Treatment With AZD5582 + hetIL-15 Disrupts the Reservoir Establishment in SIV-Infected Macaques

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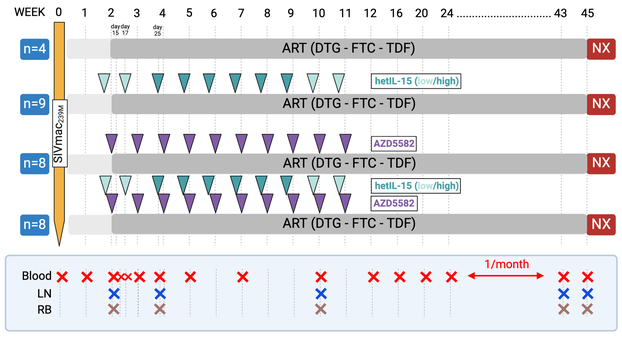
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BACKGROUND

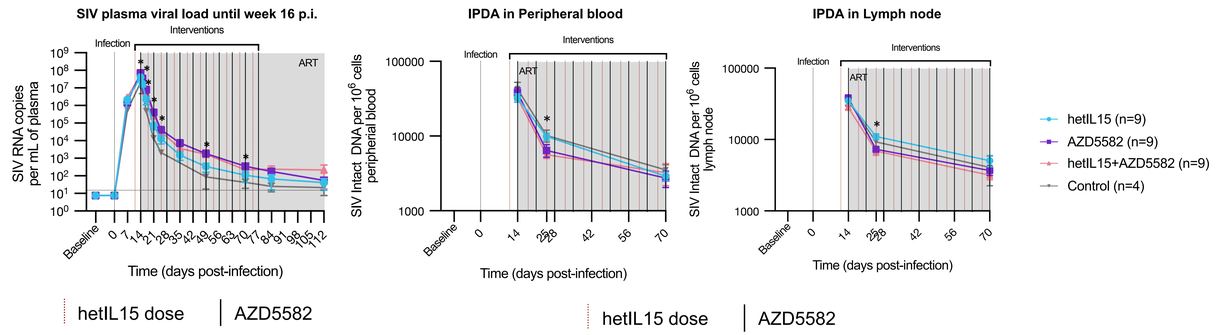
HIV infection cannot be cured despite suppressive antiretroviral therapy (ART) due to a persistent reservoir of latently-infected memory CD4⁺ T cells harboring replication competent virus. One of the many strategies explored for HIV/SIV eradication is based on the "shock & kill" paradigm, which postulates that the reservoir can be reduced or even eliminated by interventions that combine the reactivation of virus production in latently-infected cells (i.e., "shock", as induced by latency-reversing agents, LRA) with the immune-mediated killing of these cells ((i.e., "kill", as mediated by cytotoxic T lymphocytes, NK cells, antibody-dependent cellular cytotoxicity and other mechanisms).
Here, we tested the SMACm/cIAP antagonist AZD5582 (shock) in combination with the heterodimeric interleukin-15 (hetIL-15), the native form of the cytokine that activates and expands cytotoxic T and NK cells (kill), as a novel approach to prevent the establishment of the virus reservoir during the early stages of infection and/or ART.

METHODS

31 rhesus macaques (RMs) were infected with genetically barcoded SIVmac239M and started ART at 2-weeks p.i..
9 RMs received hetIL-15 via sq injections of escalating dose of 10-40 ug/kg (weekly for 10 weeks) starting 3 days before ART initiation; 9 RMs received i.v. AZD5582 at 0.1 mg/kg weekly for 10 weeks starting at ART initiation; 9 RMs received the combination of hetIL-15 and AZD5582 over the same experimental phase as outlined above. 4 animals served as treatment-naïve, ART-only controls. Plasma viral loads were measured longitudinally for 16 weeks and the reservoir size was estimated in PBMC and lymph nodes (LN) by IPDA. CD8⁺ T cells, CD4⁺ T cells, and NK cells phenotypes were characterized by flow cytometry.

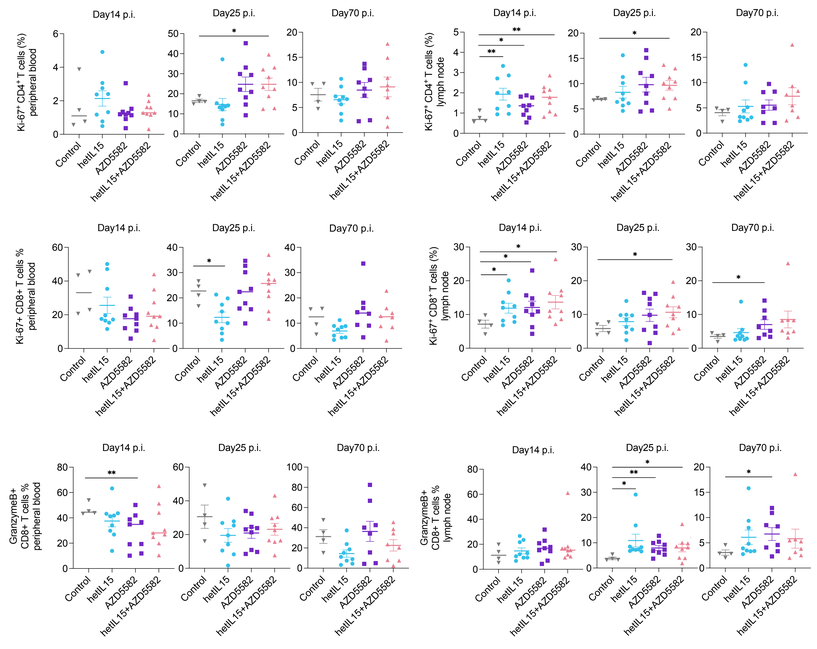


Treatment with AZD5582, alone or in combination with hetIL-15, perturbs the establishment of the virus reservoir when administered at the time of ART initiation during acute SIV infection of rhesus macaques



RESULTS

- Treatment with AZD5582, alone or in combination with hetIL-15, resulted in slower decline of plasma viremia after ART initiation, and SIV viral load was significantly higher at day14-15-17-21-25-49 and 70p.i. in AZD5582 treated RMs.
- Levels of peripheral and lymph node CD4⁺ T cell intact proviral SIV DNA declined in all the groups over the treatment course. The frequency of IPDA⁺ CD4⁺ T cells tended to be lower in the animals receiving AZD5582, alone or in combination with hetIL-15, with a statistically significant difference that emerged at day25p.i in both PBMC and lymph node.
- Levels of granzyme B at day25p.i. were higher in lymph node CD8⁺ T cells of the treated animals compared to the controls, and at day70p.i. in the AZD5582 alone group.
- The frequencies of CD4⁺ and CD8⁺ T cells expressing Ki-67 in lymph node tended to be increased at all timepoints in the RMs treated with AZD5582, alone or in combination with hetIL-15, compared to the control.



RMs RDg18 from ARM 3 and MN32 from ARM 2 were euthanized at day 69 p.i. and 63 p.i. respectively due to severe side effects to the AZD5582.

CONCLUSIONS

These results indicate that treatment with the SMAC mimetic AZD5582 was associated with a longer *in vivo* lifespan of the productively infected cells, or higher production of viral RNA from these cells.

Altogether, these findings suggest that treatment with AZD5582, alone or in combination with hetIL-15, may reduce the size of virus reservoir when administered at the time of ART initiation during acute SIV infection, thus suggesting a disruptive effect on the reservoir establishment. These data are consistent with previous work on the latency reversing activity of AZD5582 and provides rationale for further exploring this compound as a curative agent for HIV infection.

ADDITIONAL KEY INFORMATION

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