COMBINATION OF PD-1 BLOCKADE AND AZD5582 THERAPY IN SIV+ MONKEYS

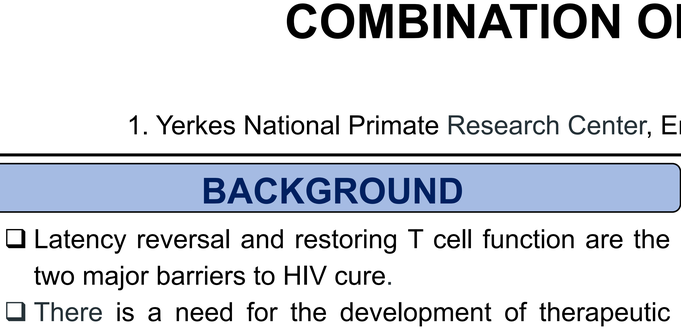
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BACKGROUND

- Latency reversal and restoring T cell function are the two major barriers to HIV cure.
- There is a need for the development of therapeutic strategies that accomplish both goals to facilitate immune mediated clearance of the reactivated latent CD4 T cells.
- PD-1 blockade has not only been shown to potentiate HIV/SIV latency reversal, but also to reverse immune exhaustion, improve antiviral immunity, and reduce viral reservoirs.
- Therefore, the objective of this study was to combine PD-1 blockade with AZD5582 (a potent latency reversal agent, LRA) as a "shock and kill" approach and evaluate safety, virological and immunological effects in SIV infected and ART suppressed rhesus macaques (RMs).



METHODS

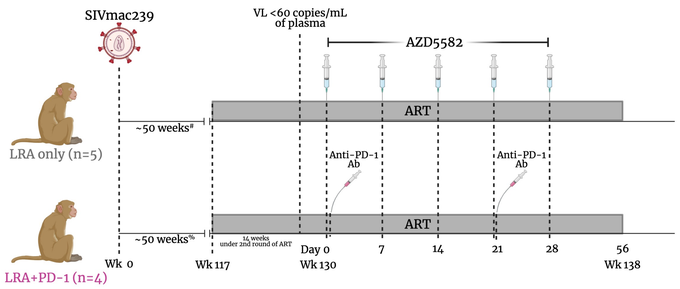


Fig. 1. Study design. A total of 9 RMs were chronically infected with SIVmac239 for 2 years and were on a second cycle of daily ART for 14 weeks with complete viral suppression. Infusion dose of AZD5582 and anti-PD-1 antibody were 0.1 mg/kg and 10 mg/kg body weight, respectively.
#, %Rahman and Yagnik et al., Sci. Immunol. 2021 Sep 10;6(63):eabh3034

RESULTS

Strong latency reversal as well as instances of sustained viremia were observed in both the groups, with no significant difference in events of viral rebound between the groups.

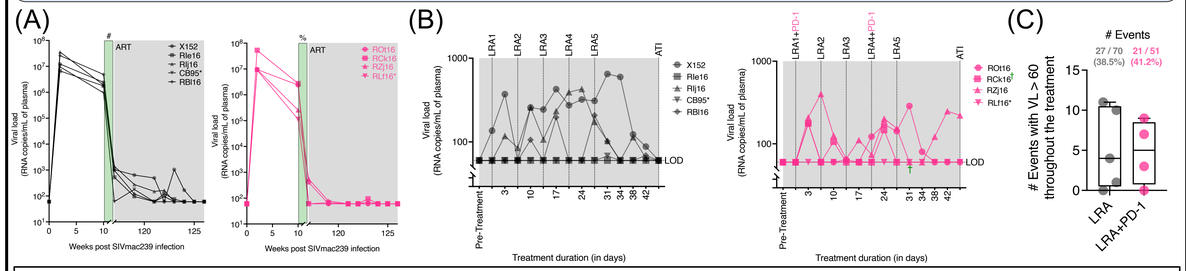


Fig. 2. (A) Plasma viral load (VL) following 2nd cycle of ART initiation and prior to treatment with AZD5582 and anti-PD-1 antibody. (B) Plasma VL measured at days 0, 3 and 7 post each infusion. LOD, Limit of detection. (C) Comparison of no. of plasma VL measurements, above LOD events between the group.

Combination of PD-1 blockade and AZD5582 but not AZD5582 alone, showed a robust increase in proliferating total and memory CD4 and CD8 T cells with each AZD5582 administration in PBMCs.

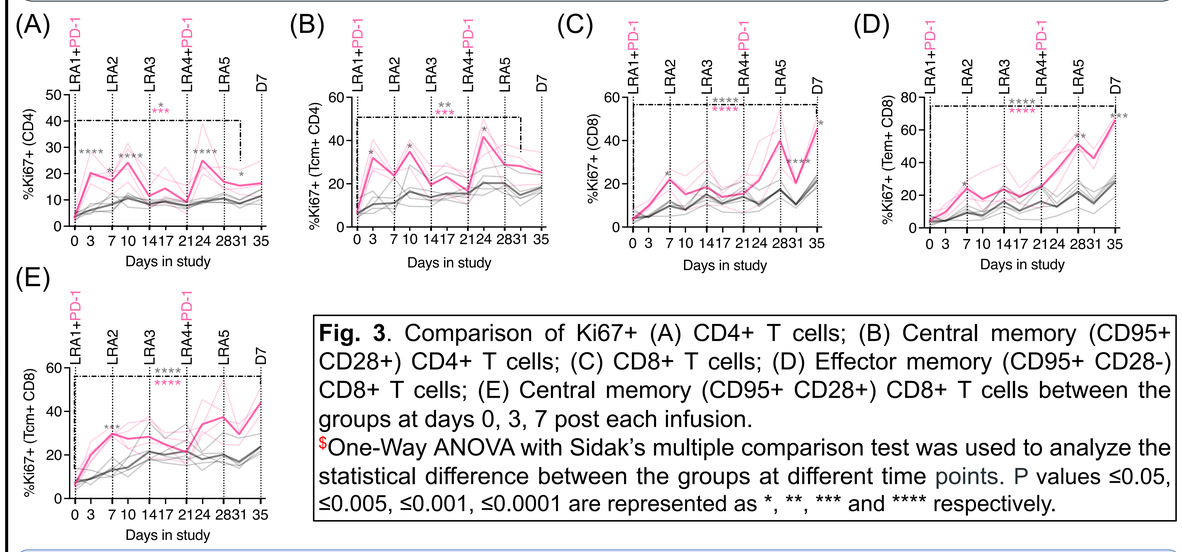


Fig. 3. Comparison of Ki67+ (A) CD4+ T cells; (B) Central memory (CD95+ CD28+) CD4+ T cells; (C) CD8+ T cells; (D) Effector memory (CD95+ CD28-) CD8+ T cells; (E) Central memory (CD95+ CD28+) CD8+ T cells between the groups at days 0, 3, 7 post each infusion.
$One-Way ANOVA with Sidak's multiple comparison test was used to analyze the statistical difference between the groups at different time points. P values ≤0.05, ≤0.005, ≤0.001, ≤0.0001 are represented as *, **, *** and **** respectively.

Co-treatment of AZD5582 and anti-PD-1 antibody resulted in increase in cytolytic potential of CD8 T cells, and also an increase in CD4 T regulatory cells in PBMCs.

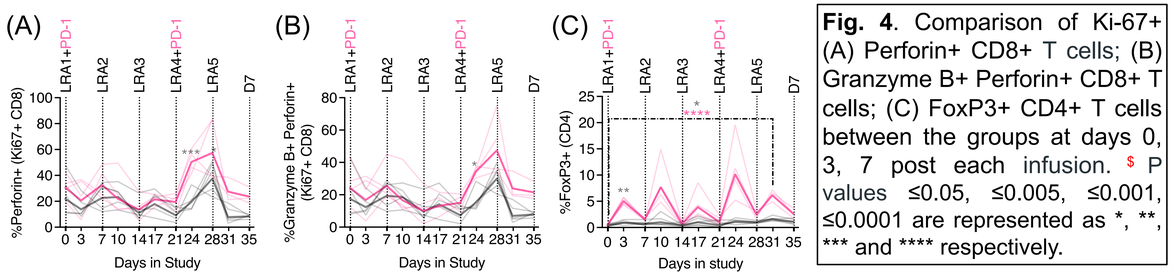


Fig. 4. Comparison of Ki-67+ (A) Perforin+ CD8+ T cells; (B) Granzyme B+ Perforin+ CD8+ T cells; (C) FoxP3+ CD4+ T cells between the groups at days 0, 3, 7 post each infusion. $ P values ≤0.05, ≤0.005, ≤0.001, ≤0.0001 are represented as *, **, *** and **** respectively.

Co-treatment of AZD5582 and anti-PD-1 antibody exhibited immunophenotypic changes in lymph node and gut compartment similar to PBMCs.

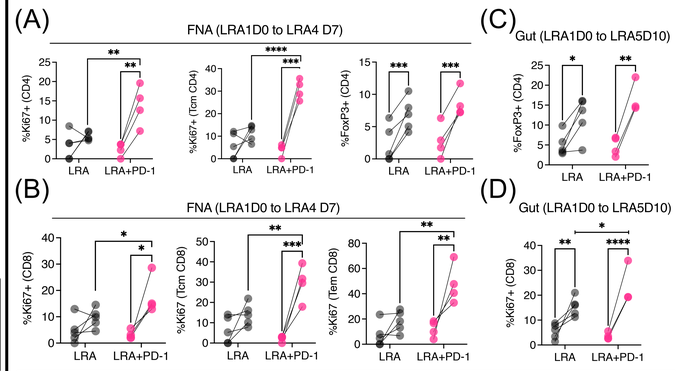


Fig. 5. Change in the frequency of (A) proliferating CD4+, CD95+ CD28+ CD4+ (Tcm) and FoxP3+ CD4+ T cells (left to right); (B) proliferating CD8+, CD95+ CD28+ (Tcm) and CD95+ CD28- (Tem) CD8+ T cells (left to right) in Fine Needle Aspirate (FNA) of LN samples; (C) FoxP3+ CD4+ T cells; and (D) proliferating CD8+ T cells in gut samples. $ P values ≤ 0.05, ≤0.005, ≤ 0.001, ≤ 0.0001 are represented as *, **, *** and **** respectively.

Treatment with AZD5582 decreased cell associated RNA copies in PBMCs, and addition of PD-1 blockade didn't reduce it further.

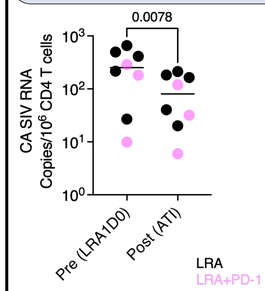


Fig. 6. Cell associated (CA) SIV RNA copies, an indicator of viral reservoir, prior to treatment (Day 0 of 1st LRA/LRA+PD-1 infusion) with post-treatment (Interruption of ART, ATI) in PBMCs.
Wilcoxon matched-paired signed rank test was used for statistical analysis.

CONCLUSION

In summary, combined treatment of PD-1 blockade and AZD5582 is safe and effective in inducing latency reversal. Despite no additive advantage on reservoir size, the combined treatment changed the landscape of T cell responses in blood and tissues.

ADDITIONAL KEY INFORMATION

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

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