Stable Autologous Neutralizing Antibody Activity Despite Persistent Nonsuppressible HIV-1 Viremia

Poster #419

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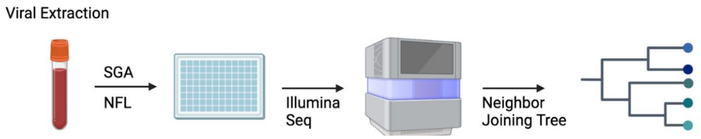
Background

- Nonsuppressible viremia (NSV) represent a subset of individuals with persistent low-level viremia due to a hyperactive HIV-1 reservoir.
- Autologous neutralizing antibodies (aNAbs) represent a key adaptive immune response in people with HIV-1.
- aNAbs have been observed to mature over time despite suppressive antiretroviral therapy (ART).
- Little is known about whether persistent antigenemia during NSV can also induce stronger humoral immune responses.
- Understanding the activity of aNAbs in NSV can help clarify one mechanism underlying NSV establishment and immune escape.

Methods

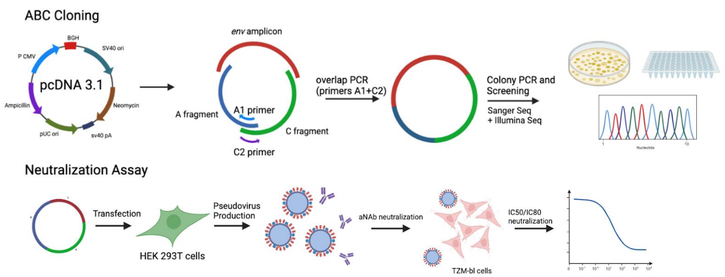
Participant Sample Collection and Characterization

- Identification of producer and nonproducers:
  - Single-genome amplification (*pol-env*) for RNA sequences
  - Near full-length (NFL) single-genome sequencing for proviral sequences
  - Neighbor-Joining Tree



Cloning and Neutralization

- Pseudovirus production:
  - ABC cloning of producer and nonproducer *env*
- Neutralization of pseudoviruses:
  - IgG purification from plasma collected at longitudinal timepoints
  - Neutralization evaluated through IgG serial dilutions that neutralized 50% of viral infections (IC50) of TZM-bl cells



Results

Figure 1: Producer proviruses are associated with non-evolving identical plasma viruses

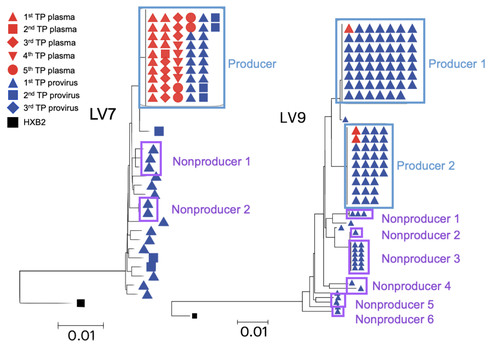
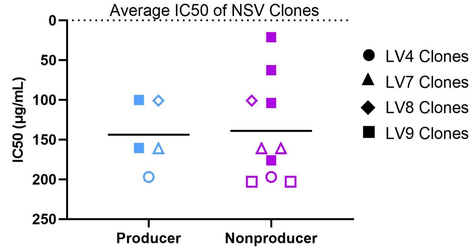
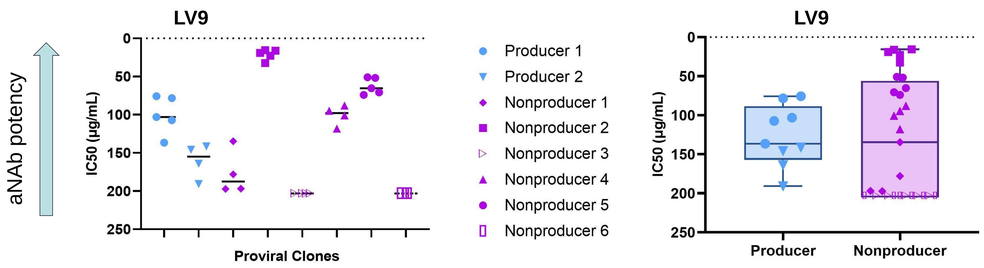


Figure 2: Differing neutralization is difficult to observe for producers and nonproducers



- Producer and nonproducer proviral clones across NSV participants show similar average neutralization.

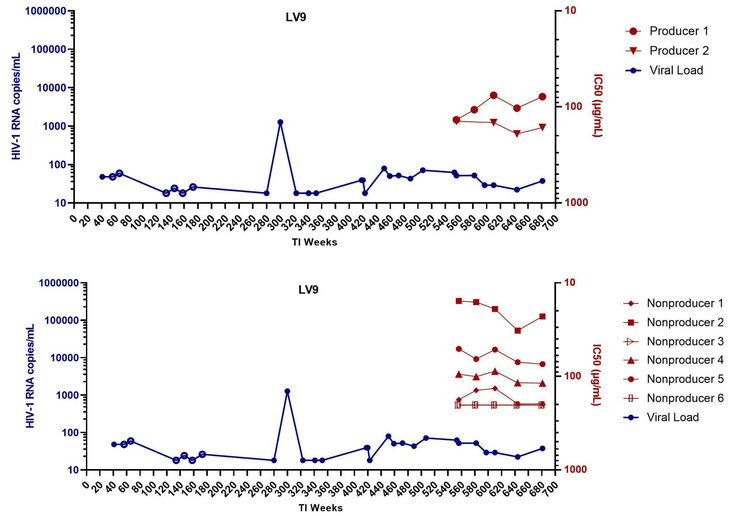
Figure 3: Producers and nonproducers exhibit a range of sensitivities to aNAbs



- Each data point represents a different timepoint of IgG used against the producer/nonproducer virus
- Open shapes indicate values above the limit of detection threshold

During NSV, plasma virus can show a **sustained** neutralization level to aNAbs over several years despite no changes in the plasma HIV-1 *env* sequence. The underlying proviral reservoir demonstrated a **wider range** of aNAb sensitivity.

Figure 4: Improved neutralization is not consistently observed for producer and nonproducer viruses



- Consistent aNAb maturation is not seen against producer viruses over the course of 2.3 years.
- Changes in aNAb responses also not consistently observed for nonproducers.

Conclusions

- The reservoir is comprised of intact proviruses with a broad range of sensitivity of autologous neutralizing antibodies.
- Persistent low-level viremia did not consistently increase aNAb responses.
- Additional studies are needed to explore why detectable viremia may not stimulate a more robust HIV-specific humoral response during ART.

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