

Association of Susceptibility to Broadly Neutralizing Antibodies and Presence of Capsid CTL Epitopes During Acute HIV-1 Infection

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Key Findings

- A significant number of participants with acute or early HIV infection (AEHI) had virus exhibiting conserved, highly networked cytotoxic T-lymphocyte (CTL) epitopes
- The prevalence of CTL epitopes appeared to be independent from predicted susceptibility to broadly neutralizing antibodies (bNAbs) in the participants analyzed

Conclusions

These data provide proof-of-concept that people with AEHI may be candidates for future studies investigating a combination of bNAbs and therapeutic vaccine to elicit bNAb and CTL or CTL-only post-treatment control

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Introduction

- Suppression of viral replication in the absence of antiretroviral therapy (ART) is the hallmark of functional HIV cure
- Broadly neutralizing antibodies (bNAbs) that bind to HIV-1 envelope (env) glycoproteins may recognize provirus-containing cells and target them for elimination during ART suppression to delay or prevent viral rebound^{1,2}; however, high env diversity can result in bNAb resistance
- HIV-1 capsid peptides presented by major histocompatibility complex/human leukocyte antigen (HLA) class I molecules are associated with viral control; peptide network scores further refine the correlation between viral peptides and cytotoxic T-lymphocyte (CTL) response³
- A combination of bNAbs and an HIV-1-specific CTL vaccine holds promise to achieve post-treatment remission
- Starting ART during acute or early HIV infection (AEHI) may limit reservoir genetic diversity and size^{4,5}
- Understanding the susceptibility to bNAbs in people with HIV initiating ART during AEHI as well as the presence of conserved epitopes may inform HIV cure strategies

Objectives

- To characterize the association between HIV-1 capsid epitopes and predicted susceptibility to the bNAbs, teropavimab (3BNC117-LS) and znlirvimab (10-1074-LS), during acute HIV-1 infection

Methods

- Pre-ART plasma virus was sequenced from 105 participants in the Italian Network of Acute HIV Infection (InAction) cohort diagnosed with AEHI (Fiebig stages I-V)⁶
- HIV-1 env and capsid were genotyped by next-generation sequencing (MiSeq System; Seq-IT, Kaiserslautern, Germany)
- Susceptibility to the bNAbs teropavimab and znlirvimab was predicted using previously developed genotypic signatures (Table 1).⁷ Briefly, neutralization data combined with virus sequence information derived from CATNAP⁸ and an internal Gilead database were used to identify HIV env amino acid positions important for susceptibility to bNAbs. Sequence variability was evaluated per participant and by amino acid position. Only positions with variability < 1% in viral quasi-species were considered part of a signature
- HIV-1 capsid sequences were evaluated for the presence of 40 peptides derived from the Los Alamos Immunology Database Best-Characterized HIV-1 CTL Epitopes List, ranked by normalized network scores. Deep sequencing reads were aligned to a de novo assembly, translated, and chopped into epitopes of 8-11 aa length. The position coordinates of each epitope were adjusted based on alignment of de novo assembly to HXB2 (GenBank accession K03455). The prevalence of each HIV optimal CTL epitope⁹ was evaluated based on a perfect sequence match to participants' observed epitopes. Network scores for each HIV optimal CTL epitope were assigned³

Table 1. bNAb genotypic susceptibility signatures⁷

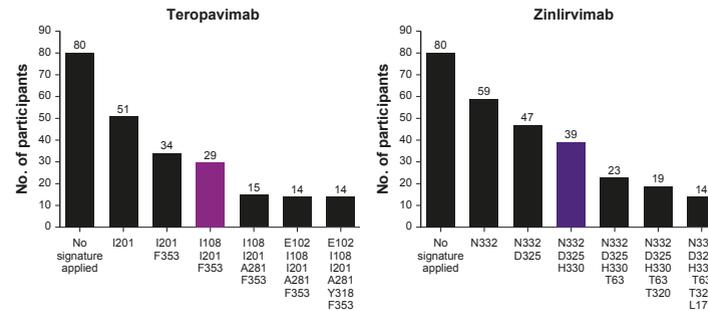
	Teropavimab		Znlirvimab	
	HIV env amino acid positions	PPV (%)	HIV env amino acid positions	PPV (%)
	No signature	75	No signature	73
1	I201	78	N332	87
2	I201/F353	84	N332/D325	90
3	I201/F353/I108	86	N332/D325/H330	92
4	I201/F353/I108/A281	91	N332/D325/H330/T63	98
5	I201/F353/I108/A281/E102	92	N332/D325/H330/T63/T320	99
6	I201/F353/I108/A281/E102/Y318	93	N332/D325/H330/T63/T320/L179	100

Note. HXB2 numbering was used for HIV env amino acid positions. bNAb, broadly neutralizing antibody; env, envelope; N332, N332 glycan N-X-S/T; PPV, positive predictive value (probability that a virus with a given signature is sensitive to bNAb).

Results

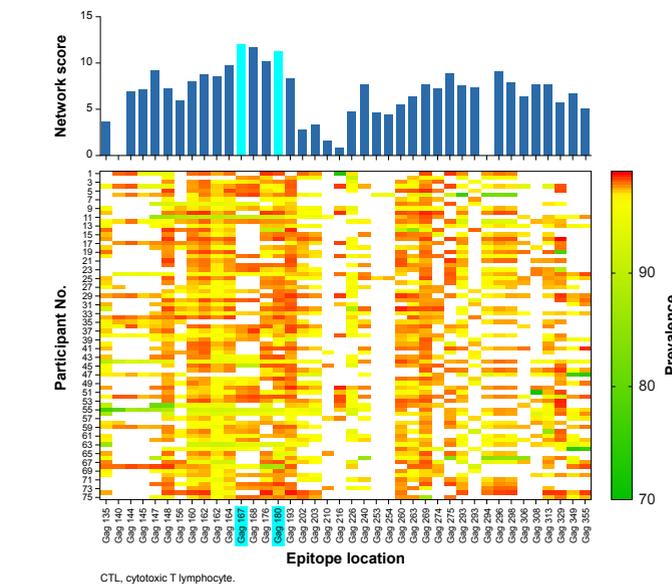
- HIV-1 env sequences were obtained for 80 of 105 participants
- Applying HIV env genotypic signatures to these sequences identified a high number of participants with virus predicted to be susceptible to teropavimab or znlirvimab (Figure 1)
- The prevalence of signatures is similar to those previously reported for an early-treated cohort⁷

Figure 1. Prevalence of HIV-1 env genotypic signatures for teropavimab and znlirvimab



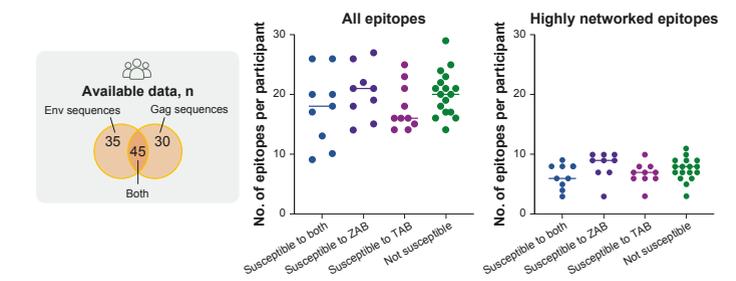
- HIV-1 capsid sequences that were available for 75 of 105 participants had a median of 20 (9-31) CTL epitopes per participant (Figure 2)
- The most highly networked peptides varied in prevalence; gag 180-188 was present in 83% (62/75) of participants and gag 167-175 in 49% (37/75) of participants (Figure 2)
- Additional studies to assess HLA presentation within individual participants would be of interest

Figure 2. Prevalence of capsid CTL epitopes and their network scores for participants



- For 45 participants with env and capsid sequences, assessment of viral susceptibility to bNAbs based on signature 3 indicated that 9 were susceptible to both bNAbs, 10 to teropavimab alone, 9 to znlirvimab alone, and 17 to neither (Figure 3)
- The numbers of total and highly networked CTL epitopes per participant were comparable across bNAb susceptibility groups (Figure 3)

Figure 3. Number of detected CTL epitopes (> 95% prevalence) per participant vs bNAb susceptibility group (based on signature 3)



Highly networked epitopes defined as network score > 8. CTL, cytotoxic T lymphocyte; env, envelope; TAB, teropavimab; ZAB, znlirvimab.

- The prevalence of individual epitopes was similar across bNAb susceptibility groups (Figure 4)

Figure 4. Percent of participants with CTL epitopes (> 95% prevalence) vs network scores per bNAb susceptibility group (based on signature 3)

