
  - But, predictors of virologic control not fully understood
- *Clinical trials of cure strategies – open questions*
  - What is the best timing for cure interventions?
  - Will interventions be as effective during ART or in the absence of ART?
  - How long do interventions need to be?
  - Will ART-free control of HIV require additional immune modulation and antigen expression?

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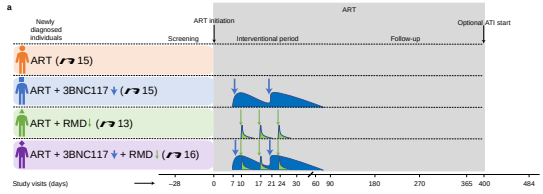
eCLEAR Study: 3BNC117 +/- romidepsin (LRA) at *ART initiation*



Gunst et al, 2022

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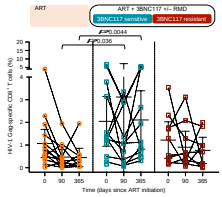
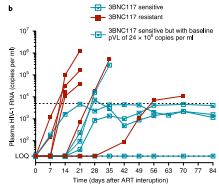
Increased T cell responses prior to ATI and delayed viral rebound among participants with 3BNC117 sensitive virus

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



Gunst et al, 2022

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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 – Malvesutto)

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 – Ridler)

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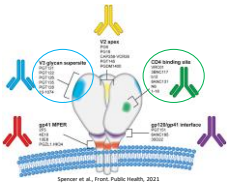
Clinical Trials of bNAbs in Children

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



Spencer et al., Front. Public Health, 2021

IMPAACT P1112: Safety and dose finding studies (VRC01, VRC01-LS, VRC07-523LS) in newborns exposed to HIV
(Cunningham C et al. IID 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

(CROI 2022, Shapiro R et al.)

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

PAVE IMPAACT

Slide 26 *Courtesy of Debbie Persaud (Johns Hopkins)*

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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

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Acknowledgements

Study participants

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John Frater

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Michael Seaman

Dartmouth
Margie Ackerman

IAVI
Pat Fast
Vince Philiponis
Angela Lombardo
Harriet Park

Duke University
Georgia Tomaras
Kelly Seaton
David Montefiori

REACH for the Cure · The Rockefeller University · CHAR · NIH National Institute of Allergy and Infectious Diseases · Bill & Melinda Gates foundation · hhmi Howard Hughes Medical Institute · Robertson Foundation

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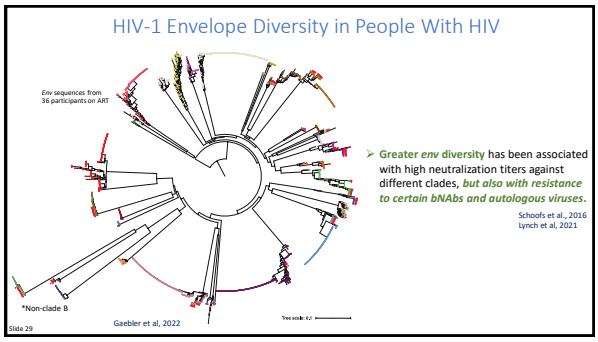
HIV-1 Envelope Diversity in People With HIV
Env sequences from 36 participants on ART
*Non-clade B
Gaebler et al, 2022
Slide 29
Greater env diversity has been associated with high neutralization titers against different clades, but also with resistance to certain bNAbs and autologous viruses.
Schoofs et al., 2016
Lynch et al, 2021

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Question-and-Answer Session
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IAS USA

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