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Vectored Delivery of Closer-to-Germline Antibodies Can Mediate Long-term SHIV Suppression

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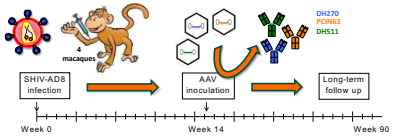
BACKGROUND

Delivery of potent broadly neutralizing antibodies by recombinant adeno-associated virus (AAV) vectors can strongly and durably suppress ongoing viral replication after a single vector administration. We have successfully and durably suppressed viral replication in three SHIV-infected monkeys with this approach, including the “Miami monkey” with over 8 years of plasma viremia below 15 copies/mL of SHIV RNA.

However, the generation of anti-drug antibody responses (ADAs) against the AAV-delivered antibodies often limits the efficacy of this approach. Due to extensive affinity maturation, most potent broadly neutralizing antibodies exhibit unusually high levels of somatic hypermutation that can be seen as ‘non-self’ by the recipient’s immune system. To overcome this important challenge, delivery of less extensively mutated (i.e., closer-to-germline) antibodies was evaluated.

METHODS

In a pilot experiment, four Indian-origin rhesus macaques were experimentally infected with SHIV-AD8. At week 14 post-infection, and with plasma viremias ranging from 5,100 to 130,000 copies/mL of SHIV RNA, all four monkeys received AAV vectors expressing anti-HIV antibodies DH270, PCIN63 and DH511. These antibodies are naturally closer-to-germline than those we had previously used.



Antibody	Class	IC50 (µg/mL)	Identity (HC %)
DH270	V3	0.03	89
PCIN63	CD4bs	0.16	83
DH511	MPER	0.75	81

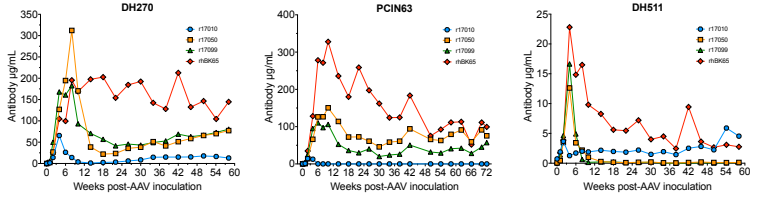
IC50 = 50% inhibitory concentration; HC = heavy chain

Our results indicate that potent broadly neutralizing antibodies which are closer-to-germline can mediate long-term virologic suppression following gene therapy with AAV vectors with potentially lower incidence of ADA responses. They also highlight the difficulties associated with achieving long-term, antibody-mediated suppression.

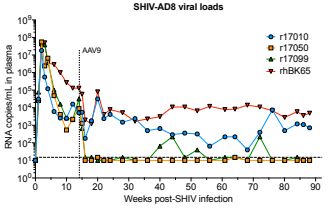
RESULTS

Three of the four macaques showed high levels (20-320 µg/mL) of two AAV-delivered antibodies through 60 weeks of follow up measurements. Sustained viral load suppression was achieved in two of these three monkeys. Only transient effects on viral load levels were observed in the third monkey suggesting viral escape mutations; sequencing to confirm escape is currently in progress. The fourth monkey showed low levels of AAV-delivered antibodies due to ADAs and little or no virologic suppression.

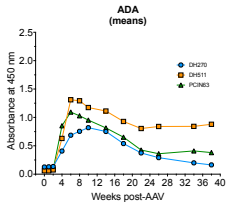
1. Serum levels of AAV-delivered antibodies in the four recipient macaques:



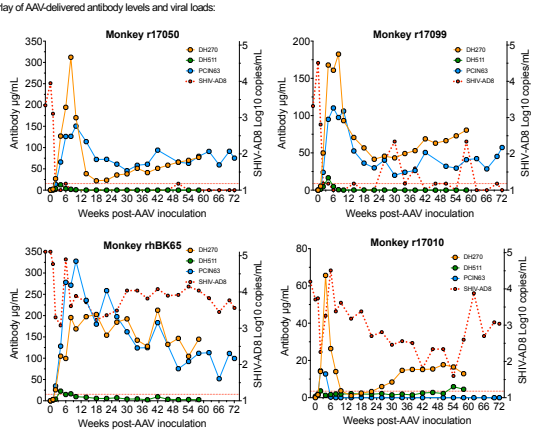
2. Plasma viral loads:



3. Serum levels of anti-drug antibodies:



4. Overlay of AAV-delivered antibody levels and viral loads:



CONCLUSIONS

Our data show that durable, continuous antibody expression can be achieved with AAV vectors and support the potential for lifelong suppression of viral loads with the AAV-antibody approach.

The use of closer-to-germline anti-HIV antibodies may be a viable strategy for overcoming ADA responses following gene therapy with AAV-antibody vectors.

Our data also highlight the difficulties associated with achieving long-term suppression. Eradicating or minimizing ADA responses is crucial to make the AAV-delivery of antibodies a consistent and reliable approach against HIV.

ACKNOWLEDGEMENTS

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