New Drug-based Approaches to Purge Persistent HIV in Individuals on ART

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Abstract: There is an ongoing need to identify strategies that will lead to long-term remission in HIV-infected individuals. One approach that has been widely pursued to achieve this is the 'shock and kill' approach, where a latency reversing agent (LRA) is administered to 'shock' HIV out of latency and 'kill' the infected cells by cytolytic or viral cytopathic effects. Early attempts aimed at purging the latent HIV reservoir were focused primarily on modulating HIV transcription through the use of histone deacetylase inhibitors. While these early studies identified some perturbations in HIV transcription, there was universally no change in the size of the HIV latent reservoir. More recent approaches have focused on combination strategies such as dual LRAs or combining an LRA with a kill compound. In addition to combination strategies, new LRAs have been identified with varying mechanisms of action, such as the toll-like receptor agonists, protein kinase C agonists, and immune checkpoint inhibitors. Identification of novel LRAs usually starts with drug screens in cell line assays. Prior to clinical evaluation, LRAs need to be tested using ex vivo patient-derived cells for potency and toxicity, however, there are many different ways to define potency when it comes to HIV latency reversal. Recently, our lab has shown that quantification of cell-associated multiply spliced (MS) HIV RNA is a strong predictor of extracellular virion production. This finding suggests that future evaluation of putative LRAs ex vivo and potentially in vivo, should focus on changes in MS HIV RNA as a measure of LRA potency.