bNAb Sensitivity Continuously Enhances Immune Response in an HIV Dynamics Model

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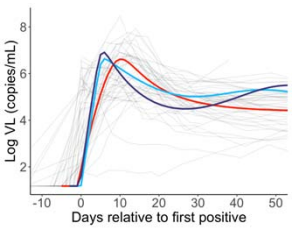
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BACKGROUND

- Several studies now show broadly neutralizing antibodies (bnAbs) may induce an immune enhancement ("vaccinal effect") that helps certain individuals control rebound HIV viremia after stopping ART.
  - E.g., eCLEAR, TITAN, RIO, Amfar
- We previously trained an HIV+bnAb viral dynamics model to data from antibody mediated prevention (AMP) trials [Reeves et al. Nat Comm 14:8299 (2023)].
- **eCLEAR study** [Gunst et al. Nat Med 28(11):2424 (2022)]
  - Newly diagnosed PWH were randomized to start
    - ART only
    - ART+bnAb 3BNC117
    - ART+romidepsin (RMD, a latency reversal agent)
    - ART+3BNC117+RMD
  - One year later, 20 PWH underwent ATI.
  - Individuals whose plasma viruses were sensitive to 3BNC117 (defined as IC90<1.5 μg/mL) at initial treatment experienced delayed or no rebound.
- Open question(s):
  - How does bnAb enhancement mechanistically work?
  - Does bnAb sensitivity continuously relate to host-immune responses and subsequent viral rebound kinetics?

METHODS

- We adapted our HIV+bnAb model to include how antibody sensitivity influences the killing rate of infected cells and the recruitment of adaptive immunity (**Fig 1**).
- Model validation:
  - Ensure can recapitulate primary infection viral loads (N=46 individuals from the RV217 study), which behave distinctly from rebound viremia as immunity is not already developed.

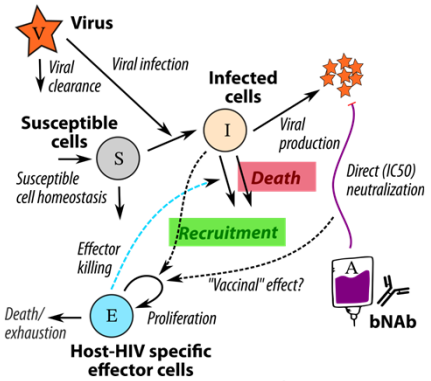


Parameter	DD	Effector	Combo
α_S	38.2	37.4	66.7
δ_S	0.00067	0.010	0.0064
$log_{10}(\beta)$	-4.33	-3.27	-3.74
δ_I	0.43	0.29	0.26
h	0.14	0	0.13
π	20.89	39.52	43.39
$log_{10}(\alpha_E)$		-4.41	-4.99
w		0.27	0.37
N_{E50}		49.37	51.42
δ_E		0.1	0.1

Figure 1. Model validation on HIV primary infection data from N=46 participants in RV217 trial in Thailand and Uganda.

Density-dependent (DD): Cellular death increases with size of infected cell compartment. Simple and flexible, easy to calibrate (one parameter: h). Interpretation: Innate immunity.
Effector cell: Presence of infected cells triggers immune cells recruitment which then kills infected cells. Interpretation: Adaptive immunity.
Combination model: Both innate and adaptive immunity.

Modeling connects broadly neutralizing antibody (bnAb) levels and sensitivity to viral rebound to estimate immune enhancement and HIV post-treatment control.



$$\frac{dS}{dt} = aS - d_S S - \beta SV$$
$$\frac{dI}{dt} = \beta SV - EI - \delta_I I^{h+1}$$
$$\frac{dV}{dt} = \pi I - \gamma V - \beta SV$$
$$\frac{dE}{dt} = \alpha_E + \frac{wEI}{I + N_{E50}} - \delta_E E$$

Figure 2. Mechanistic model for rebound viral load. Key additions are Recruitment (green) and death (red) terms in which bnAb levels enhance immunity.

Equations formalize the mechanistic model terms and highlight key parameters to investigate immune enhancement.

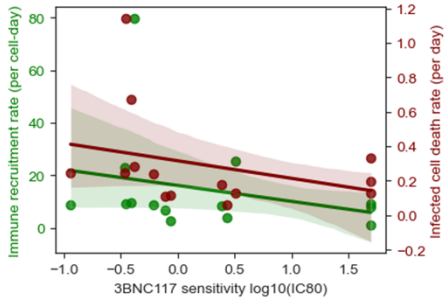


Figure 4. Relationship between model estimated parameters and bnAb sensitivity. The model suggests that there is a continuous relationship between sensitivity and a faster immune recruitment rate as well as a higher infected cell death rate

- Exploring the immune enhancement:
  - Fit the model to rebound viral load kinetics from the eCLEAR study (N=20)
  - Fit to additional 9 PTCs and 15 'placebo-treated' individuals collected from ACTG studies [Sharaf et al. J Clin Invest 128:4074 (2018)].
- Population nonlinear mixed effects used to estimate parameters including the underlying day that viral load began to rebound (before becoming detectable), the death rate of infected cells, and the initial size as well as growth rate of the adaptive immune compartment.
- We tested whether any of these parameters were associated with pre-treatment bnAb sensitivity using IC80 on a continuous scale.

RESULTS

- By changing the parameters of the model, we were capable of matching viral loads from primary HIV infection, typical ATI rebound and PTC (**Fig 3**).
- We found a continuous dose-response effect whereby increased pre-ART bnAb sensitivity was associated with faster death of infected cells as well as faster recruitment of the adaptive immune compartment during ATI (**Fig 4**).
  - Both infected cell death rate and immune recruitment rates approximately doubled between the most and least sensitive IC80s.

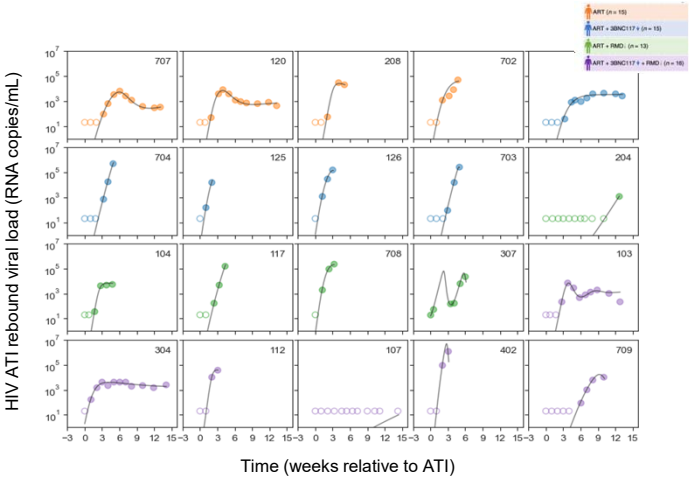


Figure 3. Model fits to eCLEAR ATI rebound data from N=20 participants in 4 cohorts (colors, PIDs noted in each panel).

CONCLUSIONS

- The sensitivity of an individual's HIV virus to a potent bnAb enhances both infected cell killing and immune recruitment to help control viremia after ATI in a continuous fashion.
- Our modeling approach provides a generalized framework to integratively analyze the several types of data and multifactorial relationship between therapy and host immune responses to HIV.

PLAIN LANGUAGE SUMMARY

We modeled data from eCLEAR, a human clinical study that treated people with HIV with a broadly neutralizing antibody (bnAb). When some of those people stopped ART their immune system could help control HIV rebound. Our model informs how this control might work via "immune enhancement", and estimates that a better match of the persons' virus to the bnAb leads to more enhancement.