**Title: The challenge of finding a cure for HIV infection**

**Título: El desafío de encontrar una cura para la infección por VIH**

**Abstract:** Despite the efficiency of the antiretroviral treatment, the infection caused by HIV remains to be incurable. Different strategies are being developed to tackle the viral reservoir that constitute the actual unsurmountable obstacle for the cure. The better is the understanding about how the reservoir is formed and maintained, the better chance we have to destroy it.

**Resumen:** A pesar de la eficacia del tratamiento antirretroviral, la infección por VIH sigue siendo incurable. Se están estudiando distintas estrategias para destruir el reservorio viral que constituye el verdadero obstáculo para conseguir la curación. Cuanto mejor sea nuestra comprensión de cómo se forma y se mantiene el reservorio, más posibilidades tendremos de destruirlo.

**Keywords**: HIV reservoir, antiretroviral treatment, homeostatic proliferation, HIV cure

**Palabras clave:** reservorio del VIH; tratamiento antirretroviral; proliferación homeostática; curación de la infección por VIH.

The main challenge for the eradication of the infection caused by human immunodeficiency virus (HIV) is represented by its ability to integrate the genome into the cellular chromosome, producing long half-life, latent reservoirs. These reservoirs are formed very early after the infection (*Whitney et al., Nature 2014*) and they cannot be eliminated with the present combined antiretroviral therapy (cART) or be detected by the immune system (*Siliciano et al., Nat Med 2003*). The main components of the viral reservoir are CD4+ T cells and it is nearly impossible to avoid the reservoir formation even with very early cART (*Henrich et al., PLoS Med 2017*). However, early cART has greatly improved life quality of HIV-infected patients and has reduced the possibility of spreading the infection to other people. Moreover, early cART can significantly reduce the reservoir size, which has been related to a sustained control of viremia in the absence of cART in some patients (*Colby et al., Nat Med 2018*). Therefore, cART has transformed HIV infection into a chronic disease but it cannot cure it. In fact, more than 80 years of cART would be necessary to induce just a significant reduction of the reservoir size (*Crooks et al., J Infect Dis 2015*). Due to continuous cART may lead to harmful side effects that have been related to the most important comorbidities of HIV infection such as cancer and liver, lung and cardiovascular diseases (*Lorenc et al., London J Prim Care 2014*), new strategies are needed to avoid the formation of the reservoir and eradicate the infection.

It is quite complex to avoid completely the formation of the reservoir because it likely occurs within hours after the infection (*Whitney et al., Nature 2014*). Therefore, only taking pre-exposure prophylaxis (PreP) just before infection could be helpful to avoid the reservoir formation. Until now, only cART based on tenofovir/emtricitabine has been appointed as an effective and safe therapy for preventing HIV transmission and reservoir formation (*Riddell et al., JAMA 2018*). Our group described that tyrosine kinase inhibitors (TKIs) such as dasatinib can also be used to interfere in vivo with the reservoir formation (*Salgado et al., Biochem Pharmacol 2019*), although this is not relevant for patients with chronic infection in which the reservoir is already established. Therefore, other strategies should be envisaged in order to eliminate the reservoir in these patients.

In this regard, we may consider that although the formation of the reservoir cannot be completely avoided, we could interfere with its replenishment and maintenance. The reservoir is very stable over time and it remains quite unchanged in patients even with tightly controlled viremia (*Siliciano et al., Nat Med 2003*) due to it can be sustained by the homeostatic proliferation of latently infected cells. This proliferation is induced by cytokines such as IL-2 or IL-7 that allow the evolution of the reservoir by low proliferation of infected cells without inducing proviral reactivation (*Hosmane et al., J Exp Med 2017*). In fact, it is believed that the reservoir is mostly maintained by clonal expansion of a low number of cells with efficiently integrated provirus, rather than by infection of new targets due to low blips of viremia (*Anderson & Mandarelli, Retrovirology 2018*). Therefore, the interference with homeostatic proliferation of cells harboring provirus could be useful to stop the reservoir replenishment. Theoretically, this would permit the progressive decline of the reservoir size until it can be controlled by the immune system (functional cure) or is completely eliminated (eradication). In this regard, some TKIs such as dasatinib may also impede the homeostatic proliferation of latently infected T cells induced by IL-2 or IL-7. Therefore, these drugs may be considered as a new perspective in the fight against HIV as they are able to stop the formation of the reservoir and its replenishment (*Rodríguez-Mora et al., Curr HIV/AIDS Rep 2019*).

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