EBioMedicine 58 (2020) 102889

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

Towards the next step: LoViRet patients for HIV-1 cure studies

Raquel Crespo[a], Casper Rokx[b], Tokameh Mahmoudi[a,*]

[a] Department of Biochemistry, Erasmus University Medical Center, Ee622 PO Box 2040, 3000CA Rotterdam, the Netherlands
[b] Department of Internal Medicine, Section of Infectious Diseases, Erasmus University Medical Center, Rg-530, PO BOC 2040, 3000CA Rotterdam, the Netherlands

ARTICLE INFO

Article History:
Received 24 June 2020
Accepted 26 June 2020

The persistence of a viral reservoir in HIV-1 infected patients under suppressive antiviral treatment has thus far prevented achieving a functional HIV-1 cure. Crucial in these initial strides to identify cure strategies is patient selection. Interventional research on cure in HIV-1 patients usually aims to demonstrate at least one of the following outcomes: a significant depletion of the inducible viral reservoir or the stable absence of renewed viral replication as the infected patient discontinues antiviral therapy. In this article of *EBioMedicine*, Gálvez et al. [1] identify a unique "LoViRet" patient category with an exceptionally low viral reservoir under c-ART, despite starting therapy during the chronic phase of the disease. So how do the different parameters to assess the success of investigational HIV-1 cure strategies apply to LoViRet patients and how can we harness these insights into meaningful interventional studies?

First, the presence of a small inducible latent viral reservoir that can be therapeutically targeted, as present in LoViRet patients, is likely essential for current pilot studies that aim to demonstrate the possibility of an antiretroviral drug-free life in patients with chronic HIV-1 infections. One of the promising strategies studied over the last decade to achieve HIV-1 cure addresses the caveat that latent HIV-infected cells remain invisible to antiviral host responses. By pharmacologically triggering HIV-1 gene expression through so-called latency reversing agents (LRA), we can reverse latency [2,9]. Hope is then put on elimination of reactivated cells via (drug-boosted) viral cytopathic or intrinsic host cell pro-apoptotic mechanisms or via extracellular immune effector cell-based clearance [3,9]. Hence, the presence of a small limited reservoir in LoViRet patients is likely beneficial to achieve significant reservoir elimination via curative intervention strategies.

Secondly, a competent immune compartment is key to eliminate residual reservoir cells. Because chronically infected individuals generally present an impaired immune compartment, harnessing potent HIV-1 specific CD8+ T cells has posed a major challenge to past eradication trials. Thus, to achieve efficient elimination of HIV-1 infected cells, latency reversal would ideally be combined with approaches that effectively trigger mechanisms of killing by enhancing extrinsic immune-based clearance or inducing intrinsic cell death [4,5]. LoViRet patients described by Gálvez et al., while chronically HIV-1 infected, have a remarkably low viral reservoir together with an overall preserved immune compartment. Notably, these exceptional characteristics are generally found in HIV-1 controllers and patients who initiate c-ART in the acute stage of the infection [6,7]. Gálvez et al. observed a direct correlation between low HIV-1 DNA levels in LoViRet individuals and a preserved CD8+ T cell compartment before treatment and higher proportion of naïve CD8+ T cells after treatment initiation. Such traits hint towards a less impaired immune system and likely better cytotoxic responses before and after c-ART, that could potentially prevent a massive reservoir seeding. In context of reservoir depletion studies that center on viral reactivation and clearance, selection of patient cohorts with not only a lower reservoir threshold but also an intrinsically preserved cytotoxic cellular immunity compartment is thus likely crucial to reach an effective elimination of HIV-1 infected cells.

Another striking observation, described by Gálvez et al., is that CD8+ T cells from LoViRet individuals do not show enhanced antiviral inhibition activity or a less immune exhausted phenotype when compared to controls, despite having low levels of circulating HIV-1 antigen. This seems to be different from CD8+ T cells from HIV controllers [6] and hints towards a different mechanism driving the low reservoir size observed in LoViRet. Assessing the relevance of the specific CD8+ *T* cell diversity and functionality in these patients is crucial to infer causality and, because the immune system is certainly not the only factor influencing reservoir size, further investigation into the intrinsic host factors (e.g. neutralizing antibodies, restriction factors or antibody-dependent cellular cytotoxicity) and viral characteristics is needed to unveil the mechanisms behind the specific reservoir dynamics observed in LoViRet individuals.

Thus, additional characterization and insights into the kinetics of the inducible reservoir in this patient population is needed to put in perspective a potential role for LoViRet patients in reservoir eradication studies. Here, future studies will have to deal with assay sensitivity issues necessitating high input numbers of cells, which limits applicability. In smaller reservoirs, it will be increasingly difficult to detect relevant reservoir decay during interventional studies, or to determine the point at which c-ART can be safely stopped. Also of

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2020.102830.
* Corresponding author.
E-mail address: t.mahmoudi@erasmusmc.nl (T. Mahmoudi).

https://doi.org/10.1016/j.ebiom.2020.102889

importance, in context of immune-mediated clearance, assessing the specificity and avidity of cytotoxic responses is essential to ensure an efficient elimination of reactivated cells [8]. Lastly, it is important to note that the far majority of people are diagnosed and treated during chronic phases of HIV-1. Of these, only a small minority will hold a LoViRet phenotype, estimated at 6% based on the current paper. Although non-LoViRet patients have a more unfavorable starting position in terms of reservoir size, the effect of any intervention on the inducible reservoir decay and its predictive biomarkers can be better studied. On the other hand, the distinguished immune features of LoViRet individuals and their correlation to reservoir dynamics accentuate their added value for customized patient cohorts in HIV-1 cure studies. Patient stratification by LoViRet state could therefore be very beneficial and serve both aspects of cure research: optimal reservoir decay study together with obtaining a functional cure.

All in all, the study presented by Gálvez et al. investigates for the first time the reservoir dynamics and immune characteristics of chronic patients with a very low level of HIV-1 DNA. Although the relevance of this cohort in future cure studies is yet to be assessed, the heterogeneity of HIV-1 patients who started c-ART during chronic infection supports using stratification by LoViRet status to identify patients in whom curative interventions is most realistic towards a c-ART-free life.

Authors' contribution

Raquel Crespo performed the literature search and the writing. Casper Rokx and Tokameh Mahmoudi performed the writing.

Declaration of Competing Interest

Dr. Rokx reports grants and other from Gilead Sciences, grants and other from GSK, grants and other from Janssen-Cilag, grants from MERCK, grants from Dutch Federation Medical Specialists, outside the submitted work. Dr. Mahmoudi reports grants from Gilead Sciences, grants from ViiV Healthcare, non-financial support from First health Pharma, outside the submitted work; In addition, Dr. Mahmoudi has an International Patent Application Serial No. PCT/US19/41466 pending. Dr Crespo has nothing to disclose.

References

[1] Gálvez C, Urrea V, Dalmau J, Jimenez M, Clotet B, Monceaux V, et al. Extremely low viral reservoir in treated chronically HIV-1-infected individuals. EBioMedicine 2020;57:102830. doi: 10.1016/j.ebiom.2020.102830.
[2] Abner E, Jordan A. HIV "shock and kill" therapy: in need of revision. Antiviral Res 2019;166:19–34.
[3] Trautmann L. Kill: boosting HIV-specific immune responses. Curr Opin HIV AIDS 2016;11(4):409–16.
[4] Kim Y, Anderson JL, Lewin SR. Getting the "kill" into "shock and kill": strategies to eliminate latent HIV. Cell Host Microb 2018;23(1):14–26.
[5] Collins DR, Gaiha GD, Walker BD. CD8(+) T cells in HIV control, cure and prevention. Nat Rev Immunol 2020.
[6] Gebara NY, El Kamari V, Rizk N. HIV-1 elite controllers: an immunovirological review and clinical perspectives. J Virus Erad 2019;5(3):163–6.
[7] Buzon MJ, Martin-Gayo E, Pereyra F, Ouyang Z, Sun H, Li JZ, et al. Long-term antiretroviral treatment initiated at primary HIV-1 infection affects the size, composition, and decay kinetics of the reservoir of HIV-1-infected CD4 T cells. J Virol 2014;88(17):10056–65.
[8] Jones RB, Walker BD. HIV-specific CD8(+) T cells and HIV eradication. J Clin Investig 2016;126(2):455–63.
[9] Stoszko M. Current Opinion in Virology 2019. https://doi.org/10.1016/j.coviro.2019.06.001.