Different Impact of Latency Reversal in Cells From People With HIV Viremia and With ART Suppression

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BACKGROUND

Induction of viral transcription using latency reversing agents (LRAs) is a promising approach to reduce the HIV reservoir but has shown modest effects in virally suppressed people with HIV (PWH) on ART. The administration of LRAs at the time of ART initiation may enhance the efficacy of this approach (*Petravic et al, JVI 2014; Chomont et al, AIDS 2018; Gunst et al, Nat Med 2022*), since latently infected cells may be more sensitive to latency reversal in a viremic setting. However, the effect of LRAs on infected cells isolated from untreated PWH is largely unknown. Here, we compared the effect of the ingenol-based PKC agonist GSK445A alone or in combination with the HDACi romidepsin on HIV transcription in cells from viremic and virally suppressed volunteers.

METHODS

Study participants were recruited in Thailand (RV254 and RV304, n=18) and in Canada (n=10).

We measured the effect of GSK445A +/- romidepsin on HIV transcription in CD4+ T cells isolated from the blood of 24 untreated volunteers (median = 1.3x10^5 HIV RNA copies/mL) and 10 PWH on ART with undetectable plasma viral load (6 participants belong to both groups).

CD4+ T cells were conditioned or not for 4h with romidepsin (40nM) and pulsed for 30min with GSK445A (5nM) in the presence of antiretroviral drugs. HIV transcription was assessed 18h post-stimulation by RT-qPCR for cell-associated LTR-gag RNA.

To determine the impact of cell death on our observations, we used the pan-caspase inhibitor Q-VD-OPh (20µM).

P values were obtained from a paired non-parametric t test (Wilcoxon).

Findings: Romidepsin potentiates the latency reversal activity of the PKC agonist GSK445A in cells from PWH with ART suppression, but reduces cell-associated viral RNA in cells from people with HIV viremia.

Implications: Romidepsin and GSK445A may be used to impede the establishment of the reservoir during ART initiation.

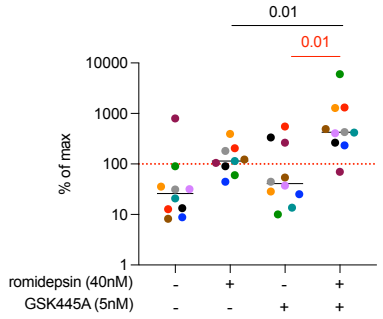

Figure 1: Impact of LRA on HIV transcription in cells from PWH with ART suppression

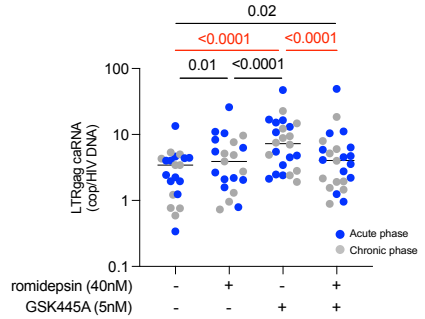

Figure 2: Impact of LRA on HIV transcription in cells from people with HIV viremia

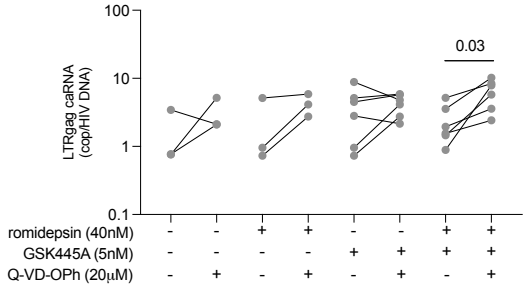

Figure 3: Impact of apoptosis inhibition on HIV transcription in cells from people with HIV viremia

RESULTS

The addition of romidepsin enhanced the GSK445A-mediated induction of HIV transcription in cells from virally suppressed PWH on ART (mean fold change over GSK445A alone 72, p=0.01) (Fig. 1).

In cells from viremic participants, stimulation with GSK445A also led to a robust induction of HIV transcription (mean fold change 3.8, p<0.0001) (Fig. 2).

However, the addition of romidepsin inhibited the induction of HIV transcription mediated by GSK445A (mean fold change 0.62, p<0.0001) (Fig. 2).

Inhibition of apoptosis by Q-VD-OPh not only rescued but also enhanced the levels of HIV transcripts measured in cells from viremic participants exposed to GSK445A in combination with romidepsin (mean fold increase in HIV RNA 3.5, p=0.03) (Fig.3).

CONCLUSIONS

The combination of GSK445A and romidepsin leads to an apparent reduction in the levels of HIV transcripts in cells isolated from people with HIV viremia. This decrease is abrogated by a caspase inhibitor, suggesting that latency reversal in a viremic setting leads to the death of the infected cells. Our results suggest that the administration of these LRAs at the time of ART initiation, when the bulk of the reservoir is established, may reduce the frequency of persistently infected cells.

ADDITIONAL KEY INFORMATION

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Acknowledgements :

The authors thank the volunteers for their generous participation to this study.

Funding: NIH/NIAID 5R01AI147749