529

Vaccination combined with PD-1 blockade provides sustained SIV suppression in Mamu-A01(+) macaques

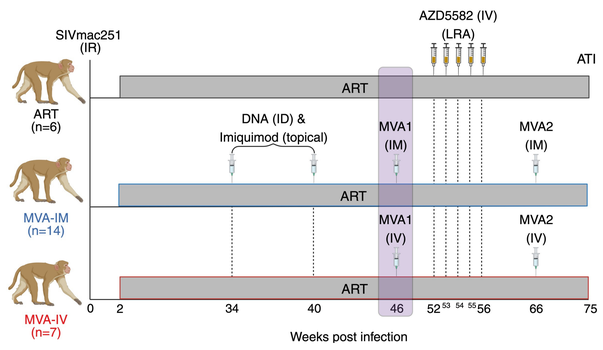
Bhrugu Yagnik[1], Sheikh Abdul Rahman[1], Sailaja Gangadhara[1], Shan Liang[1], Gordon J Freeman[2], Rafi Ahmed[3], Rama R Amara[1]

1. Emory National Primate Research Center, Emory Vaccine Center, Emory University, Atlanta, GA, USA, 2. Harvard Medical School, Boston, MA, USA, 3. Emory Vaccine Center, Atlanta, GA, USA

BACKGROUND

- Latency reversal and restoring T cell function are the two major barriers to HIV cure.
- Towards this, here we evaluated therapeutic potential of intramuscular (IM) or intravenous (IV) vaccination combined with a latency reversal agent (LRA) and PD-1 blockade in SIV infected macaques.

METHODS

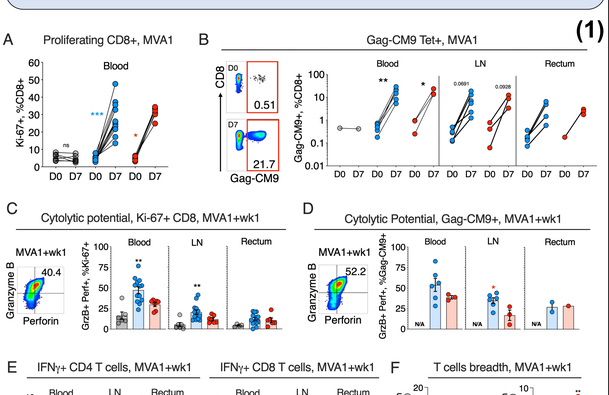


- *ART drugs (consisted of Emtricitabine (FTC) at 40mg/kg, Tenofovir Disoproxil Fumarate (TDF) at 5.1mg/kg, and Dolutegravir (DTG) at 2.5mg/kg dose) was administered subcutaneously at 1mL/kg body weight.*
- *AZD5582 was infused weekly at 0.1mg/kg body weight o all animals.*
- *At the time of ATI, 7 out of 14 MVA-IM immunized female RMs received 6 infusions of anti-PD-1 antibody (10mg/kg body weight) starting at the day of ATI.*

Results

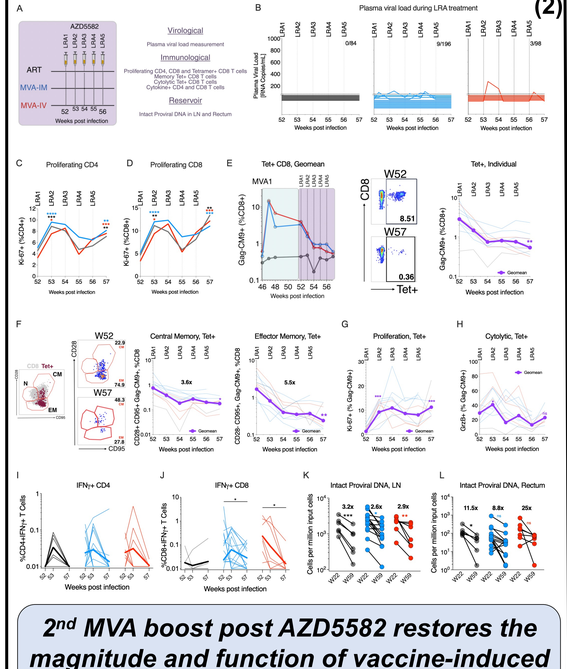
Both IM and IV MVA vaccinations improve the magnitude and functional quality of SIV-specific CD8 and CD4 T cells in Blood & LN.

(1)



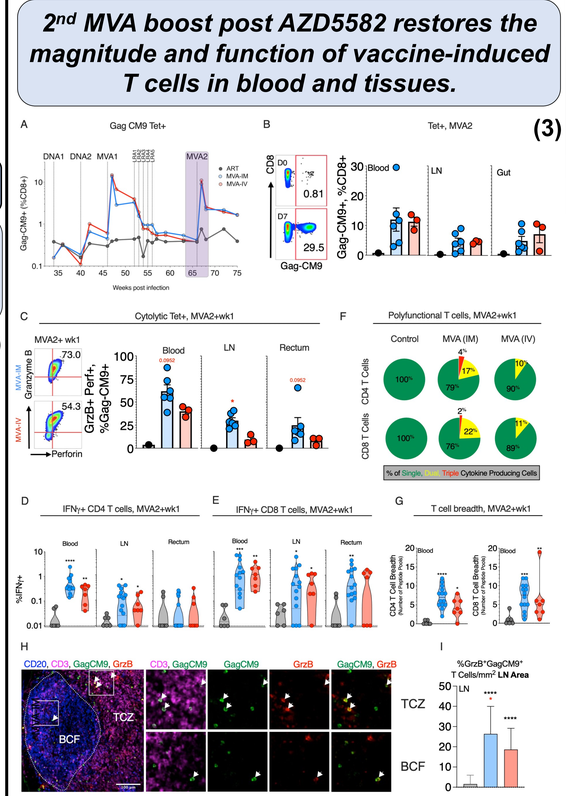
Weekly AZD5582 infusions result in a rapid loss of vaccine-induced effector CD8 T cells and do not decrease viral reservoirs.

(2)



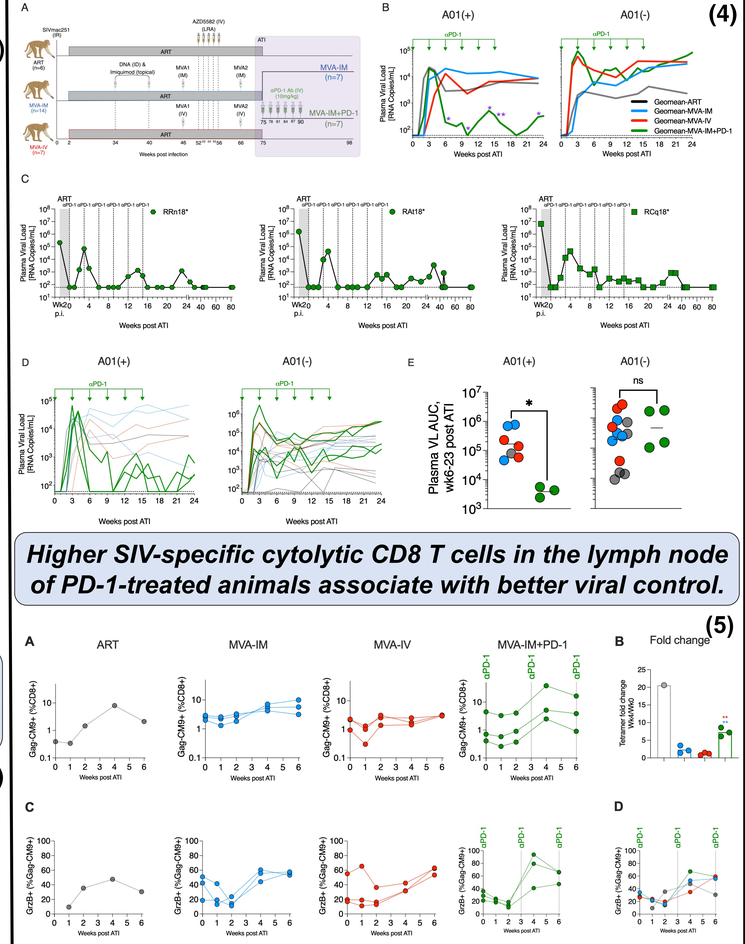
2nd MVA boost post AZD5582 restores the magnitude and function of vaccine-induced T cells in blood and tissues.

(3)



PD-1 blockade post ART interruption exhibits profound and prolonged viral suppression in Mamu-A01(+) animals.

(4)

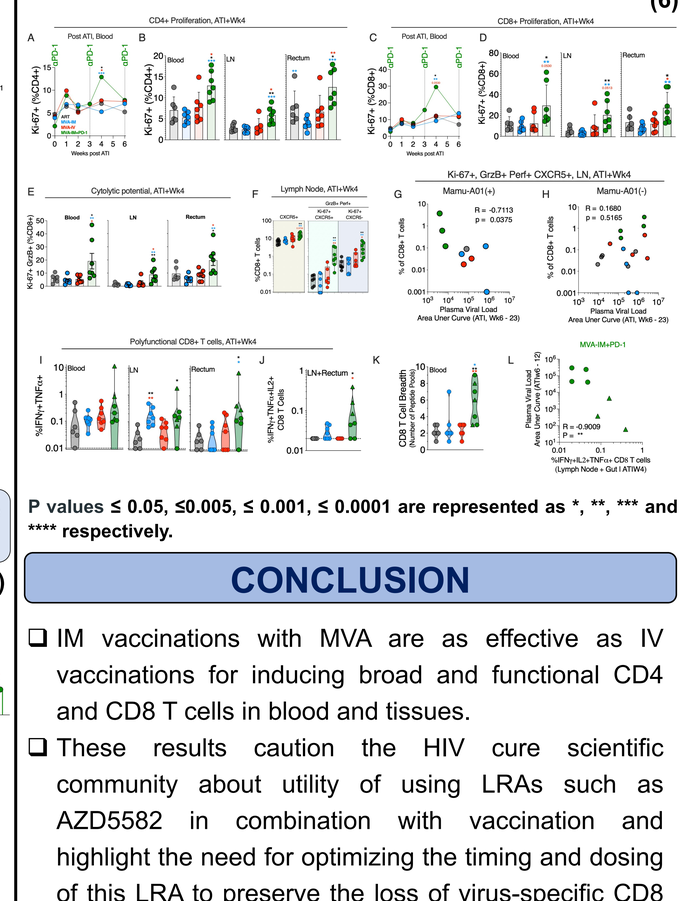


Higher SIV-specific cytolytic CD8 T cells in the lymph node of PD-1-treated animals associate with better viral control.

(5)

Polyfunctional SIV-specific and cytolytic total CD8 T cells in tissues of PD-1-treated animals associate with better viral control.

(6)



P values ≤ 0.05, ≤0.005, ≤ 0.001, ≤ 0.0001 are represented as *, **, * and **** respectively.**

CONCLUSION

- IM vaccinations with MVA are as effective as IV vaccinations for inducing broad and functional CD4 and CD8 T cells in blood and tissues.
- These results caution the HIV cure scientific community about utility of using LRAs such as AZD5582 in combination with vaccination and highlight the need for optimizing the timing and dosing of this LRA to preserve the loss of virus-specific CD8 T cells.
- This is the first report demonstrating this level of profound and sustained SIV suppression following ATI using immunotherapy in the SIV/macaque model.
- These results provide critical information to the scientific community about improving immunotherapies to achieve HIV cure.

ADDITIONAL KEY INFORMATION

Funding support: NIH R37AI112787 (R.A.R), P01AI056299 (G.J.F), P51 OD011132 (E.N.P.R.C), P30 AI050409 (Emory CFAR)

Email contact: Rama Amara; ramara@emory.edu