**Title: Can we cure HIV using allogeneic stem cell transplantation?**

**Título: ¿Podemos curar la infección por VIH con un trasplante alogénico?**

**Abstract**: The HIV latent reservoir is considered the major barrier to achieve the eradication. Allogeneic stem cell transplantation has evidenced that curing HIV is a feasible goal and new advances have been developed in this field during the last years.

**Resumen**: El reservorio latente del VIH se considera la principal barrera para lograr la erradicación. El trasplante alogénico de células madre ha puesto de manifiesto que la curación del VIH es un objetivo factible durante los últimos años se han desarrollado nuevos avances en este campo.

**Keywords**: HIV, Cure, trasplantation, stem cell

**Palabras clave**: VIH, curación, transplante, células madre

Probably the most important landmark in the history of HIV was accomplished in 1996, when long-term suppression of HIV-1 was achieved by the administration of triple-drug therapy (*Staszewski et al., AIDS 1996*). It was called highly active antiretroviral therapy (HAART), or more recently, combined antiretroviral therapy (cART). It was the first time that the idea of the HIV infection as a curable disease was on the table. Unfortunately, just one year earlier, it was demonstrated that CD4+ T cells from HIV-1-infected individuals contained integrated HIV-1 DNA (*Chun et al., Nat Med 1995*). That phenomenon was known as latent infection and it is the cause why the treatment was not able to completely eliminate the infection (*Finzi et al., Nat Med 1999*). Although the reservoir in blood is decreasing during treatment (*Ananworanich et al., EBioMed 2016; Buzon et al., J Virol 2014; Izopet et al., J Acquir Immune Defic Syndr 1998; Parisi et al., J Clin Microb 2012*), the pool of latently infected cells is so stable that it was estimated that it would take more than 80 years of cART to eradicate the infection (*Finzi et al., Nat Med 1999; Siliciano et al., Nat Med 2003*). In consequence, today the HIV latent reservoir is considered the major barrier to achieve the eradication, although some evidences indicate that curing HIV is a feasible goal.

In fact, today we can say that at least one person in the world can be considered cured from the HIV infection. The man known as the “Berlin Patient” received in 2009 an allogeneic stem cell transplant due to an acute myeloid leukemia that he was suffering *(Hütter et al., N Engl J Med 2009*). The particularity of this transplant was that the cells came from a donor with homozygosis for the CCR5Δ32 mutation, which conferred resistance to the HIV infection by blocking the entry of the virus to the cell. Timothy Brown stopped cART at the time of the transplant and has been undetectable for HIV-1 for more than 10 years now. Also, no HIV-1 RNA or HIV-1 DNA were detectable in peripheral blood, bone marrow or gut, and consequently it is considered that a sterilizing cure has been achieved *(Yukl et al., PLoS Pathog 2013*). Unfortunately, this year the leukemia resurfaced and sadly Timothy passed away few days ago. He has been a source of motivation for those living with HIV, as well as everyone working to find a cure.

In fact, this case encouraged investigators to replicate the strategy in other individuals, such as the “Boston patients”(*Henrich et al., J Infect Dis 2013)*. In those cases, the transplantation was done using a *CCR5* wild-type, but in this instance the cART was maintained after the transplantation. Thus, it was observed that the latent reservoirs were reduced after the transplantation, something that has not been achieved with any other eradication strategy. In a more recent work we have discover that different characteristics related to the transplant, as the time to reach full engraftment, the origin of the transplanted cells or the presence of the graft versus host disease, are very important to achieve that reduction of the latent reservoir *(Salgado et al., Ann Int Med 2018*). Unfortunately, the two cases from Boston, as other few cases published after those, resulted in a delayed viral rebound when the treatment was interrupted years later, despite the undetectable HIV reservoirs in blood and tissues *(Cummins et al., PLoS Med 2017; Henrich et al., Ann Int Med 2014*). That means that a reduction of the reservoir by itself might not be the only factor to have in mind in order to reach eradication, and it could be necessary to add immunogenetic strategies that might control possible residual virus persistent in the organism.

Finally, the last critical event which has marked the road towards the HIV cure has been the description of two new cases of HIV remission in London and Dusseldorf *(Gupta et al., Lancet HIV 2020; Jensen et al., CROI 2019*). Those two cases have in common the CCR5Δ32 mutated donor with the Berlin Patient, an element that has been proved to be key in this process. More than 10 years have been necessary to reproduce HIV eradication. A combination of two factors has caused this delay. First, the difficulty of finding CCR5 mutated donors, a characteristic which is present in only a 1% of the Caucasian population. Second, the high risk associated with an allogeneic stem cell transplantation, which implies that only individuals with a hematological disease that requires this process will follow it. In these times when the cART is safe and well tolerated, this kind of approach may never be applied to the majority of people living with HIV. However, it is of utmost importance to continue working for the deeply knowledge of the main factors necessary for HIV eradication and later be able to mimic them, in safer strategies that can be applied for all the people living with HIV.

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