**The Failure of Current Latency Reversal Agents at Reducing the HIV Reservoir**

Despite antiretroviral therapy (ART), HIV persists and establishes an incurable infection in the human body that results in viral rebound after therapy interruption. One of the main mechanisms of viral persistence during ART is the establishment of latent infection principally within CD4 T cells, which are not recognized by the immune system (*Chun et al., PNAS 1998*). In this regard, the strategy called "shock and kill" is the central therapeutic approximation directed to eliminate HIV from cellular reservoirs, and is based on the use of Latency Reversal Agents (LRAs); drugs that reactivate the expression and production of viral particles (shock phase) with the hope that infected cells will be identified and killed by the immune system (kill phase) (*Deeks, Nature 2012*). The success of this strategy is based on the premises that i) LRAs are capable of reactivating HIV expression in all cells that compose the latent HIV reservoir, and ii) the immune system is competent for the specific killing of viral-reactivated cells. However, clinical trials testing LRAs have shown disappointing results; in vivo administration of these compounds increases transcription of HIV but the latent HIV reservoir remains unaltered (*Rasmussen et al., Lancet HIV 2014; Sogaard et al., Plos Path 2015*). Several explanations might help to explain these results. First, infected CD4 T cells are a heterogeneous population, and they might respond differently to LRAs. For instance, a new investigation has shown that current drugs are only able to reactivate HIV in a small fraction of the cells that compose the total reservoir. Moreover, the different populations of CD4 T cells are not equally impacted by the same LRA (*Grau-Exposito et al., Plos Path 2019*), manifesting the difficulty to eliminate HIV with the currently available LRAs. Further, multiple rounds of the activating stimuli might be needed to awake latent HIV (*Hosmane et al., JEM 2017*), fact that is limited by the in vivo toxicity of LRAs which precludes its prolonged exposure.

The identification of new LRAs with broader viral reactivating capacity and better safety profile to ensure its daily administration during prolonged periods of time, might help to overcome these limitations. Second, the immune system might not be able to kill viral reactivated cells. In fact, CD8 T cells and NK cells, the main antivirals immune cells, are heavily affected by HIV replication and are not properly restored after the introduction of ART (*Shan et al., Immunity 2012; Nabatanzi et al., AIDS Res and ther 2018*). As a consequence, viral-reactivated cells might not be properly killed. For this reason, new combined interventions with LRAs are directed to boost HIV-immune responses, but with limited success so far (*Leth et al., Lancet HIV 2016*). The presence of anatomical sites where the immune system might have difficulties to enter (i.e. B cell follicles within lymph nodes) (*Fukazawa et al., Nat Med 2016*), the existence of specific microenvironments where immune responses might be inhibited, or immune editing mechanism by which infected cells acquire intrinsic resistance to immune-mediated killing (*Huang et al., Front Immunol 2019*), could preclude the final elimination of HIV even with a full restoration or potentiation of the immune system. And third, the presence of pharmacological tissue sanctuaries sites. As previously shown for some antiretroviral drugs (*Fletcher et al., PNAS 2014*), LRAs might not be able to fully penetrate in all tissues where HIV persists. If these drug sanctuaries would exist, the elimination of latent HIV with LRAs will be very improbable.

In summary, several non-exclusive mechanisms could be involved in the failure of current LRAs at impacting the HIV reservoir. New LRAs with broader viral reactivation capacity and less toxicity, and an in-deep understanding of the immune-mediated control mechanisms of the HIV reservoirs might help to design new strategies to fully eliminate HIV.

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