Effect of Broadly Neutralizing Antibody Exposure on HIV Rebound Following Combination Immunotherapy

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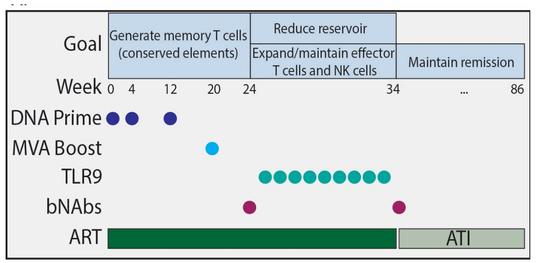
Background

- Waning broadly neutralizing antibody (bNAb) levels and emergence of resistance have been associated with viral rebound during analytic treatment interruption (ATI) studies.
- In a study of 10 participants (9 cis men, 1 trans woman) receiving combination immunotherapy with a boosted DNA vaccine, lefitolimod, and bNAbs (10-1074 and VRC07-523LS) (NCT04357821), 7/10 individuals exhibited altered post-intervention rebound dynamics.



- In this pharmacokinetic/pharmacodynamic (PK/PD) analysis, we evaluated the impact of bNAb exposure, susceptibility, and antidrug antibody (ADA) formation on rebound kinetics.

Methods

- Plasma bNAb PK using population PK modeling approaches in Monolix.
- Spearman correlations or Wilcox's test to determine the relationship between bNAb exposure and/or susceptibility, and rebound kinetics.
- Competitive and functional ADA assays for both bNAbs.

Abbreviations (lay definitions)

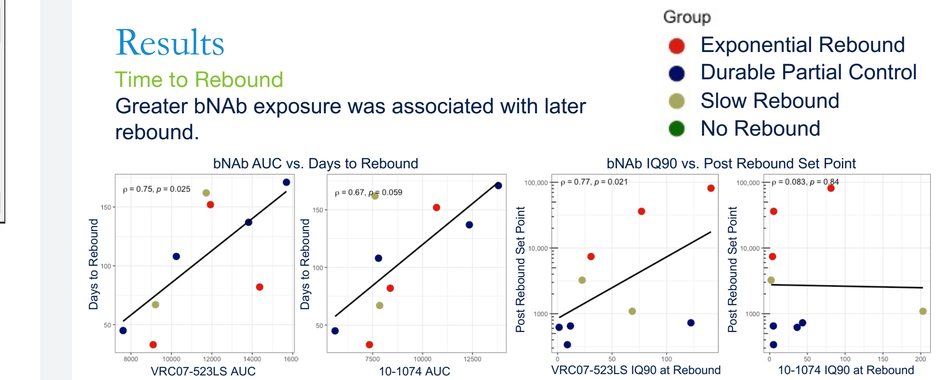
AUC: Area under the bNAb concentration-time curve (total bNAb plasma exposure)
Cmax: Peak bNAb concentration
IC90: 90% Inhibitory concentration (amount of drug needed to inhibit virus 90%)
IQ90: Ratio of bNAb level to IC90 (how high the bNAb level is relative to the amount needed to inhibit virus 90%)

While higher bNAb exposure was associated with delayed viral rebound, bNAb exposure and susceptibility could not be consistently linked to lower observed post-treatment set points. This suggests significant contribution of immunologic changes to post-treatment control (see poster 446).

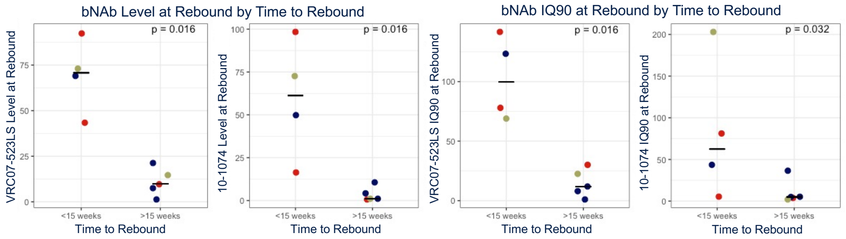
Results

Time to Rebound

Greater bNAb exposure was associated with later rebound.



In those who rebounded later (>15 weeks), VRC07-523LS and 10-1074 levels and IQ90 values were lower at the time of rebound. There was no association between IC90 and time to rebound.



Antidrug antibody

While ADA was detected for two participants in competitive assays for both bNAbs, no functional ADA impacting PK was observed.

Conclusions

- Increased bNAb exposure was consistently associated with delayed viral rebound.
- Post-treatment set point was not driven by bNAb susceptibility. Further association of VRC07-523LS IQ90 and set point is likely driven by higher levels at the time of rebound in those who rebounded earlier and had higher set points.
- Thus, bNAb PK-PD does not fully explain lower observed post-treatment set points, suggesting significant contribution of changes in anti-HIV immune function. (See poster 446)

Post-Intervention Set Points

Although there was no association between VRC07-523LS IC90 and set point, higher VRC07-523LS IQ90 at the time of rebound was associated with higher post-intervention set point. No associations between 10-1074 IQ90 or IC90 and set point were observed. (Plots under "Time to Rebound" results on Left, IC90 plot not shown)

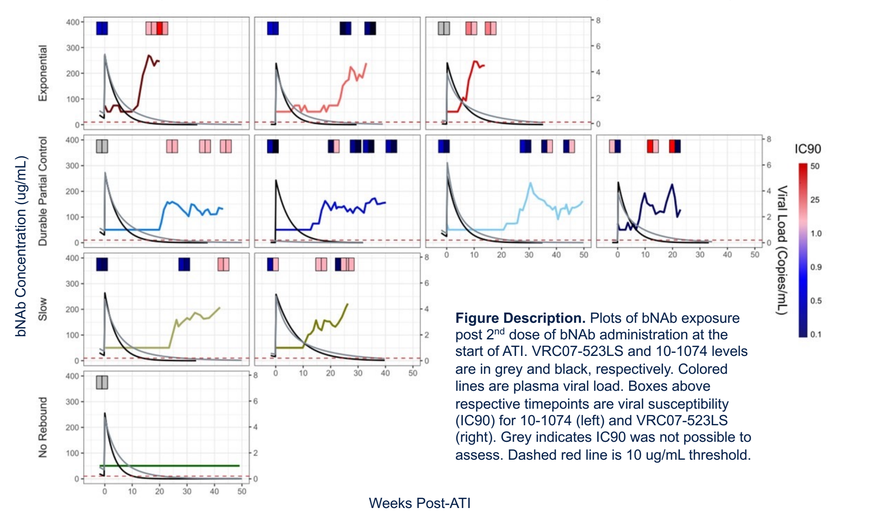


Figure Description. Plots of bNAb exposure post 2nd dose of bNAb administration at the start of ATI. VRC07-523LS and 10-1074 levels are in grey and black, respectively. Colored lines are plasma viral load. Boxes above respective timepoints are viral susceptibility (IC90) for 10-1074 (left) and VRC07-523LS (right). Grey indicates IC90 was not possible to assess. Dashed red line is 10 ug/mL threshold.

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