

11<sup>TH</sup> EDITION

DECEMBER 10-13, 2024

# HIV PERSISTENCE DURING THERAPY

Reservoirs & Eradication Strategies Workshop



## **Durable Viral Load Remission in SHIV-infected Macaques after Vectored Delivery of Monoclonal Antibodies**

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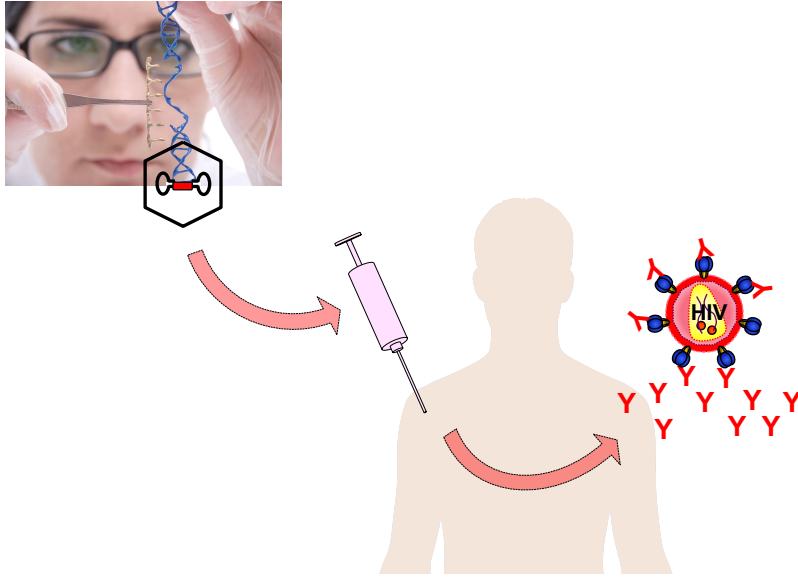
[www.hiv-persistence.com](http://www.hiv-persistence.com)

# CONFLICTS OF INTEREST

(I wish)\*

\* Joke borrowed from Tom Hope

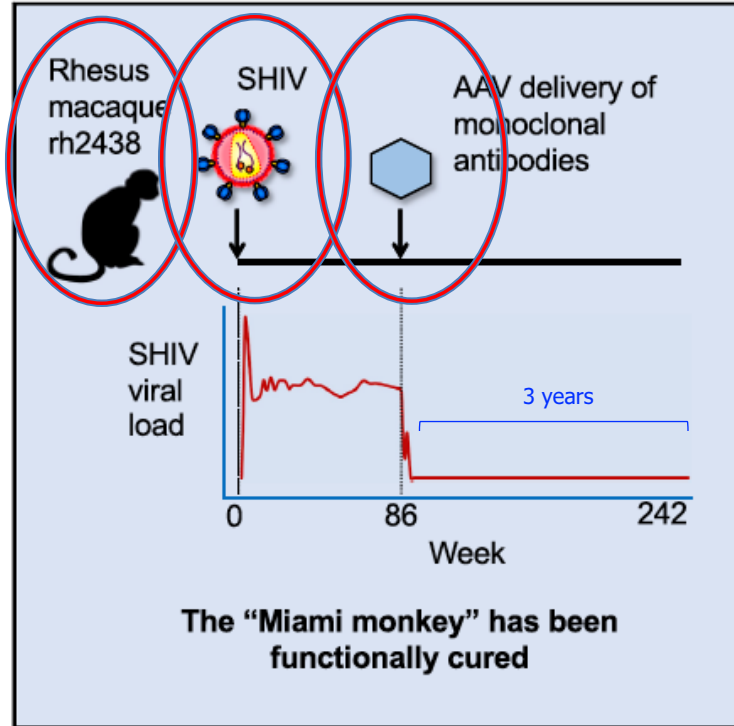
# AAV-mediated delivery of broadly neutralizing antibodies against HIV



1. Circumvents the difficulties of generating a successful immunogen or vaccine.
2. Well-characterized, broad and potent monoclonal antibodies.
3. No need to produce large amounts of pharmaceutical grade antibody.
4. No need for repeated inoculations.
5. One inoculation could account for years of expression: cost-effective.

🌀 **Delivery of neutralizing antibodies with AAV is a promising approach for the prevention and treatment of HIV infection.**

# AAV-mediated delivery of antibodies as a therapy:



## Immunity

Adeno-Associated Virus Delivery of Anti-HIV Monoclonal Antibodies Can Drive Long-Term Virologic Suppression

## Immunity Previews



## The Miami Monkey: A Sunny Alternative to the Berlin Patient

Rachel A. Liberatore<sup>1</sup> and David D. Ho<sup>2,\*</sup>

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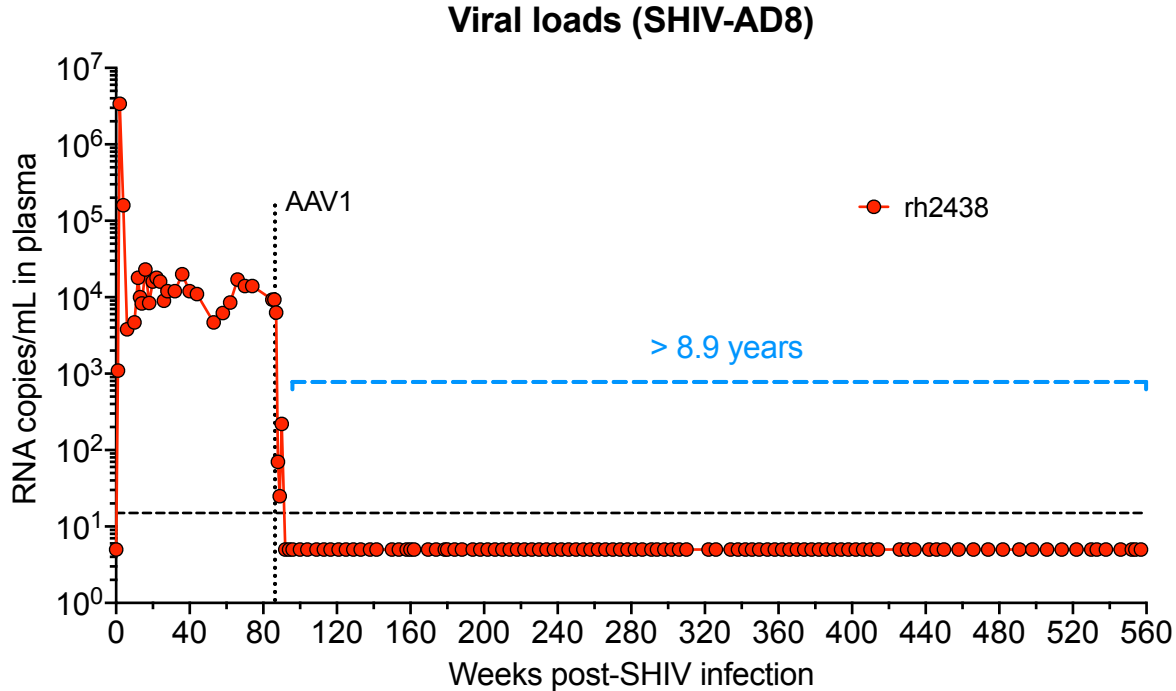
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<https://doi.org/10.1016/j.immuni.2019.02.010>

Curing HIV infection has been impossible, with the exception of the "Berlin Patient." [Martinez-Navio et al. \(2019\)](#) in Miami herein present a rare monkey whose virus was controlled for >3 years after a single genetic intervention that led to persistent production of HIV-neutralizing antibodies *in vivo*.

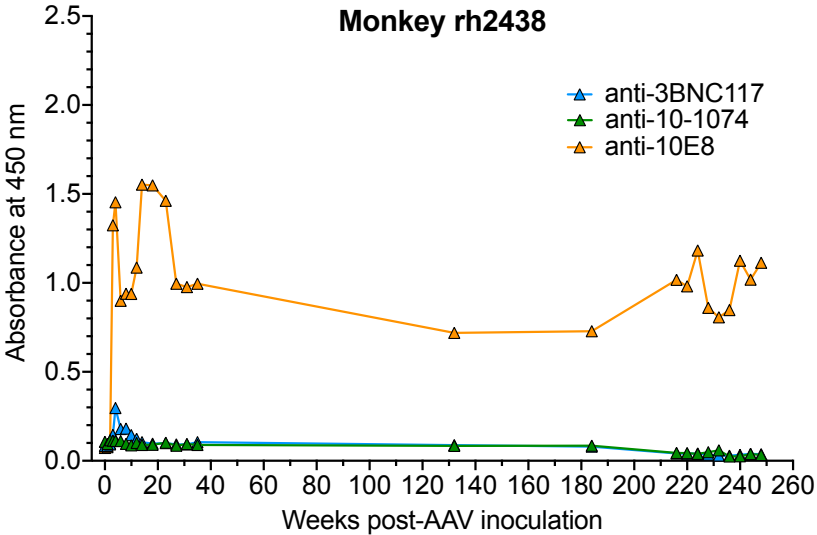
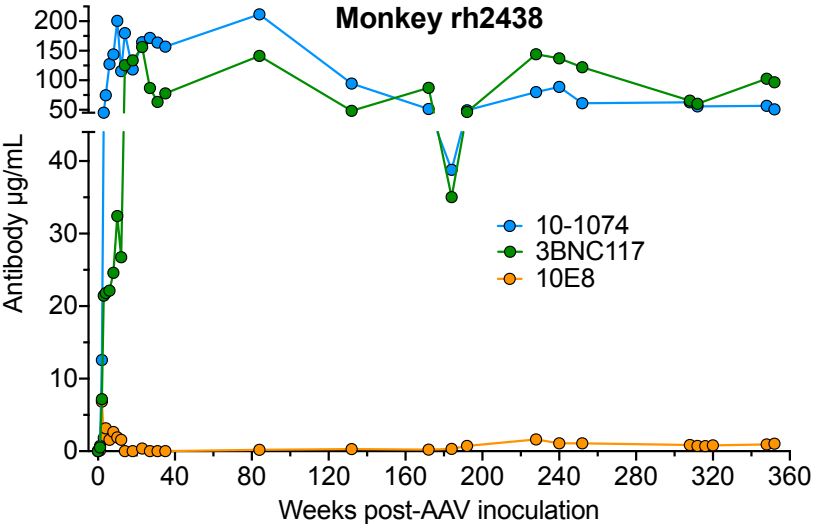


# Impressive level of suppression in monkey rh2438:

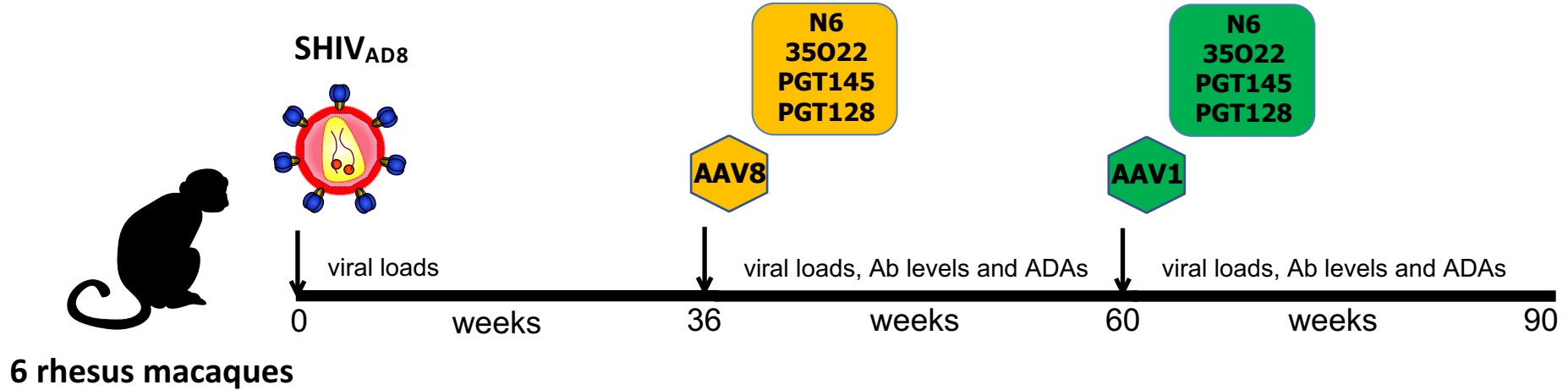


- Long-term suppression in the absence of ART.
- Long-term suppression after a single administration of AAV.
- Large amounts of lymph node cells from rh2438 were not able to transfer infection to naïve macaques (two separate attempts).

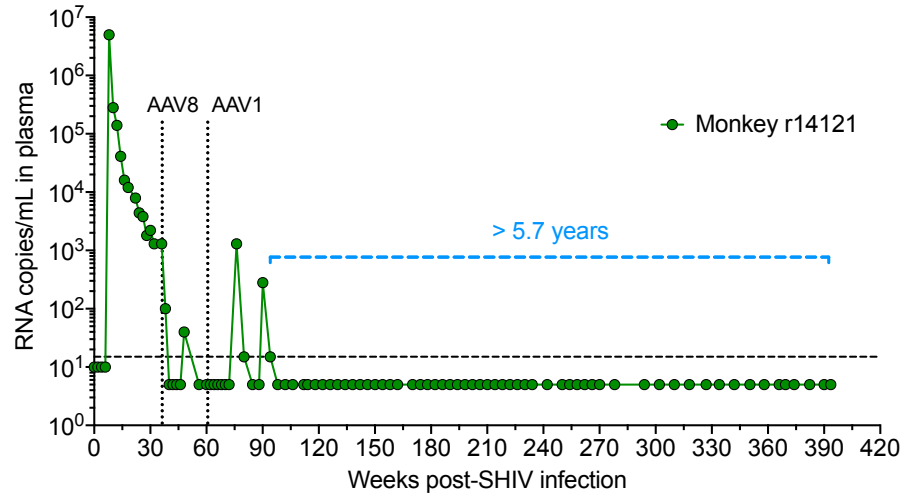
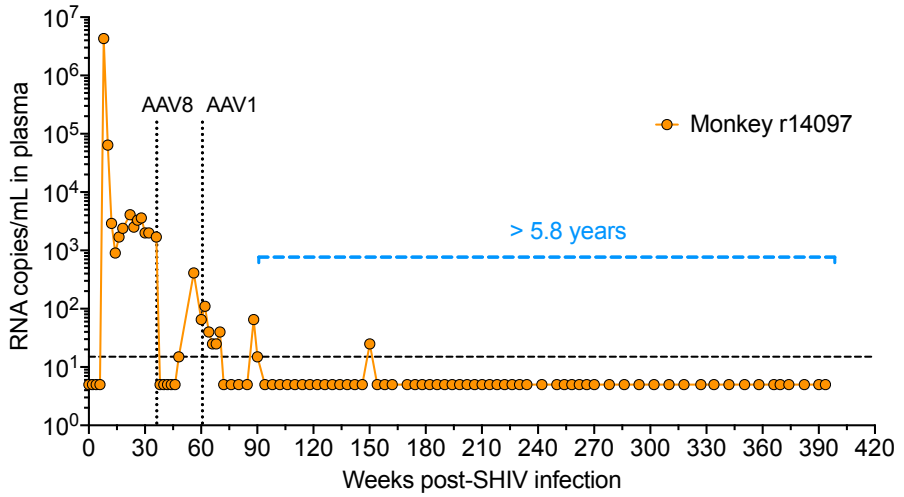
# Successful antibody delivery in monkey rh2438:



# Therapy experiment 2: can we prevent ADA responses?

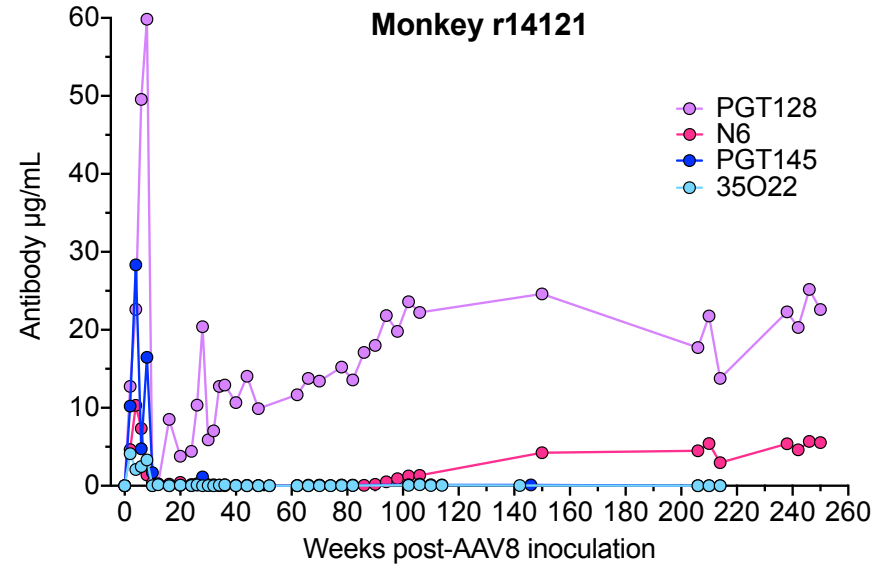
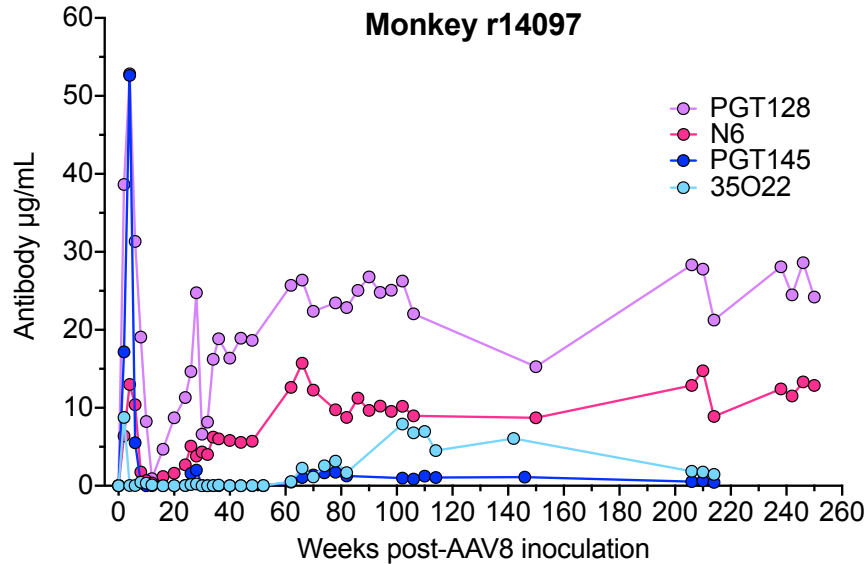


# Two more cases of viral remission:

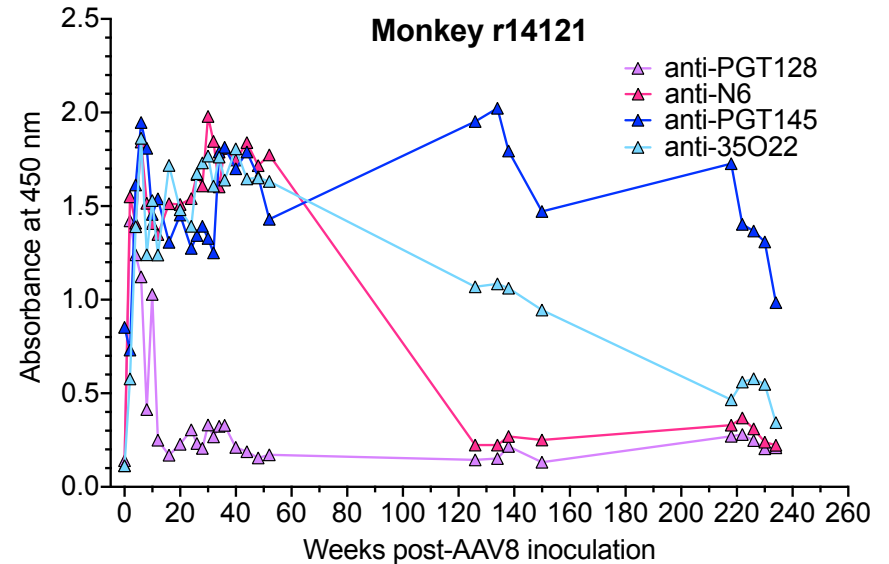
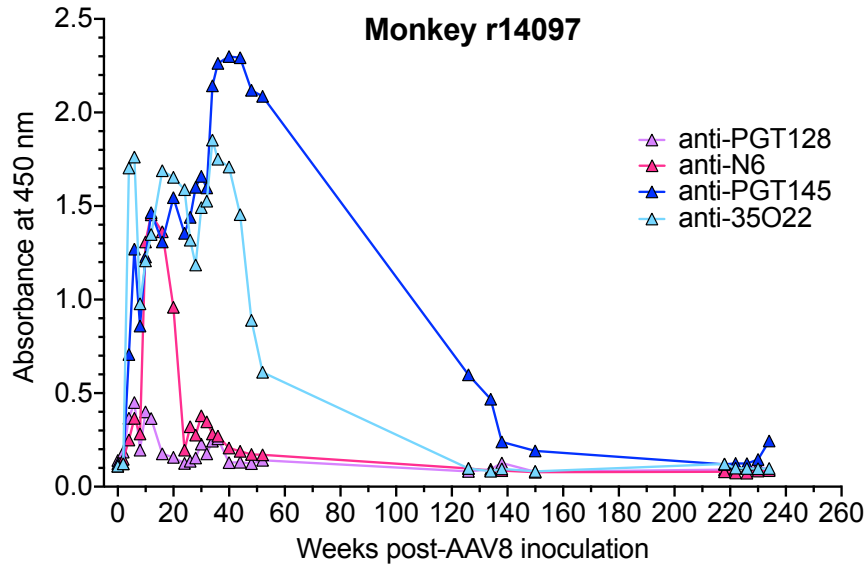




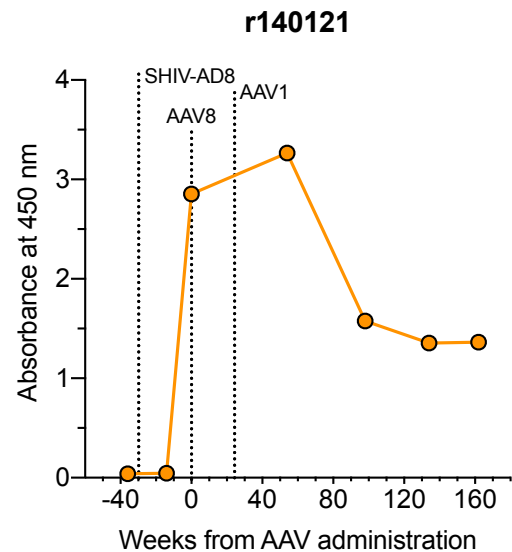
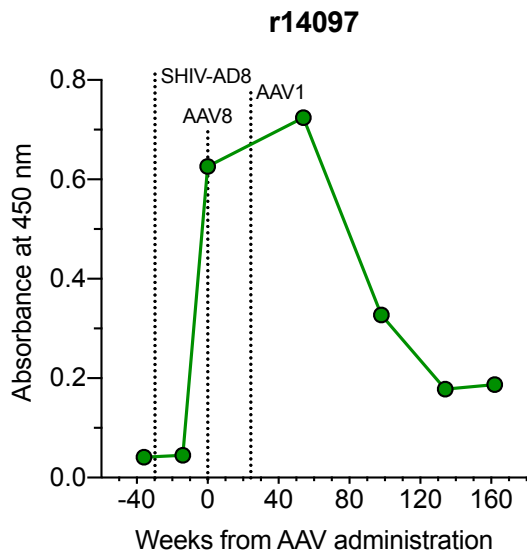
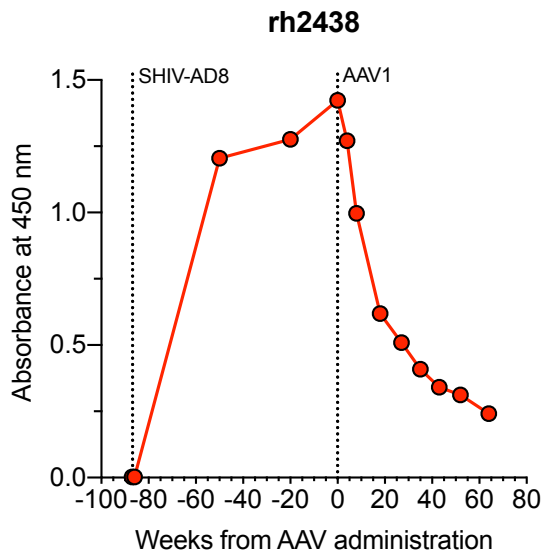
# These two monkeys had good levels of PGT128 and N6:



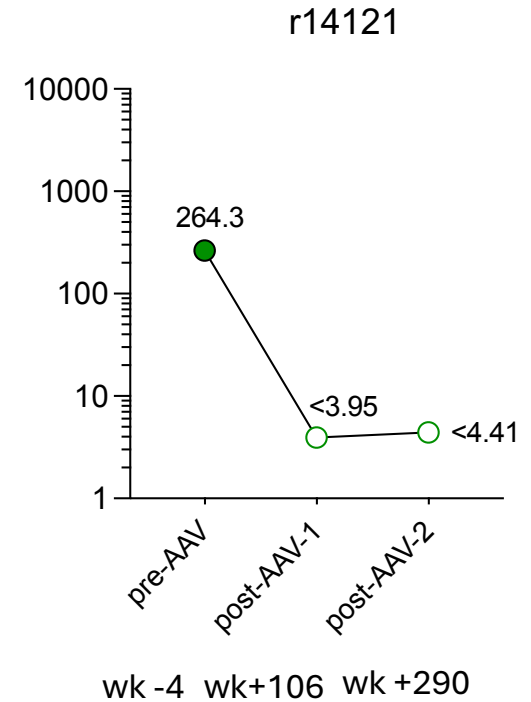
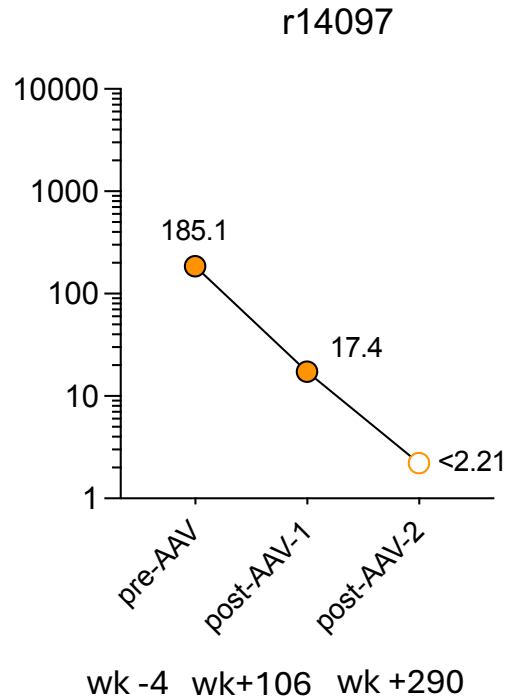
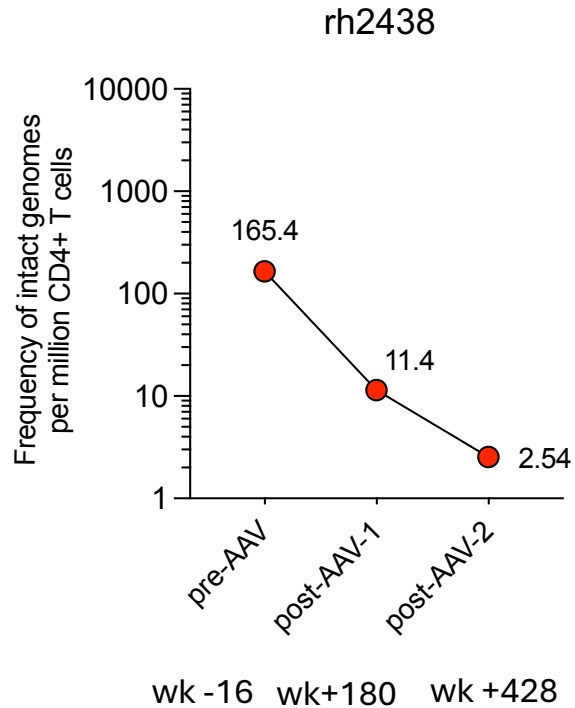
# The antibody levels correlated with the levels of ADAs:



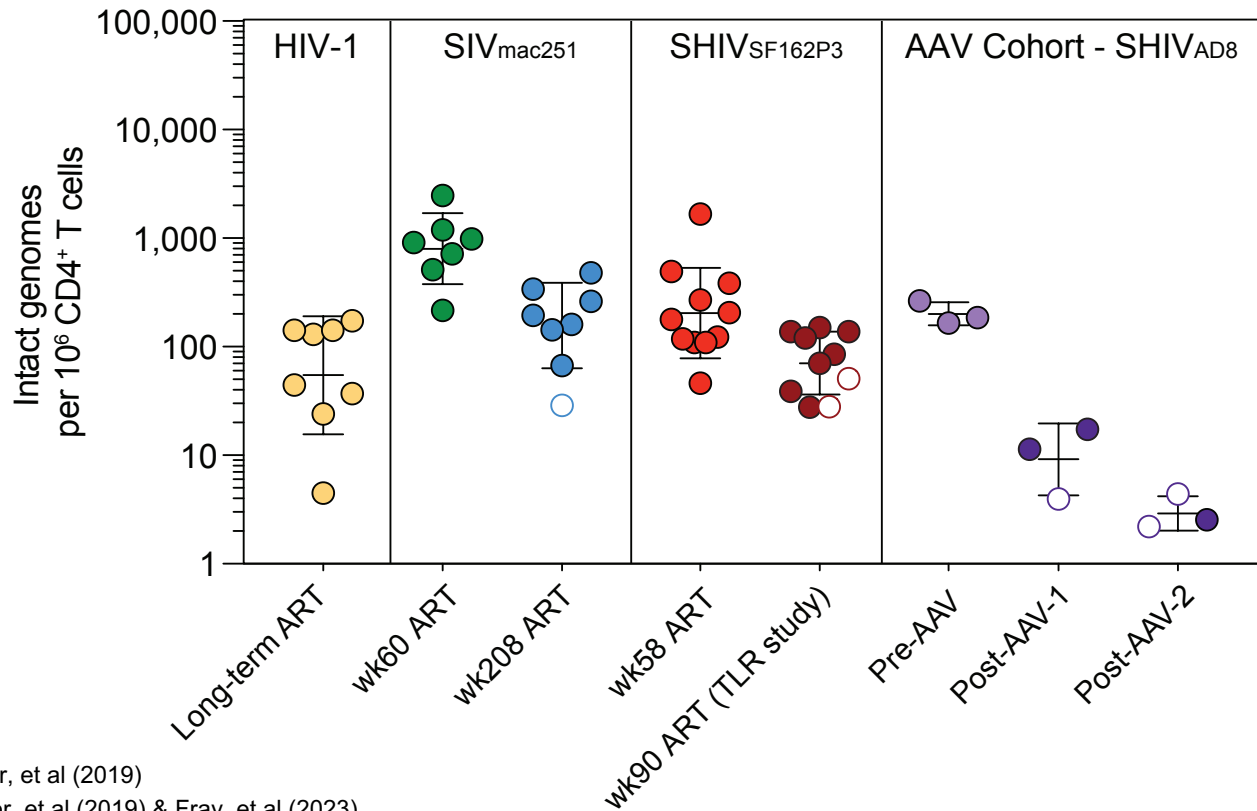
# Antibodies against p27 in the three suppressed macaques:



# Reservoir size measured by IPDA (intact proviral DNA assay):



# Reservoir size – comparison to other cohorts:



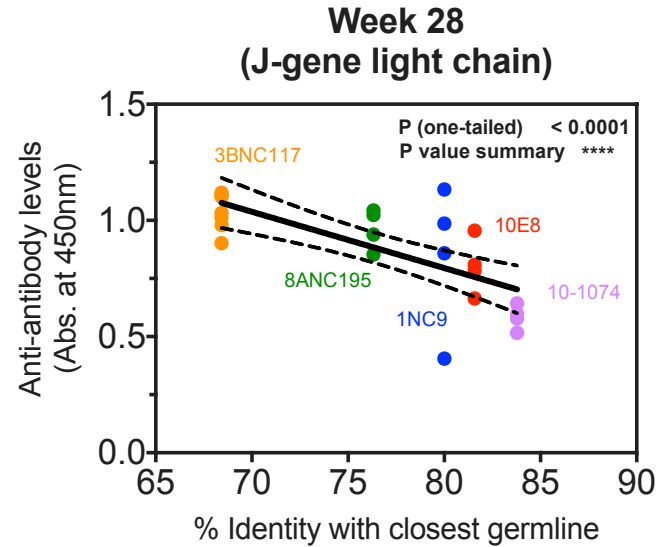
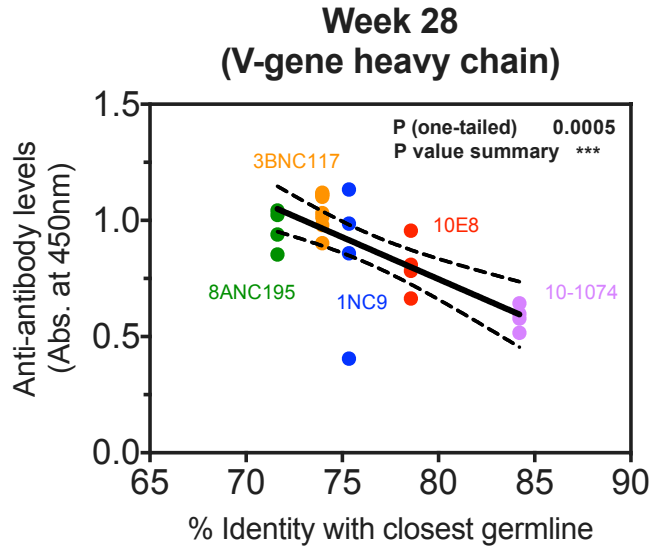
HIV data – Bruner, et al (2019)

SIV data – Bender, et al (2019) & Fray, et al (2023)

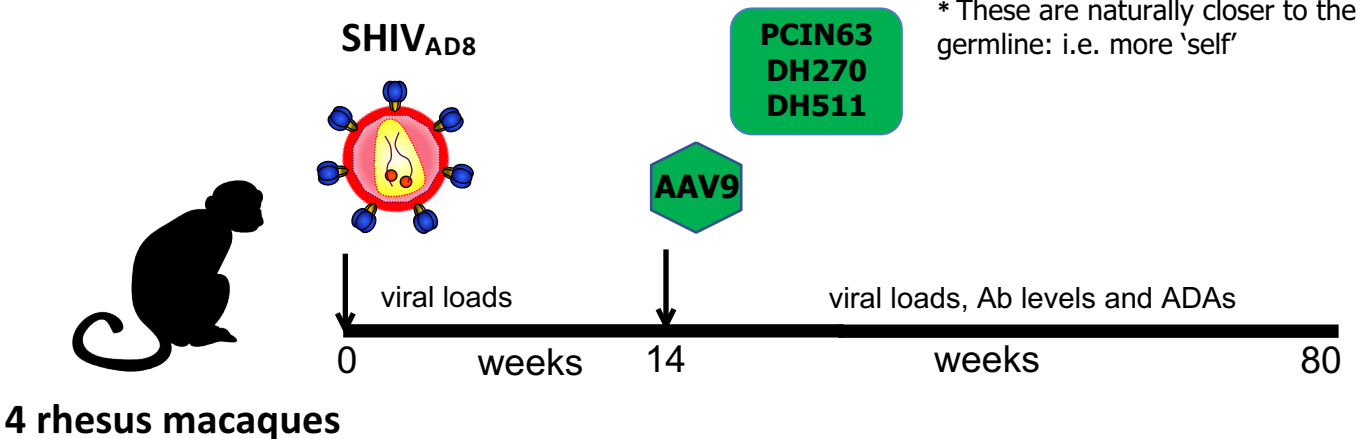
SHIV data – Kumar, et al (2023)

Measurements by Bob Siliciano

# ADA correlation: the more divergent from its original germline, the more immunogenic an antibody is.

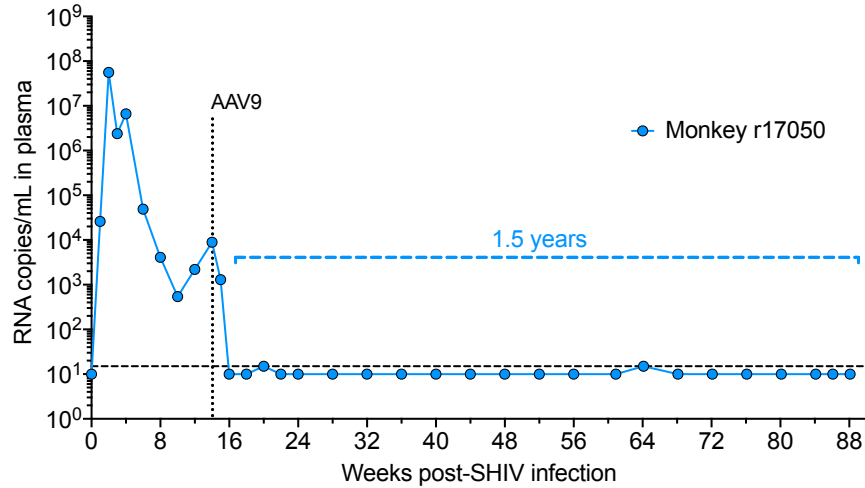


# Therapy experiment 3: use of more "self" antibodies

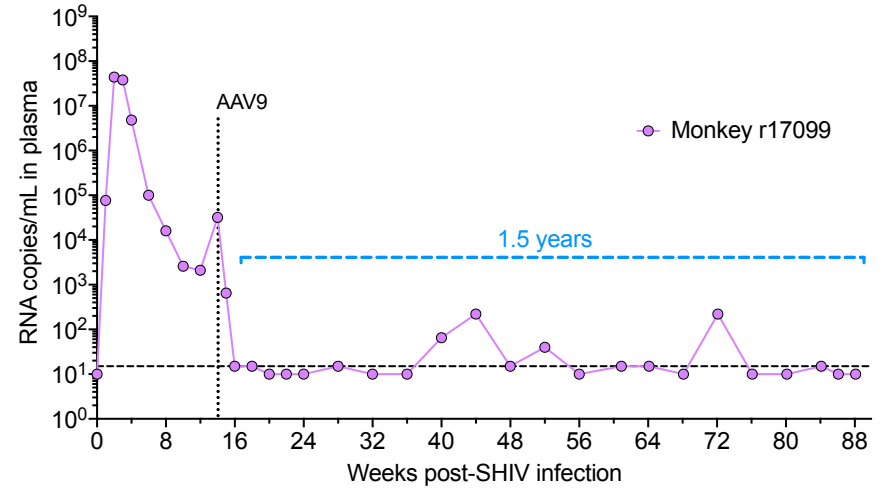


# Two additional cases of viral remission:

Viral loads (SHIV-AD8)

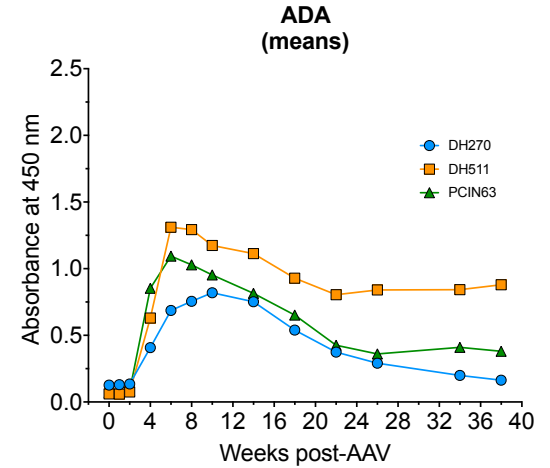
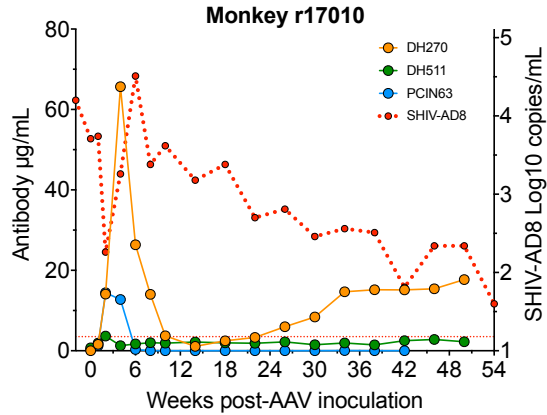
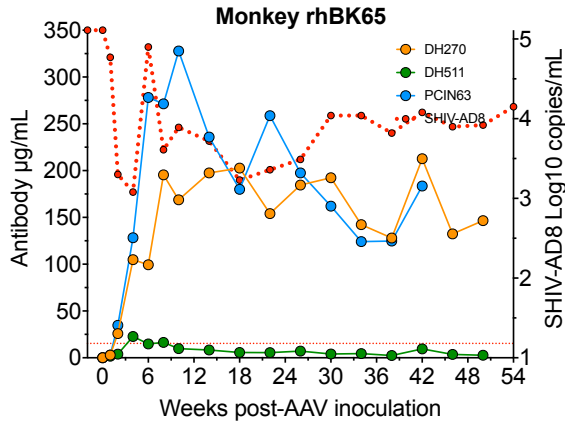
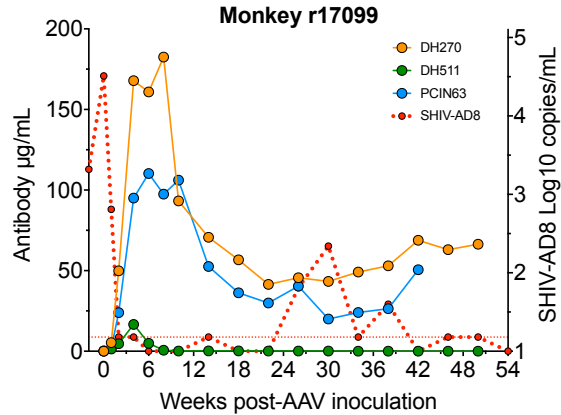
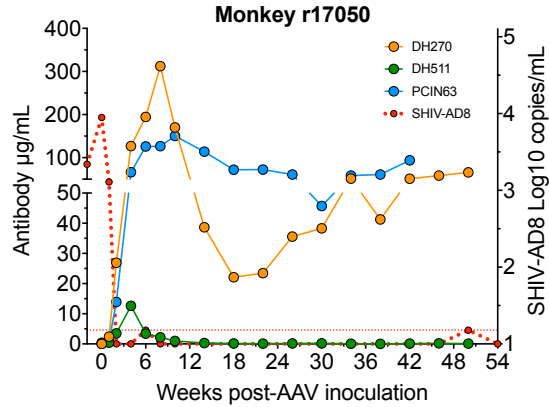


Viral loads (SHIV-AD8)





# Three out of four monkeys had good levels of two AAV delivered antibodies:



# Conclusions

1. AAV-delivered antibodies can suppress viremia for extended periods of time when used as a therapy.
2. Persistently high levels of antibody in circulation can be achieved with AAV vectors for years, maybe decades, and perhaps for life.
3. Anti-drug antibodies (ADAs) are an issue when using AAV to deliver broadly neutralizing antibodies (bNAbs) but the use of closer-to-germline bNAbs may be a viable strategy to overcome them.
4. Long-term delivery of bNAbs with AAV is a very promising approach against HIV.

## University of Miami:

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## SHIV-AD8:

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## Thank you!

