One of the strategies, called “kick-and-kill” or “shock-and-kill”, been studied to eliminate the latent virus, based on its reactivation. The latency allows the virus to integrate the viral DNA in the host DNA, remaining transcriptionally silent. Some strategies have been tested in humans and demonstrated capacity in reversal the latent reservoir in HIV-infected patients on antiretroviral therapy. In 6 of 7 patients who received VOR doses at 72-hour intervals was observed an increase of rca-HIV RNA levels, however, the study demonstrated that was no depletion of persistent HIV infection in those patients [6]. Panabinostat was used in a clinical trial for 8 weeks demonstrating to be well tolerated and significant increased HIV transcription in patients on antiretroviral therapy. This study also demonstrated no reduction in the number of latently infected cells [7]. Studies involving associations or others HDAC inhibitors, such as valproic acid and romidepsin, are currently being performed and there is not results published up to this moment (www.clinicaltrials.gov).

The protein kinase C (PKC) agonists induces the latent HIV-1 through activation of the transcription factors NF-κB1 and AP-1 [5], since the insufficient levels of host transcriptional factors are one of the proposals for HIV latency [4]. There only PKC inhibitor tested in humans was bryostatin-1, in a phase 1 study. The results showed that the drug was safe administered once a day, but the dosage was not sufficient to demonstrate alterations in the PKC activity or on the transcription of latent HIV [8].

Histone deacetylase (HDAC) enzymes are responsible for eliminate the re-actived HIV-infected cells (kill-agent). Histone deacetylase (HDAC) inhibitors, bromodomain (BRD) inhibitors and protein kinase C (PKC) agonists are the most studied “kick-agents”.

Histone deacetylase (HDAC) enzymes are responsible for the deacetylation of lysine residues in the histone tails, leading to a compact condensation of the chromatin and contributing with HIV-latency through transcriptional repression. The inhibition of these enzymes allows the acetylation by histone acetyltransferase (HATs) enzymes providing a relaxation of the chromatin and contribute to recruitment of transcriptional factors [5]. Some HDAC inhibitors have already been tested in clinical to evaluated the capacity to induce latent HIV-1, as is the case of HDAC inhibitor as vorinostat (VOR), which was tested in and ex vivo demonstrating capacity in reversal the latent reservoir in HIV-infected patients on antiretroviral therapy. In 6 of 7 patients who received VOR doses at 72-hour intervals was observed an increase of rca-HIV RNA levels, however, the study demonstrated that was no depletion of persistent HIV infection in those patients [6]. Panabinostat was used in a clinical trial for 8 weeks demonstrating to be well tolerated and significant increased HIV transcription in patients on antiretroviral therapy. This study also demonstrated no reduction in the number of latently infected cells [7]. Studies involving associations or others HDAC inhibitors, such as valproic acid and romidepsin, are currently being performed and there is not results published up to this moment (www.clinicaltrials.gov).

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remodeling and transcriptional control of chromatin [9]. BRD inhibitors can contribute to the reactivation of latent reservoirs since the bromodomain 4 (BRD4) competes with Tat protein for the transcription factor P-TEFB, blocking the Tat-P-TEFB interaction on the HIV promoter [9].

This strategy is new and different molecules and combinations of doses are being tested to reach more information about the real applicability of the latency reverse agents (LRAs) [10].

The kick-and-kill strategy has been explored through different molecules and approaches, but still requires an intense investigation. The development of new compounds can help achieving results for the best understanding and improvement of this strategy. The combination of different types of LRAs in an attempt to obtain a synergistic effect can also be a good way to explore this, as suggested in a study of the joint action of a PKC agonist and a HDAC inhibitor in inducing latent virus from a HIV-1 patient PBMCs ex vivo [11]. Besides that, the development of a powerful molecule to target the reactivated HIV infected cells, the “kill agent”, it is still necessary and an important key factor for this strategy to function. As described in the name itself, “kick-and-kill” strategy needs a combination between effective “kick” and “kill” agents, besides being necessary to maintain the ART during the treatment. The understanding and improvement of this approach is a promising pathway to eliminate HIV from infected people completely reaching the cure.

REFERENCES


