UNC SCHOOL OF MEDICINE

Where do bNAbs Fit in the Treatment Landscape?

Joe Eron, MD

Professor Medicine
UNC Chapel Hill

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bNAbs for HIV Treatment

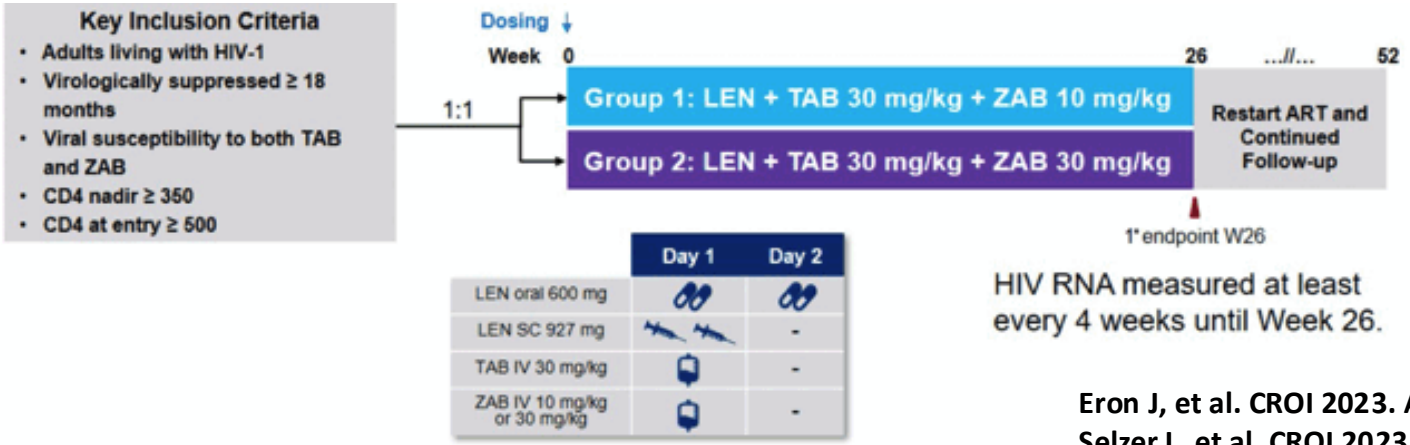
- **Opportunity for very long-acting therapy**
  - Setting
    - Current long-acting small molecules lack partners
    - Substantial proportion of PWH on treatment desire long-acting therapy
      - Convenience, stigma, anxiety, daily reminder of HIV
    - People with HIV who cannot access, cannot navigate or are endangered by frequent oral therapy or a not reached by our current system
      - Potential to help end HIV epidemic (final 5% of 95:95:95)
  - Populations
    - PWH – suppressed on therapy
    - PWH – naïve to ART or viremic with or without resistance

bNAbs for HIV Treatment

- **Potential treatments**
  - bNAbs combined with small molecules
    - Need similar half-lives
    - Examples – bNAb with lenacapavir or bNAb with LA cabotegravir
  - bNAb combinations
    - Different targets on HIV envelope (CD4 binding, V3, V2)
  - Tri or Quad-specific antibodies
    - e.g. SAR441236, a Tri-specific Broadly Neutralizing Antibody (a5377)
  - Combination with other long-acting antibodies
    - bNAb plus CD4 binding antibodies (e.g UB421 or ibalizumab)

Lenacapavir with bNAbs Teropavimab and Zinlirvimab Dosed every 6 Months in ART-suppressed PWH

- Teropavimab (TAB; 3BNC117-LS) and Zinlirvimab (ZAB; 10-1074-LS); long acting bNAbs
- Required susceptibility to both antibodies to enter
- Evaluated whether LEN + TAB + ZAB can maintain HIV suppression for 6 months
  - Study enrollment halted due to pause in availability of lenacapavir IV formulation.

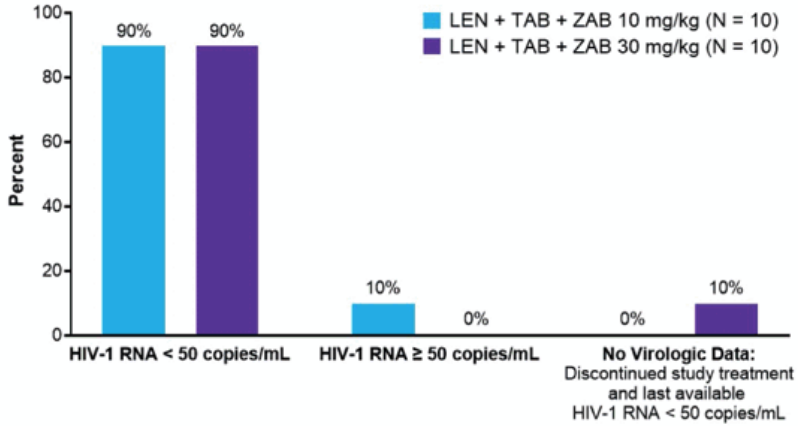


Eron J, et al. CROI 2023. Abstract 193.
Selzer L, et al. CROI 2023. Abstract 580.

Lenacapavir with bNAbs Teropavimab and Zinlirvimab Dosed every 6 Months in ART-suppressed PWH

- Screened 124 individuals; 55 met bNAb susceptibility criteria; 21 enrolled
- Participants received LEN with 10 mg/kg TAB + ZAB or 30 mg/kg TAB + ZAB
- 18 of 20 maintained HIV suppression
- 1 participant withdrew at wk 12 with VL <50
- 1 participant had confirmed virologic rebound at wk 16; resuppressed on baseline RPV/F/TAF
- Phase 2 study launched

Virologic outcomes, wk 26



Duration of baseline ART: median 2.6 y

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Pilot study with sensitivity to single antibody (data pending)

bNAbs for HIV Treatment

- **Ongoing examples (all in PWH suppressed on ART)**
  - A5357 VRC07 523LS plus cabotegravir-LA (submitted to CROI)
  - Teropavimab, zinlirvimab, lenacapavir Phase 2b – recruiting (NCT05729568)
  - N6 (VH3810109) plus cabotegravir LA Phase 2 Phase 2b recruiting (NCT05996471)
  - PGDM1400 and PGT121 and VRC07-523LS Monoclonal Antibodies in HIV-infected and HIV-uninfected Adults (Juelg et al CROI 2022) (NCT03205917)
  - TMB-365 (2^{nd} Gen Ibalizumab) and TMB-380 (VRC07-523LS) in Suppressed PWH (NCT05275998)

bNAbs for HIV Treatment

- **Hurdles**
  - Susceptibility testing vs. broadly active combination
  - Administration
    - IV infusion vs. SQ dosing (likely requires increased potency)
  - Need for multiple antibodies, complex structures or partner with small molecules
  - Putting small molecules at resistance risk at failure
  - Emergent ADA related treatment failure
    - Could be a late phenomena
  - Pharma preference for the “sure thing” before exploring the “hard thing”
    - All initial studies likely to be done in PWH suppressed on ART (in care and adherent)

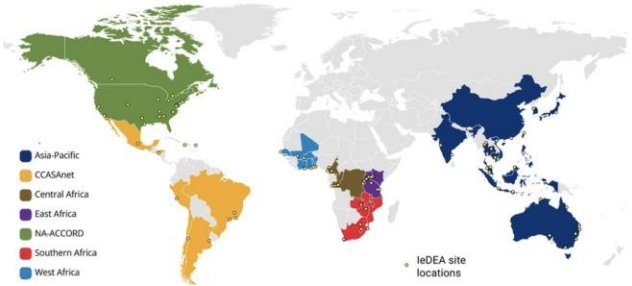
It all starts with “U”

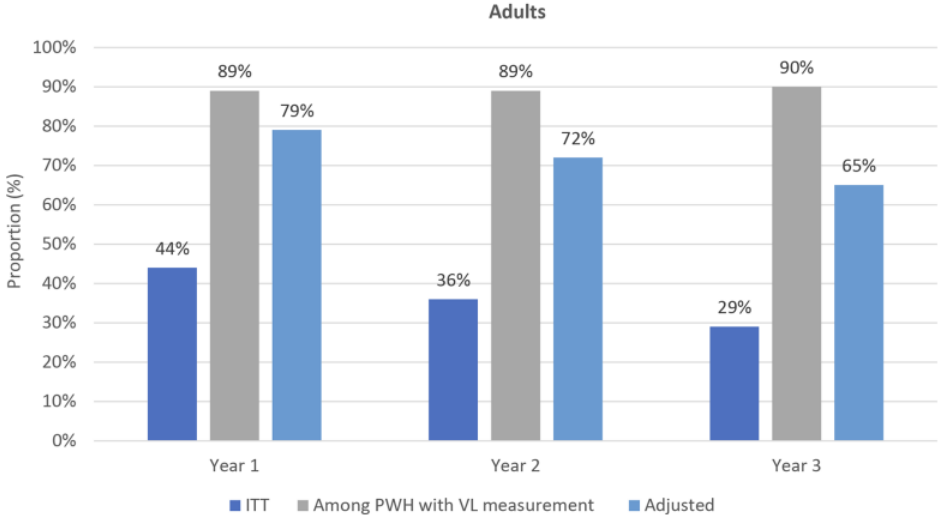
United States - CDC

*Viral load <200 copies/mL or undetectable based on most recent test in the past 12 months.
†Sustained viral suppression defined as having all viral load tests in the past 12 months <200 copies/mL or undetectable.

https://www.cdc.gov/hiv/images/library/reports/hiv-surveillance-special-reports/no-32/infographics/cdc-hiv-mmp-report-32-figure-download-4.png

Global estimates IDEA Network





https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8782625/pdf/nihms-1769075.pdf

bNAbs for HIV Treatment

- **Treatment of those with “untreatable” MDR HIV**
  - Resistance, multi-agent intolerance, limited treatment options
  - Should we be urgently studying antibody combinations in people with untreatable MDR HIV?
  - Very limited toxicity and less costly than many interventions the medical community explores for people with limited treatment options in other disease states.
  - Compassionate access across multiple bNAb sponsors?

bNAbs as Component of Functional Cure or Reservoir Reduction Strategies

bNAb for Function Cure or Reservoir Reduction

- Evidence of prolonged suppression post infusion of bNAb
  - SIV/SHIV models
  - Small numbers in PWH
    - ? Effect on reservoir
- Combine with LRA
- Vaccinal effect –
  - Facilitates long-lasting T cell immunity (SHIV, ? Humans)
- Clearance of infected cells
- Targeting arm
  - CAR-T, BYTES, DARTs

Shingai M, et al. Antibody-mediated immunotherapy of macaques chronically infected with SHIV suppresses viraemia. Nature 2013;503:277-80.

Nishimura Y, et al. Early antibody therapy can induce long-lasting immunity to SHIV. Nature. 2017;543:559–563. doi: 10.1038/nature21435. - DOI - PMC - PubMed

Gaebler C, et al. Prolonged viral suppression with anti-HIV-1 antibody therapy. Nature 2022;606(7913):368-374.

Sneller MC, et al. Combination anti-HIV antibodies provide sustained virological suppression. Nature. 2022;606:375–381. doi: 10.1038/s41586-022-04797-9. - DOI – PubMed

Gunst JD, et al, Impact of a TLR9 agonist and broadly neutralizing antibodies on HIV-1 persistence: the randomized phase 2a TITAN trial.. Nat Med. 2023 Oct;29(10):2547-2558. doi: 10.1038/s41591-023-02547-6. Epub 2023 Sep 11.

Borducchi, E. N. et al. Antibody and TLR7 agonist delay viral rebound in SHIV-infected monkeys. Nature563, 360–364 (2018). - PMC – PubMed

Nishimura Y, et al. Immunotherapy during the acute SHIV infection of macaques confers long-term suppression of viremia. J. Exp. Med. 2021;218:e20201214. doi: 10.1084/jem.20201214. - DOI - PMC - PubMed

Rosás-Umbert M, et al. Administration of broadly neutralizing anti-HIV-1 antibodies at ART initiation maintains long-term CD8+ T cell immunity. Nat. Commun. 2022;13:6473. doi: 10.1038/s41467-022-34171-2. - DOI - PMC - PubMed