SIV CLEARANCE FROM NEONATAL MACAQUES FOLLOWING TRANSIENT CCR5 DEPLETION

459

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BACKGROUND

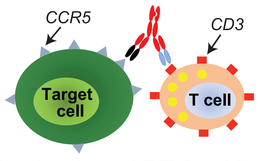
Previous work demonstrating functional HIV cure following total ablative therapy for cancer followed by HSCT from a CCR5Δ32/Δ32 donor suggests that ablation of CCR5 makes an important contribution to eradication of the virus. Here, we tested whether targeted depletion of potential reservoir cells bearing CCR5 impacts long-term SIV remission in a nonhuman primate model for AIDS.

METHODS

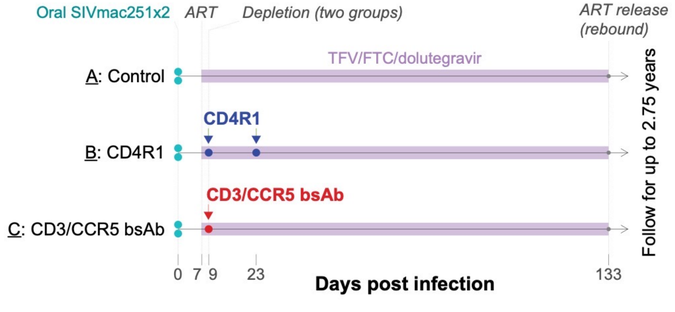
Neonatal rhesus macaques were inoculated orally with **SIVmac251** (two inoculations each with 50,000 $TCID_{50}$). cART was initiated one week after infection.

Two days after ART initiation, two groups of macaques were administered candidate reservoir-depleting therapies:

- Group A controls received ART alone
- Group B received **CD4-specific antibody** (CD4R1 infused at 50 mg/kg). These macaques received a second infusion of antibody two weeks later.
- Group C received **CD3/CCR5 bi-specific antibody** (infused at 3 mg/kg).



The macaques were maintained on ART for 18 weeks until viremia was eliminated, then ART was withdrawn to assess for viral rebound. Tissue reservoirs were assessed by qPCR in some non-rebounding macaques following necropsy.



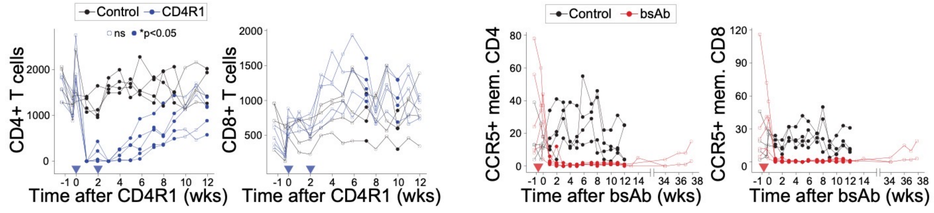
Newborn macaques receiving depletion therapy can achieve **SIV remission, including aviremia maintained for >3 years** following treatment interruption and despite depletion of CD8+ T cells.

Delayed viral rebound was observed in 4/7 anti-CD3/CCR5 bi-specific antibody treated macaques. SIV clearance was achieved in 2/7.

RESULTS

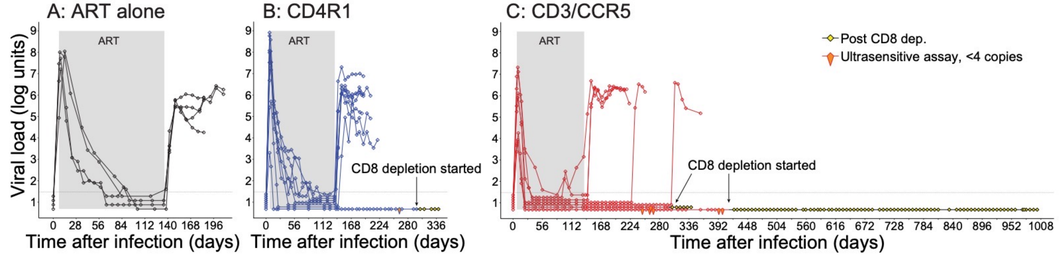
Target cell depletion: Administration of antibody efficiently and transiently depleted target cells in peripheral blood, gut, and lymph nodes.

- Results in peripheral blood:

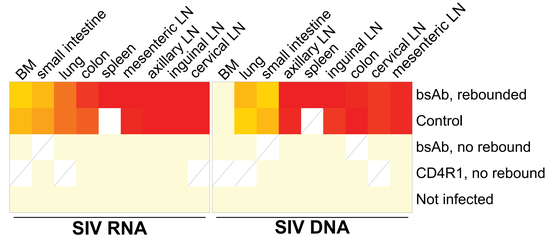


Delayed rebound or long-term remission: Aviremia off ART was maintained to the end of the experiment in 1/8 animals treated with CD4R1 and 2/7 treated with CD3/CCR5 bi-specific antibody.

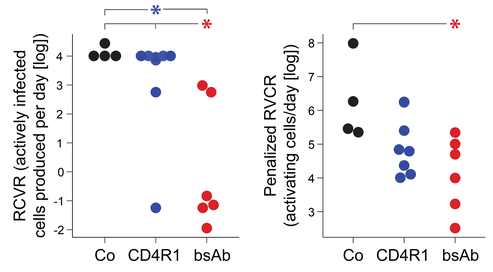
- A significant delay in viral rebound was observed in 4/7 treated with CD3/CCR5 bsAb
- Depletion of CD8+ T cells in the aviremic animals did not result in viral rebound



Impact of depletion on the viral reservoir: No vRNA or vDNA was detected by qPCR in tissues collected at necropsy in the aviremic animals.



CD3/CCR5 bsAb reduced the replication-competent viral reservoir (RCVR): Mathematical modeling of rebound times and viral-outgrowth assays results demonstrated that treatment with CD3/CCR5 bi-specific antibody significantly reduced the RCVR.



CONCLUSIONS

160,000 infants and children are infected with HIV annually. Current treatment requires lifelong administration of ART. We modeled perinatal HIV infection in neonatal macaques including early treatment with ART followed by reservoir-depleting antibody treatment.

We found that long-term SIV remission and apparent cure can be achieved for infant macaques via targeted depletion of potential reservoir cells bearing the chemokine receptor, CCR5. Our results show that CD3/CCR5 bi-specific antibody treatment can achieve meaningful depletion of the RCVR and suggest that early initiation of ART combined with cytotoxic depletion of potential reservoir cells is a viable approach to HIV cure strategies. Our results also suggest that CCR5 may be an "Achilles' heel" in early HIV infection and that CCR5 targeting can make a crucial contribution to early cure strategies.

ADDITIONAL KEY INFORMATION

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