Long-term Passive Infusion of Broadly Neutralizing Antibodies with Markedly Enhanced ADCC

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BACKGROUND

Broadly neutralizing antibodies (bNAbs) can suppress diverse HIV strains and are being explored for long-term protection. Although our lab has demonstrated that long-term expression of AAV-delivered bNAbs can lead to a functional cure, persistent viral reservoirs are still detectable for many years. To better target this reservoir, we evaluated the deliverability and antiviral potential of bNAbs engineered for 80-100-fold enhanced antibody-dependent cellular cytotoxicity (ADCC).

METHODS

Six rhesus macaques chronically infected with SHIV-AD8 received passive infusions of 3BNC117 and 10-1074 (30 mg/kg every 3 weeks). Three controls received wildtype bNAbs, while three animals received glycoengineered variants with Fc receptor mutations previously shown to enhance ADCC 80–100-fold. Viral loads, serum antibody levels, anti-drug antibody (ADA) responses, and reservoir size were monitored. Animals were followed for 45 weeks total (study ongoing).

RESULTS

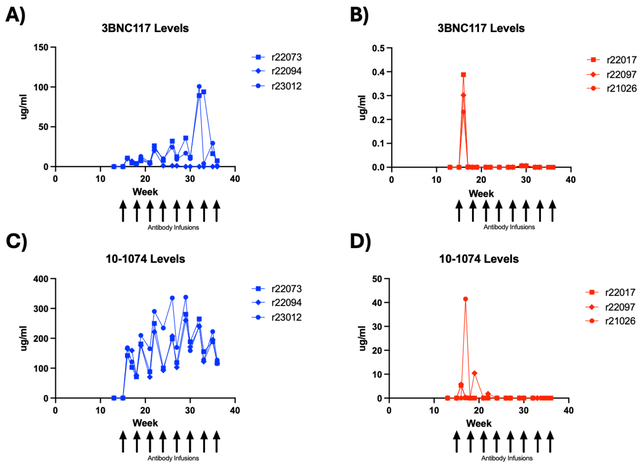


Figure 1: Serum levels of infused broadly neutralizing antibodies over time.
Serum concentrations of 3BNC117 and 10-1074 were measured longitudinally in SHIV-AD8 infected rhesus macaques receiving either wildtype bNAbs **(blue, left panels)** or ADCC-enhanced Fc-engineered variants **(red, right panels)**. Each line represents an individual animal. Antibody infusions are noted by arrows at the bottom of each graph.

Engineered bNAbs with 80-100 fold enhanced ADCC caused infusion-related reactions, rapid clearance, and failed to sustain viral suppression, whereas wildtype bNAbs achieved stable serum levels and durable control of viremia.

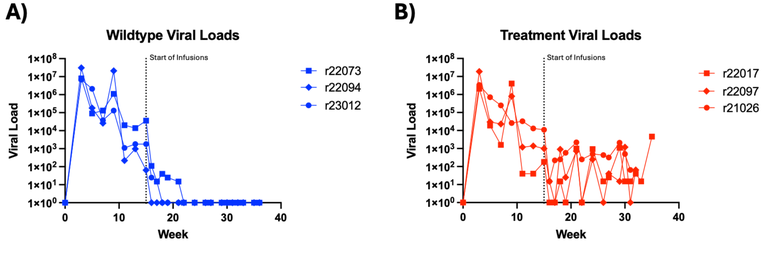


Figure 2. Plasma viral loads.
Plasma viral loads were measured longitudinally in rhesus macaques receiving either wildtype bNAbs **(blue, left panel)** or ADCC-enhanced Fc-engineered variants **(red, right panel)**. Wildtype bNAb treatment was associated with rapid viral suppression followed by sustained control, whereas ADCC-enhanced variants produced less consistent and more fluctuating suppression over time. Each line represents an individual animal. Start of antibody infusions denoted by the dashed line at week 15.

Macaques were infected with SHIV-AD8 15 weeks prior to infusion. Wildtype bNAbs achieved serum concentrations of 70-320 µg/ml 10-1074 and 5-100 µg/ml 3BNC117. In contrast, ADCC-enhanced variants were rapidly cleared, with transient levels detectable only 1-week post-infusion. For 3BNC117, these levels remained under 1ug/ml. While ADA responses were low compared with those commonly observed with AAV delivery, detectable ADA levels were observed against the ADCC-enhanced 3BNC117 (O.D. 0.2-0.4). Infusion-related reactions occurred in all 3 macaques receiving ADCC-enhanced bNAbs and required diphenhydramine and dexamethasone premedication. Viral suppression was durable in wildtype recipients but inconsistent and fluctuating in ADCC-enhanced animals.

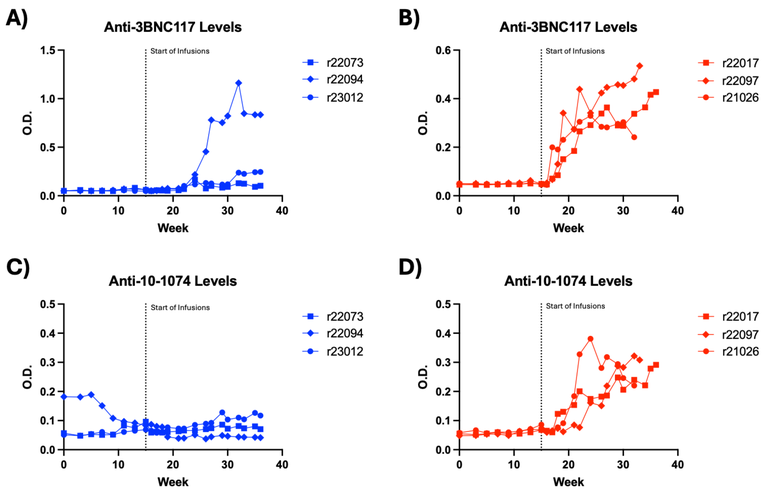


Figure 3. Development of anti-drug antibody (ADA) responses to infused bNAbs.
Serum ADA levels against 3BNC117 and 10-1074 were measured longitudinally in SHIV-AD8 infected rhesus macaques receiving either wildtype bNAbs **(blue, left panels)** or ADCC-enhanced Fc-engineered variants **(red, right panels)**. Wildtype bNAb recipients showed minimal or low ADA responses over time, whereas animals receiving ADCC-enhanced variants developed higher and more consistent ADA responses following infusion. Each line represents an individual animal. Start of antibody infusions denoted by the dashed line at week 15.

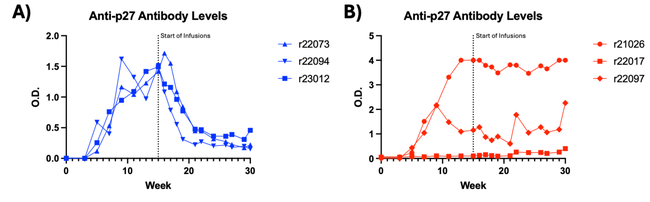


Figure 4. Serum anti-p27 antibody responses measured by ELISA.
Serum antibodies against SHIV p27 were measured by ELISA over time in rhesus macaques treated with either wildtype bNAbs **(blue, left panel)** or ADCC-enhanced Fc-engineered variants **(red, right panel)**. Wildtype bNAb-treated animals showed a decline in anti-p27 antibody levels following the start of bNAb treatment, whereas animals receiving ADCC-enhanced variants exhibited higher and more variable anti-p27 antibody responses. Each line represents an individual animal. Time is shown relative to initial SHIV infection. Start of antibody infusions denoted by the dashed line at week 15.

CONCLUSIONS

- ADCC enhancement increased infusion-related toxicity and accelerated bNAb clearance, preventing durable viral suppression
- This toxicity was likely due to strong FcγRIIIa activation, as reactions occurred even after the first infusion
- ADCC enhancement increased ADA responses to the delivered bNAbs
- Wildtype bNAbs achieved more stable serum levels and more consistent viral suppression.
- While Fc engineering remains promising for reservoir clearance, moderate ADCC enhancement may maximize therapeutic efficacy.

ADDITIONAL KEY INFORMATION

This work was made possible by the generous support of the Miami CFAR, HEIDI, and amfAR (Target Grant 110554-75-RPRL)

PLAIN LANGUAGE SUMMARY

In monkeys with chronic SHIV infection, antibodies engineered to be much more potent were cleared quickly, caused side effects, and didn't control the virus well. In contrast, the non-engineered antibodies stayed in the blood longer and kept the virus suppressed more reliably.