Evidence for an Actual Cure of a SHIV-infected Monkey

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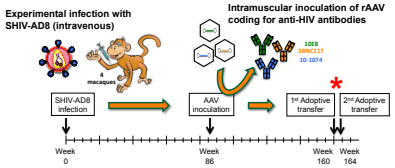
Abstract

Four rhesus monkeys were infected with SHIV-AD8 for 86 weeks before receiving adeno-associated virus (AAV) vectors expressing *rhesusized* IgG1 versions of anti-HIV monoclonal antibodies 10E8, 3BNC117, and 10-1074 in a therapeutic approach. 10E8 was successfully delivered to none of the four monkeys; 3BNC117 to one of the four monkeys; 10-1074 to three of the four monkeys. SHIV-infected monkey rh2438 maintained serum concentrations of 3BNC117 and 10-1074 of 75 – 150 µg/ml for 17 months after AAV administration. Monkey rh2438 never received antiviral drugs at any time. The viral load set point in rh2438 was 10,000 – 20,000 viral RNA copies per ml of plasma for the prolonged period leading up to the time of AAV administration. Following the initial decline in viremia after AAV administration, viral loads remained suppressed to below the limit of detection of 30 RNA copies per ml of plasma for 17 months. During this time rh2438 anti-p27gag antibodies declined more than 10-fold. Attempts to recover SHIV from the peripheral blood of rh2438 were unsuccessful, including *in vitro* cultures of 10^8 CD8-depleted PBMCs. Two attempts to adoptively transfer infection to naïve recipients using lymph nodes taken from rh2438 failed to transmit the infection. These findings highlight the potential of AAV-mediated antibody expression for impacting HIV-1 infections.

Methods

After 86 weeks of SHIV-AD8 infection, four rhesus macaques were inoculated intramuscularly with three different AAVs coding for three different broadly neutralizing anti-HIV antibodies in a therapeutic approach:



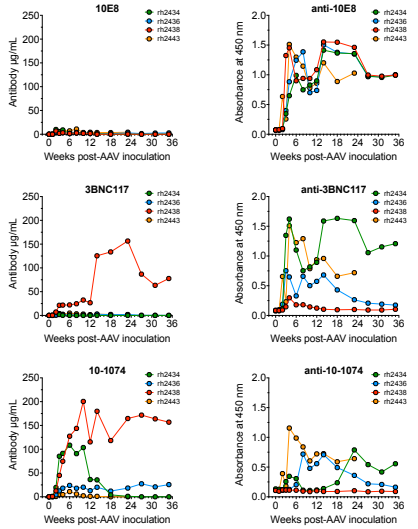
Viral loads were measured by RT-PCR. Antibody and anti-antibody levels were measured by standard ELISA. Adoptive transfer involved surgical removal of lymph nodes from the monkey with undetectable viremia, single cell suspension preparation and inoculation of the cells in two separate naïve recipient animals.

Background

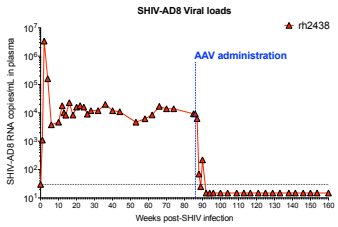
HIV infection can be suppressed with anti-retroviral treatment (ART) but the existence of long-term reservoirs allows the viral load to rebound quickly after ART interruption[1]. Attempts to purge these reservoirs in vivo have not been successful and viral inducers may have serious undesirable effects[2,3]. Consequently, there is intense interest at the current time in finding strategies to prevent this rebound, i.e. finding a "functional cure". Passive transfer of broadly neutralizing antibodies (bNAbs) can prevent infection[4-6], and also suppress active infection in humanized mice and macaques[7-10]. Importantly, bNAbs can also suppress HIV emerging from the viral reservoir[11] and therefore they could be a good alternative to ART[12,13]. However, periodic administrations of large amounts of protein would be required for long-term effects, otherwise and similarly to ART, discontinuation of bNAb therapy would result in viral rebound[12]. A potential solution for overcoming this, is the use of recombinant adeno-associated virus vectors (AAV)[13]. AAV has an outstanding safety record in clinical trials[14] and, as long as the delivered protein is viewed as self[15], it can result in continuous durable expression of the transgene product for years[16-20]. The idea is that HIV-infected people could get one shot of AAV making a cocktail of bNAbs and if satisfactory levels of antibody could be maintained *in vivo*, those individuals would remain suppressed for years without having to take ART or receive regular antibody administrations. Our intention is to perform experiments in monkeys that will inform and guide development of this concept for use in people.

Results

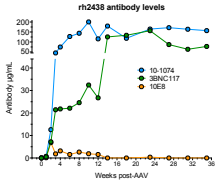
1. Antibody and host anti-antibody levels were quantified by ELISA in all four AAV recipients:



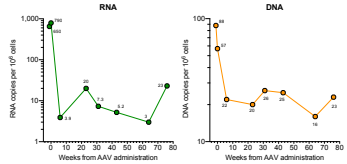
2. After AAV administration, animal rh2438 achieved profound and sustained virologic control during the chronic phase of the infection:



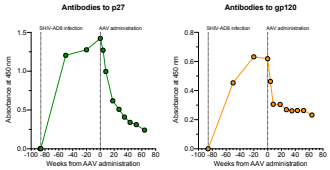
3. Monkey rh2438 persistently maintained high concentrations of broadly neutralizing anti-HIV antibodies 3BNC117 and 10-1074 in serum following the AAV administration:



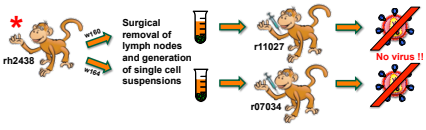
4. Analysis of the viral reservoir in PBMCs isolated from rh2438 revealed a drop in both, viral RNA and viral DNA, after the AAV inoculation:



5. Serum from rh2438 showed a sudden and marked decrease in antibody reactivity to p27/gag and g120/envelope after AAV inoculation :



6. Attempts to recover SHIV from the peripheral blood of rh2438 did not yield any virus. Importantly, lymph node cells from this animal were not able to transmit infection when inoculated in two separate naïve recipient monkeys:



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Conclusions

1. We have shown evidence for an actual cure of a SHIV-infected monkey during the chronic phase of the infection.

2. Long term delivery of potent and broadly neutralizing antibodies with AAV is a very promising approach against HIV.