Methylseleninic Acid enhances PKC agonist mediated reactivation of the HIV reservoir but does not deplete it

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Background:
The latent HIV reservoir remains the major barrier to HIV cure. The reveal and reduce approach aims to reverse HIV latency, leading to viral or immune mediated clearance of the latently infected cells. However, attempts to date have failed to reduce the size of the HIV reservoir. Here we investigated whether a selenium compound, methylseleninic acid (MSA) could enhance reactivation and sensitise reservoir cells to apoptosis, when combined with other latency reversing agents (LRAs).

Methods:
Isolated CD4+ T-cells from people living with HIV were cultured for 48 hours with the protein kinase C agonist, PEP005 (ingenol-3-angelate), the mimetic of the second mitochondrial activator of caspases, AZD5582, and the bromodomain inhibitor, JQ1, with or without 10μM MSA. RNA was extracted to perform the HIV RNA profiling assay (n=7), which is a digital PCR assay quantifying HIV transcription initiation (TAR), elongation (longLTR), distal elongation (POL), completion (PolyA), and splicing (Tat-Rev). DNA was collected and used to perform the intact proviral DNA assay (n=4).

Results:
MSA in combination with PEP005 significantly increased TAR (6.0-fold cf. DMSO, 95%CI[3.0-11.7], p<0.01) LongLTR (15.8-fold, 95%CI[7.5-33.5], p<0.001), Pol (19.5-fold, 95%CI[8.0-47.8], p<0.01), PolyA (54.9-fold, 95%CI[15.3-196.6], p<0.01) and Tat-Rev (76.0-fold, 95%CI[20.5-281.4], p<0.01) transcripts. The effect of combination treatment was stronger than summed effects of monotreatment (synergy) for LongLTR (Bliss synergy 1.44±0.27SEM, p<0.01), PolyA (0.9±0.23SEM, p<0.01) and Tat-Rev (0.6±0.12SEM, p<0.01). No synergy was observed when MSA and AZD5582 or JQ1 cotreatment was compared to monotreatment. No decline in intact or defective proviruses was observed after combination treatment, however cotreatment of MSA with PEP005 induced high non-specific toxicity (52% viable, 9.9-IQR)).

Conclusion:
MSA potentiates LRA-mediated HIV reactivation, with the greatest enhancement seen in transcription completion and splicing, but does not preferentially deplete cells containing HIV. Further understanding of the mechanism of MSA-mediated latency reversal may support a more targeted approach to reactivation.

Disclosure of Interest Statement:
Authors declare no conflicts of interest