



Viral Suppression in SHIV-infected Rhesus Macaques following AAV-mediated Delivery of Closer-to-germline Monoclonal Antibodies

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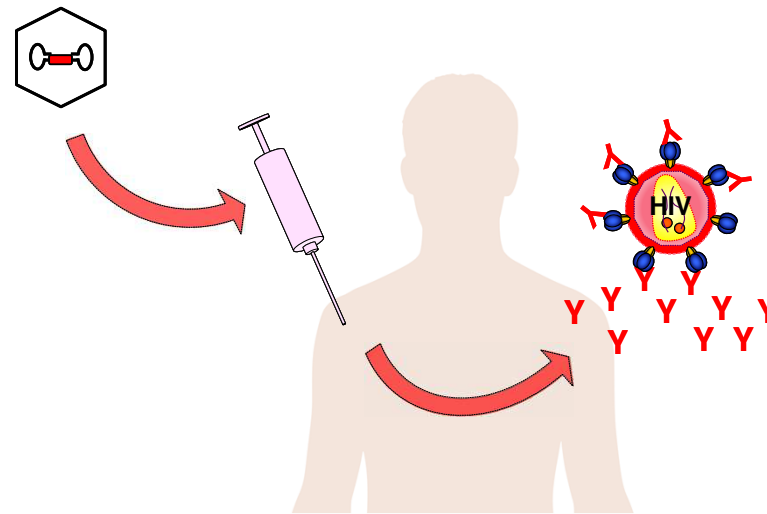


COMMUNITY SUMMARY

- **Background:** Delivery of potent and broadly neutralizing antibodies by means of a viral vector (adeno-associated virus or AAV) is a promising approach for both, the prevention and treatment of HIV infection. However, when the AAV-delivered antibodies are seen as ‘non-self’, unwanted host antibodies are raised against them, which can compromise their efficacy by reducing their concentration and functionality.
- **Key question:** Can we overcome this critical issue by using ‘more-self’ antibodies?
- **Key finding:** The use of naturally ‘more-self’ antibodies may be a viable strategy for overcoming the ‘foreignness’ problem and make the AAV-mediated delivery of antibodies more consistent.

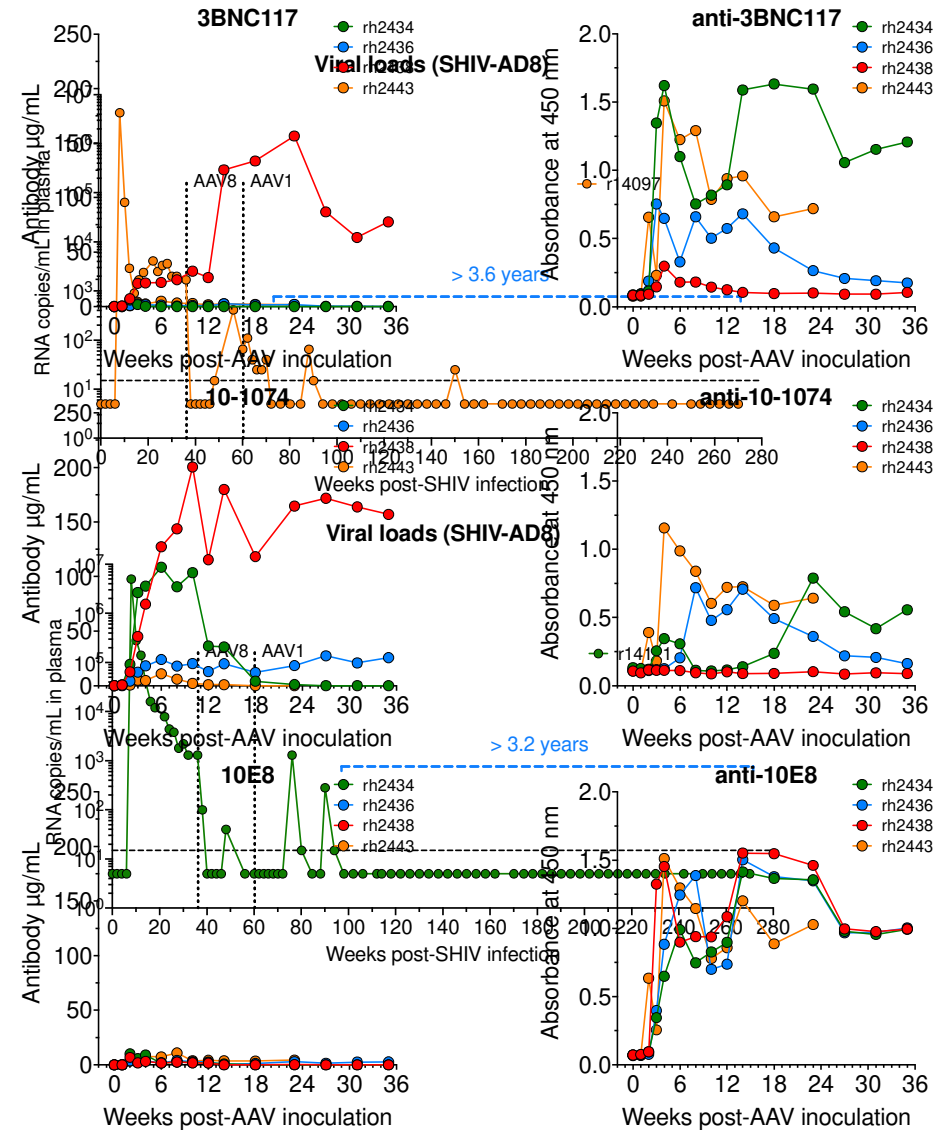
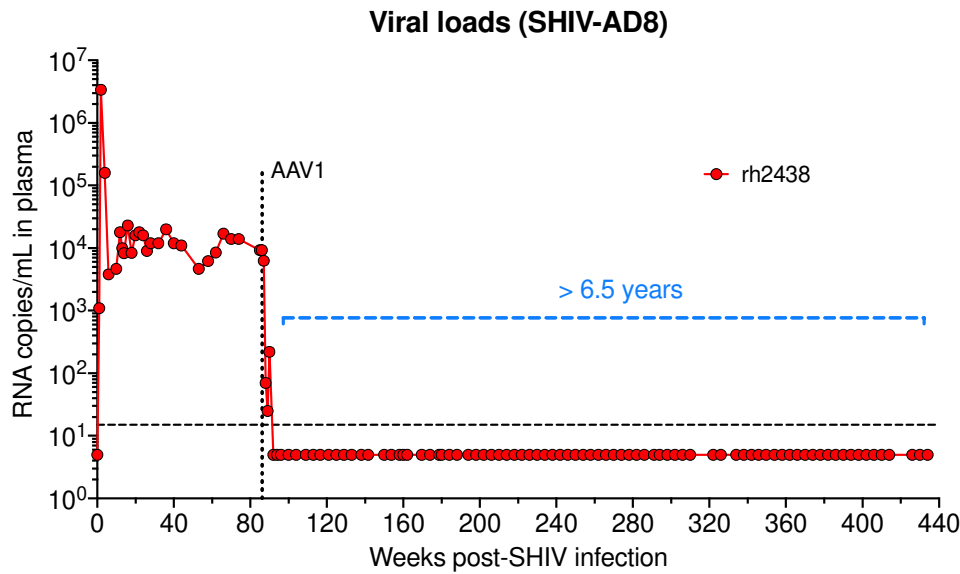
The diagram illustrates the structure and genome organization of Adeno-Associated Virus (AAV). The top part shows a 3D representation of the AAV capsid, a red icosahedron, with a diameter of 20-22 nm. The bottom part shows a linear map of the 4.7 kb genome. The genome is flanked by Inverted Terminal Repeats (ITR) at both ends. Key regions include the p5, p19, and p40 genes, which are transcribed from the left ITR. The p40 gene is further divided into the rep (green) and cap (purple) regions. The cap region contains the cap1 and cap2 genes. The polyA signal is located at the right end of the genome, transcribed from the right ITR.

AAV is a small virus which infects humans and other animals. AAV is not currently known to cause disease and is being exploited for gene therapy.



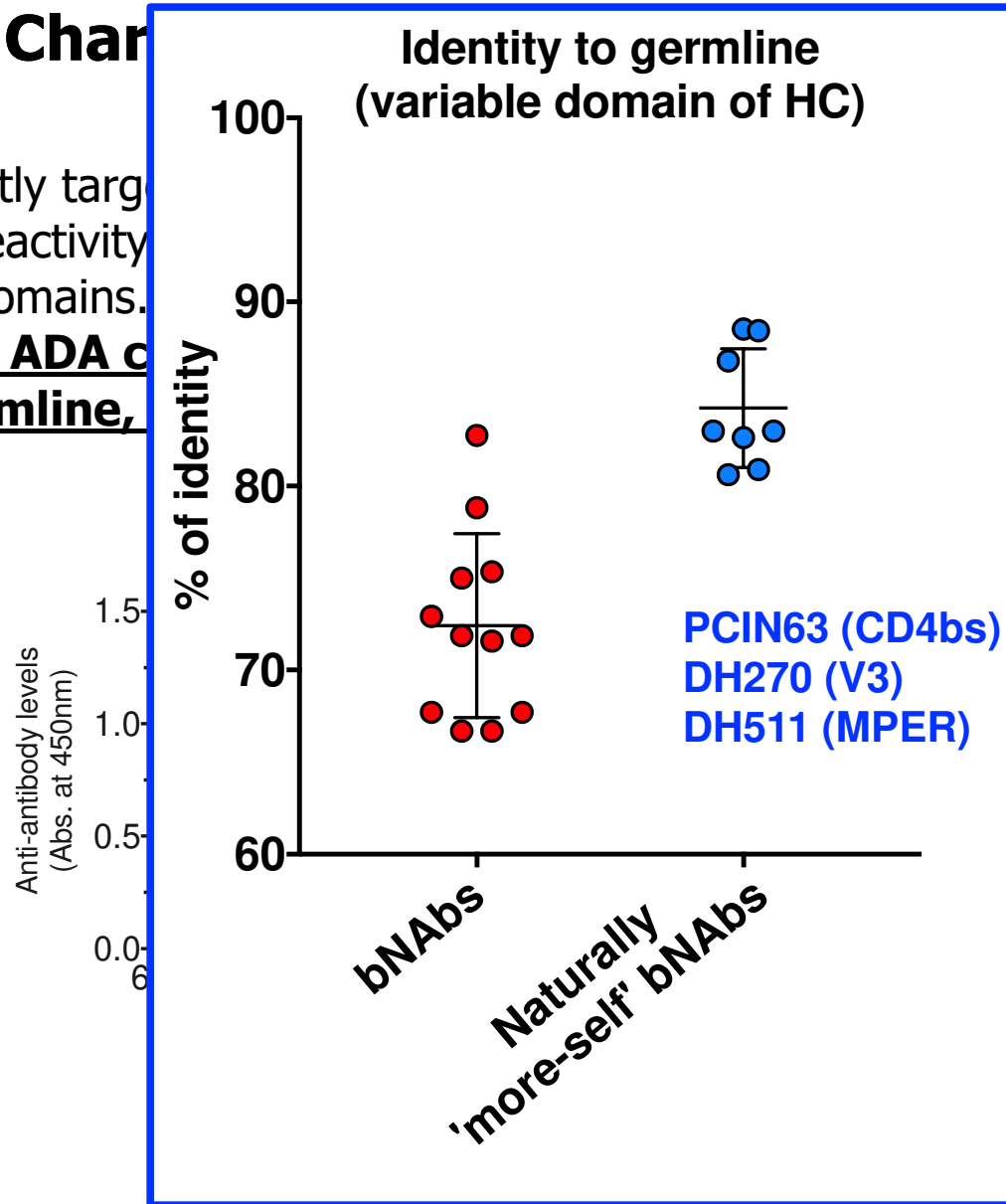
- 1. Circumvents the difficulties of generating a successful immunogen or vaccine.**
- 2. Well characterized, broad and potent antibodies.**
- 3. No need to produce large amounts of pharmaceutical grade antibody.**
- 4. No need for repeated inoculations.**
- 5. One administration could account for years of antibody expression.**
- 6. Delivery of neutralizing antibodies with AAV is a promising approach for the prevention and treatment of HIV infection.**

Therapeutic use of AAV-delivered antibodies: promise & problems



Characteristics:

1. ADAs mostly target CDR-H3
2. CDR-H3 reactivity is highly variable across different variable domains.
3. **Levels of ADA correlate with divergence from germline,**

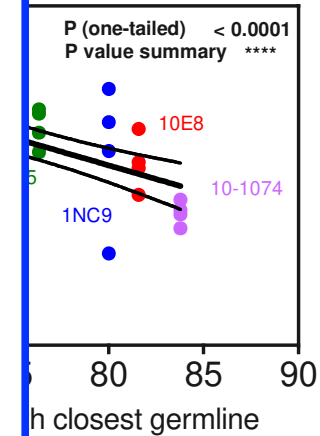


Antibodies:

peptides covering the

the more divergent

Week 28
light chain)



therapy 2016
og. 2015

Potency and breadth:

IC50 $\mu\text{g/mL}$
(SHIV-AD8)

Breadth

PCIN63 (CD4bs)

DH270 (V3)

DH511 (MPER)

Immunity
Article

CellPress

Rapid and Focused Maturation of a VRC01-Class HIV Broadly Neutralizing Antibody Lineage Involves Both Binding and Accommodation of the N276-Glycan

Jeffrey Umotoy,^{1,2} Bernard S. Bagaya,^{3,4} Collin Joyce,⁵ Torben Schiffner,^{5,6} Sergey Menis,^{1,2} Karen L. Saye-Francisco,⁵ Trevor Biddle,² Sanjay Mohan,⁷ Thomas Vollbrecht,⁷ Oleksander Kalyuzhnyi,^{1,2} Sharon Madzorera,² Dale Kitchin,² Bronwen Lamison,⁷ Molati Nonyane,⁷ William Kiembe,⁷ The IAVI Protocol C Investigators and The IAVI African HIV Research Network, Pascal Poignard,^{1,5,10} William R. Schief,^{1,5,6} Dennis R. Burton,^{1,5,6,11} Ben Murrell,^{7,15} Penny L. Moore,^{8,13,14} Bryan Briney,^{5,6} Devin Sok,^{1,2,5,6,4} and Elise Landais^{1,2,5,16,*}

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

HIV

Staged induction of HIV-1 glycan-dependent broadly neutralizing antibodies

Mattia Bonsignori,^{1,2,*†} Edward F. Kreider,^{3†} Daniela Fera,^{4†} R. Ryan Meyerhoff,^{1,2†} Todd Bradley,^{1,2†} Kevin Wiehe,^{1,2} S. Munir Alam,^{1,2} Baptiste Aussedat,⁵ William E. Walkowicz,⁵ Kwan-Ki Hwang,² Kevin O. Saunders,^{2,6} Ruijun Zhang,⁷ Morgan A. Gladden,² Anthony Monroe,² Amit Kumar,² Shi-Mao Xia,² Melissa Cooper,² Mark K. Louder,⁷ Krisha McKee,⁷ Robert T. Bailer,⁷ Brendan W. Pier,⁴ Claudia A. Jette,⁴ Garnett Kelsoe,^{2,8} Wilton B. Williams,^{1,2} Lynn Morris,⁹ John Kappes,¹⁰ Kshitij Wagh,¹¹ Gift Kamanga,^{12*} Myron S. Cohen,¹³ Peter T. Hraber,¹¹ David C. Montefiori,^{2,6} Ashley Trama,² Hua-Xin Liao,^{1,2} Thomas B. Kepler,¹⁴ M. Anthony Moody,^{2,8,15} Feng Gao,^{1,2} Samuel J. Danishefsky,⁵ John R. Mascola,⁷ George M. Shaw,³ Beatrice H. Hahn,³ Stephen C. Harrison,⁴ Bette T. Korber,^{11,*†} Barton F. Haynes^{1,2,*†}

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Potent and broad HIV-neutralizing antibodies in memory B cells and plasma

LaTonya D. Williams^{1,*}, Gilad Ofek^{2,*}, Sebastian Schätzle^{3,*}, Jonathan R. McDaniel^{3,*}, Xiaozhi Lu^{1,*}, Nathan I. Nicely¹, Liming Wu², Caleb S. Loughheed², Todd Bradley^{1,4}, Mark K. Louder⁵, Krisha McKee⁵, Robert T. Bailer⁵, Sijy O'Dell⁵, Ivelin S. Georgiev⁵, Michael S. Seaman⁷, Robert J. Parks¹, Dawn J. Marshall¹, Kara Anastasi¹, Guang Yang¹, Xiaoyan Nie¹, Nancy L. Tumba^{8,9}, Kevin Wiehe^{1,4}, Kshitij Wagh¹⁰, Bette Korber¹⁰, Thomas B. Kepler¹¹, S. Munir Alam^{1,4,12}, Lynn Morris^{9,9}, Gift Kamanga¹³, Myron S. Cohen¹⁴, Mattia Bonsignori^{1,4}, Shi-Mao Xia¹, David C. Montefiori^{1,15}, Garnett Kelsoe^{1,16}, Feng Gao^{1,4}, John R. Mascola⁵, M. Anthony Moody^{1,16,17}, Kevin O. Saunders^{1,15}, Hua-Xin Liao^{1,4}, Georgia D. Tomaras^{1,15,16,18}, George Georgiou^{3,19,*†}, and Barton F. Haynes^{1,4,16,*†}

Sequence and Structural Convergence of Broad and Potent HIV Antibodies That Mimic CD4 Binding

Johannes F. Scheid,^{1,2} Hugo Mouquet,^{1,*} Beatrix Ueberheide,^{3,*} Ron Diskin,^{4,*} Florian Klein,¹ Thiago Y. K. Oliveira,¹ John Pietzsch,^{1,5} David Fenyö,³ Alexander Abadir,² Klara Velinzon,² Arlene Hurley,⁶ Sunnie Myung,² Farid Boulad,⁷ Pascal Poignard,^{6,9} Dennis R. Burton,^{8,10} Florencia Pereyra,^{10,11} David D. Ho,¹² Bruce D. Walker,^{10,11,12} Michael S. Seaman,¹⁴ Pamela J. Bjorkman,^{4,12} Brian T. Chait,³ Michel C. Nussenzweig^{1,12,*†}

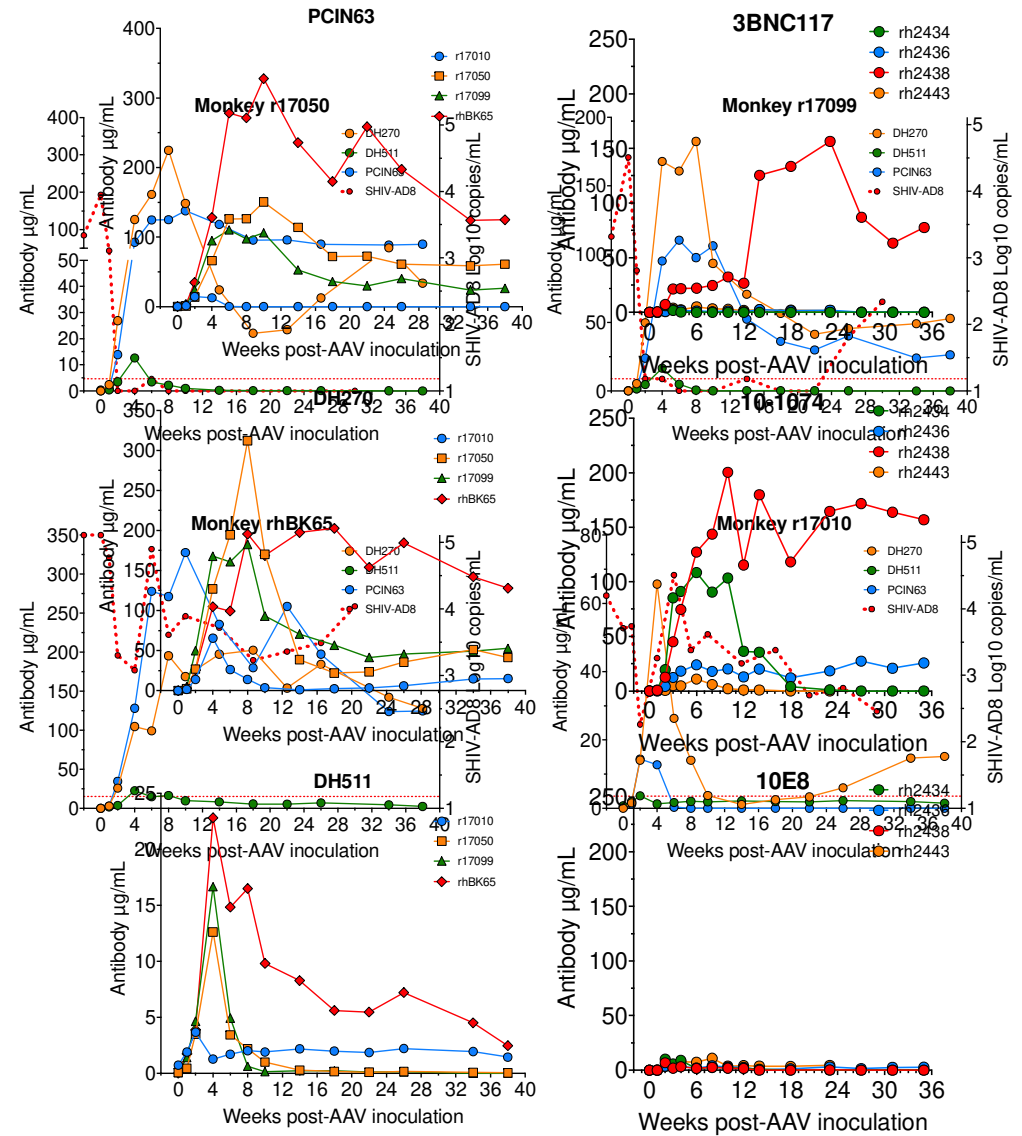
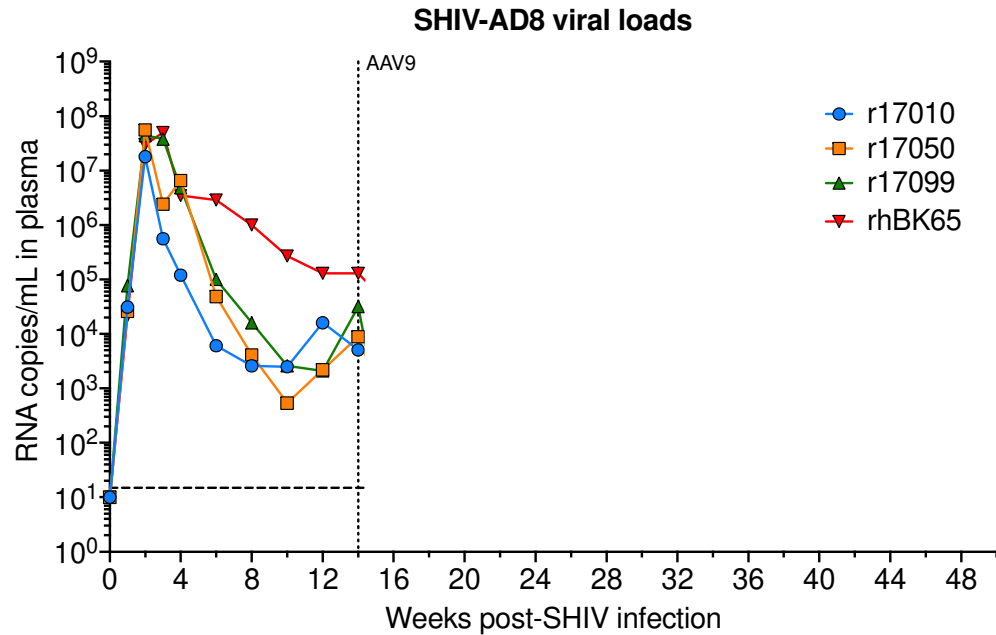
Rational Design of Envelope Identifies Broadly Neutralizing Human Monoclonal Antibodies to HIV-1

Xueling Wu,^{1,*} Zhi-Yong Yang,^{1,*} Xuxing Li,^{1,*} Carl-Magnus Hogerkerp,^{1,*†} William R. Schief,⁴ Michael S. Seaman,² Tongqing Zhou,¹ Stephen D. Schmidt,¹ Lan Wu,¹ Ling Xu,¹ Nancy S. Longo,¹ Krisha McKee,¹ Sijy O'Dell,¹ Mark K. Louder,¹ Diane L. Wycuff,¹ Yu Feng,¹ Martha Nason,² Nicole Doria-Rose,³ Mark Connors,³ Peter D. Kwong,³ Mario Roederer,³ Richard T. Wyatt,¹ Gary J. Nabel,^{1,5} John R. Mascola⁵

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Therapeutic use of AAV-delivered antibodies: promise & problems



Conclusions

- 1. The use of closer-to-germline bNAbs may be a viable strategy for avoiding ADAs following gene therapy with AAV-bNAb vectors.**
- 2. Our data support the potential for long-term suppression of viral loads with the AAV-antibody approach but also highlight the difficulties associated with achieving such long-term suppression.**
- 3. Eradicating or minimizing ADA responses is crucial to make the AAV-delivery of antibodies a consistent and reliable approach against HIV.**

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- Wendy Newton

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