Short-Term BCL-2 Inhibition at ART Initiation Reduces SIV Reservoir in Rhesus Macaques

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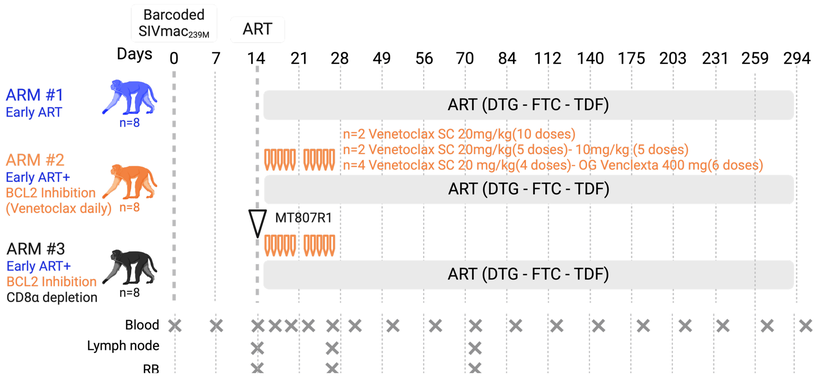
BACKGROUND

Despite the effectiveness of antiretroviral therapy (ART) in suppressing HIV replication, there is a need for additional strategies to limit the establishment and maintenance of the HIV reservoir.

Recent data has emphasized the role of BCL-2 as a crucial regulator in the establishment, persistence, and expansion of the CD4+ T cell reservoir, protecting infected cells from virus-induced or CD8+ T cell-induced cell death. Therefore, there is a strong rationale for promoting apoptosis in HIV-infected cells through BCL-2 inhibition. In this study, we assess the impact of the BCL-2 inhibitor venetoclax, either alone or in combination with a latency-reversing strategy (CD8a cell depletion), on cellular dynamics and the size of the SIV reservoir in SIV-infected, ART-treated rhesus macaques (RMs).

RESEARCH DESIGN

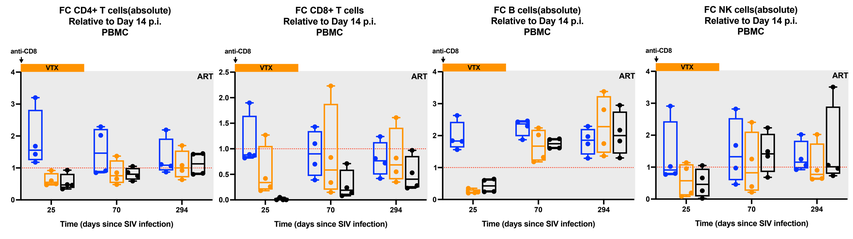
24 RMs were intravenously infected with barcoded SIVmac239 and initiated ART 2 weeks post-infection. RMs were distributed into 3 arms: 8 RMs received ART alone; 8 RMs received 10 daily doses of venetoclax as a subcutaneous injection or oral gavage starting at ART initiation; and 8 RMs received venetoclax in conjunction with a single dose of the anti-CD8a depleting antibody MT807R1 at ART initiation. Animals were followed until day 294 post-infection.



RESULTS

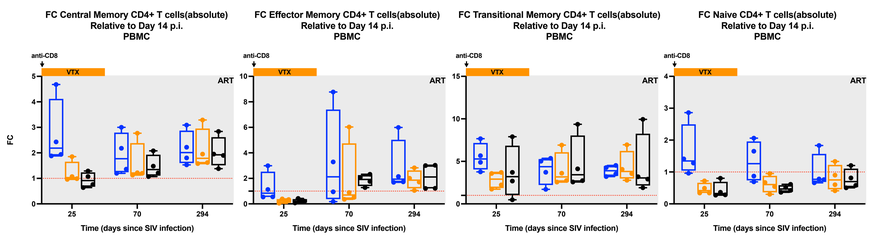
RMs treated with venetoclax or venetoclax plus MT807R1 exhibited a slower decay rate in viral plasma load compared to control RMs, resulting in prolonged on-ART viremia, suggesting a role of BCL-2 in promoting latency. In blood, venetoclax induced depletion of CD4+ T cells, including their central and effector memory subsets, with a long-term reconstitution pattern similar to animals treated only with ART. In blood-sorted CD4+ T cells, there was a pronounced, statistically significant reduction in integrated intact SIV-DNA starting immediately after venetoclax treatment and sustained up to the latest time point, week 40 post ART-initiation, indicating a preferential loss of infected cells following venetoclax administration and CD4+ T cell reconstitution. Furthermore, venetoclax-treated animals showed a faster intact SIV-DNA decay rate, consistent with the killing of SIV-DNA harboring cells. CD4+ T cells that persist after venetoclax therapy displayed overexpression of BCL-2, implying resistance to elimination.

Immunological Impact of BCL-2 Inhibition on Immune Cell Subsets

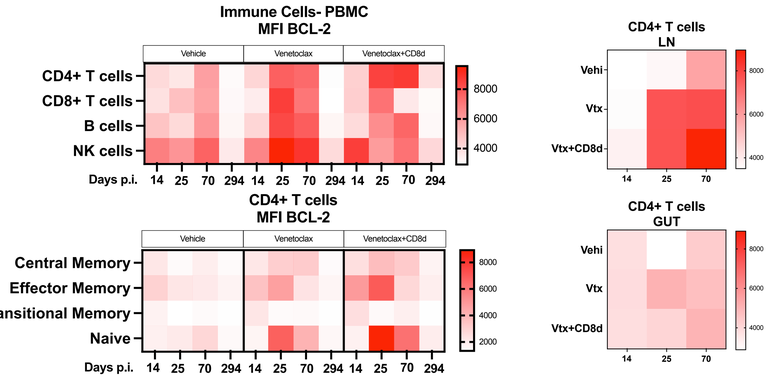


BCL-2 inhibition at ART initiation results in a ***faster decay rate and prolonged reduction*** of the intact SIV reservoir.

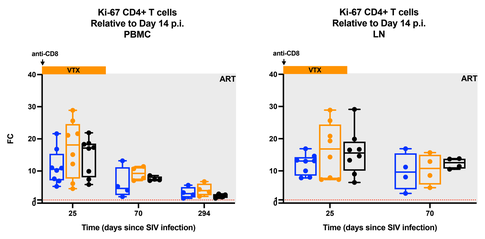
Immunological Impact of BCL-2 Inhibition on CD4+ T cell subsets



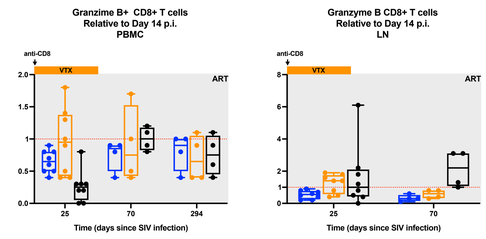
Increased BCL-2 Expression in CD4+ T cells and Other Immune Cells After Venetoclax Treatment



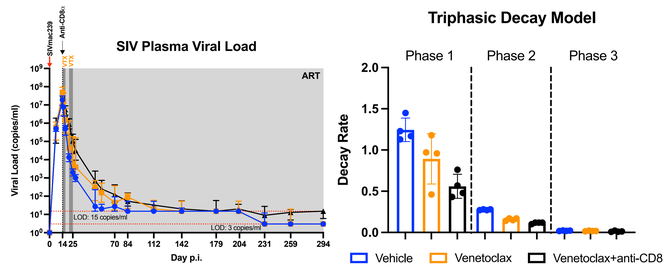
No Differences in CD4+ T cells Proliferation



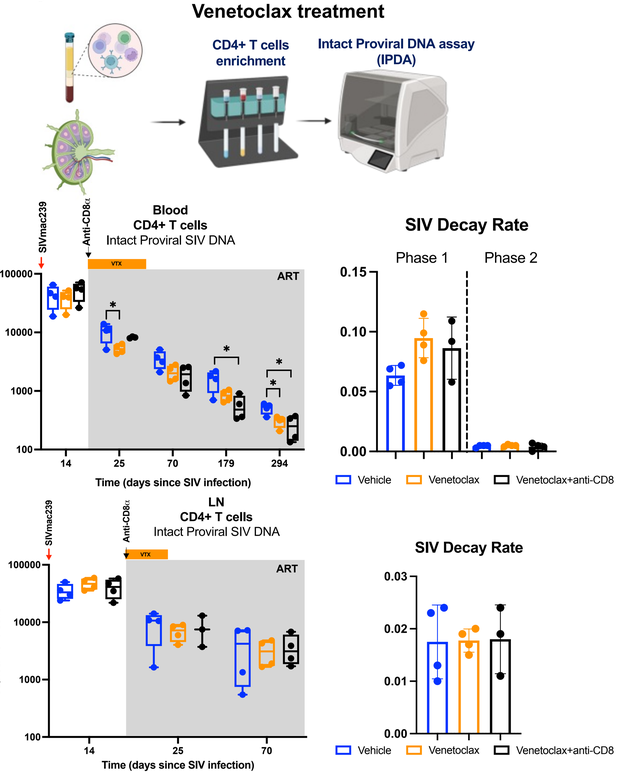
No Differences in CD8+ T cells Effector Functions



Slower Plasma Viral Load Decay in Venetoclax-treated RMs



Faster Decay and Sustained Reduction of the Intact SIV-reservoir in Blood with Venetoclax treatment



CONCLUSIONS

This study shows that venetoclax-induced BCL-2 inhibition at ART initiation can promote the elimination of SIV-infected circulating CD4+ T cells that will sustain the SIV reservoir. The results support the concept that BCL-2 expression favors the survival of infected cells and represents a potential therapeutic target. Further studies are needed to explore the effect of BCL-2 inhibition during long-term ART and prolonged exposure to BCL-2 inhibitors.

ACKOWLEDGEMENTS

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