



Commentary

Shock and kill, but don't miss the target

Georges Herbein

Department of Virology, EPILAB Pathogens & Inflammation Laboratory, University of Franche-Comté, COMUE Bourgogne Franche-Comté University, EA4266, CHRU Besançon, Besançon, France



ARTICLE INFO

Article History:

Received 1 July 2020

Revised 7 July 2020

Accepted 7 July 2020

Available online xxx

Definitive cure of HIV-1 infected patients is limited by the persistence of viral reservoirs under cART, where the interruption of the latter usually precipitates a viral rebound. Main therapeutic approaches used so far, namely the “shock and kill” and the “block and lock” strategies, have been unsuccessful [1]. In concept, the “shock and kill” strategy relies on transcriptional activation of the HIV-1 LTR by multiple compounds including PKC and MAPK agonists, CCR5 antagonist, SMAC mimetics, inducers of PTEFb release, Akt activators, benzotriazole derivatives, epigenetic modifiers such as HDACi, HMTi, and DNMTi, Tat vaccine, as well as immunomodulatory LRAs such as TLR agonists, IL-15 agonist and immune checkpoint inhibitors [2,3]. Although most of the previously mentioned compounds transcriptionally activate the virus, none is able to decrease the viral load in treated patients, pointing toward a persistence of HIV latent reservoirs. On the other hand, the “block and lock” strategy could lead to a potential functional cure by HIV-specific T cells. This is mostly mediated by the action of didehydro-Cortistatin A (dCA), an inhibitor of Tat/TAR binding that engenders a persistent “super latency” state characterized by an extremely restricted viral expression. Nonetheless, this approach is limited by resistance mutations that have been reported *in vitro* [4]. To note that, beside the canonical “shock and kill” strategy that targets solely the virus, eradication of both HIV-infected cells and virus through the use of Akt inhibitors, Bcl-2 antagonists and XIAP inhibitors for instance, is correspondingly regarded as an alternative “shock and kill” therapeutic approach [5,6].

Mann et al. study describes a “shock and kill” strategy that employs the activator vector termed ACT-VEC, a polyvalent virus like particle (VLP) formulation combining HIV quasi-species from five chronic HIV-infected volunteer's plasma samples taken immediately prior to cART initiation [7]. ACT-VEC are viral-like particles similar to human papillomavirus (HPV) VLPs used in multivalent HPV vaccines, with the advantages of increased antigenic breadth and generation a broader immune response, along with a suitable margin of safety and efficiency. In this study, virus present in latently infected HIV-specific

CD4+ T cells is reactivated more efficiently by ACT-VEC compared to other tested LRAs. In this perspective, although the ACT-VEC strategy is more efficient than other tested LRAs in terms of latent viral reactivation, several cellular and viral barriers still restrain this approach and have to be overcome to achieve a successful viral clearance.

First, HIV reservoirs encompass multiple cell types with divergent phenotypes and metabolic characteristics, including a highly heterogeneous population of latently infected CD4+ T cells composed of naive T cells, four subpopulations of memory CD4+ T cells (TCM, TEM, TTM, TSCM), CD32+CD4+ T cells, monocytes/macrophages, dendritic cells, tissue macrophages such as microglia, and hematopoietic stem cells [2,8,9]. Given the fact that ACT-VEC targets mostly latently infected HIV-specific CD4+ T cells, it will be critical to demonstrate that the virus present in other latently infected CD4+ T cell subtypes and/or myeloid cells could be reactivated. Second, it is well known that the extremely limited effect on HIV-1 reactivation exhibited by the tested LRAs is due to the heterogeneous nature of the viral reservoir, that is in turn linked to cellular factors including the cell type and tissue/compartments specificity, or alternatively factors related to the patient and gender specificity or viral aspects, for instance, virus genetic background, integration specificity and silencing mechanisms. The enrollment of only nine patients in the study by Mann et al. is too limited to address this highly heterogeneous nature of the viral reservoirs. Therefore, this study is rather a proof-of-concept to indicate that ACT-VEC is more efficient in reactivating the virus than the so far tested LRAs, with the notice that additional data to confirm its therapeutic superiority is indispensable. Although some LRAs are immunosuppressive with decreased NK activity, others LRAs improve immune surveillance through the enhancement of NK cells and HIV-specific CTLs activity. Prolonged cART treatment results in a significant reduction of HIV-specific CD8+ T cells, therefore limiting viral clearance. In contrast, stimulation of HIV-specific CD8+ T cells before cART treatment has been shown to enhance the efficiency of LRA treatment [10]. Since ACT-VEC reactivates the virus from latently infected HIV-specific CD4+ T cells, it would be worth to assess its role in the induction of HIV-specific CTLs and NK cells. Indeed, the reactivation of latent virus under the control of HIV-specific CTLs and NK cells by ACT-VEC could lead to a better control of HIV reactivation under latency reversal. Furthermore, since a higher reactivation efficiency of latent virus is usually associated with a stronger cellular activation that often prompts apoptosis, it would be interesting to assess the apoptosis levels in ACT-VEC-treated CD4+ T cells. The effect of ACT-VEC as observed in the study by Mann and colleagues is more powerful early in the disease since at that time the viral diversity is less important, the

DOI of original article: <http://dx.doi.org/10.1016/j.ebiom.2020.102853>.

E-mail address: georges.herbein@univ-fcomte.fr

<https://doi.org/10.1016/j.ebiom.2020.102906>

2352-3964/© 2020 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license. (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

immune surveillance is still functional and the heterogeneity of the HIV reservoirs is still limited. Future studies will have to assess the effect of ACT-VEC in chronically HIV-infected patients.

In conclusion, the dual action of ACT-VEC as a latency reversal agent and as an anti-HIV immunotherapy could allow a parallel targeting of both CD4⁺ T cells and APCs such as macrophages and DCs, which are at the crossroads of T cell activation, apoptosis and immune surveillance. ACT-VEC paves the way to novel therapeutic approaches in the future that could couple strong viral reactivation and immune response boosting in patients under cART. Nevertheless, the heterogeneity of the viral reservoirs still has to be better characterized with the ultimate goal of achieving total viral clearance and establishing definitive cure in HIV-infected patients.

Disclosures

Research performed in our laboratories is supported by the University of Franche-Comté and the Région Bourgogne-Franche-Comté. The authors declare no conflicts of interest.

References

- [1] Fidler S, Stöhr W, Pace M, Dorrell L, Lever A, Pett S, et al. Antiretroviral therapy alone versus antiretroviral therapy with a kick and kill approach, on measures of the HIV reservoir in participants with recent HIV infection (the RIVER trial): a phase 2, randomised trial. *Lancet* 2020;395:888–98. doi: [10.1016/S0140-6736\(19\)32990-3](https://doi.org/10.1016/S0140-6736(19)32990-3).
- [2] Ait-Ammar A, Kula A, Darcis G, Verdikt R, De Wit S, Gautier V, et al. Current status of latency reversing agents facing the heterogeneity of HIV-1 cellular and tissue reservoirs. *Front Microbiol* 2020;10. doi: [10.3389/fmicb.2019.03060](https://doi.org/10.3389/fmicb.2019.03060).
- [3] Nehme Z, Pasquereau S, Herbein G. Control of viral infections by epigenetic-targeted therapy. *Clin Epigenetics* 2019;11:55. doi: [10.1186/s13148-019-0654-9](https://doi.org/10.1186/s13148-019-0654-9).
- [4] Mousseau G, Aneja R, Clementz MA, Mediouni S, Lima NS, Haregot A, et al. Resistance to the tat inhibitor didehydro-cortistatin a is mediated by heightened basal HIV-1 transcription. *MBio* 2019;10. doi: [10.1128/mBio.01750-18](https://doi.org/10.1128/mBio.01750-18).
- [5] Kim Y, Anderson JL, Lewin SR. Getting the “kill” into “shock and kill”: strategies to eliminate latent HIV. *Cell Host Microbe* 2018;23:14–26. doi: [10.1016/j.chom.2017.12.004](https://doi.org/10.1016/j.chom.2017.12.004).
- [6] Kumar A, Abbas W, Bouchat S, Gatot J-S, Pasquereau S, Kabeya K, et al. Limited HIV-1 reactivation in resting CD4(+) T cells from aviremic patients under protease inhibitors. *Sci Rep* 2016;6:38313. doi: [10.1038/srep38313](https://doi.org/10.1038/srep38313).
- [7] Mann JFS, Pankrac J, Klein K, McKay PF, King DFL, Gibson R, et al. A targeted reactivation of latent HIV-1 using an activator vector in patient samples from acute infection. *EBioMedicine* 2020. doi: [10.1016/j.ebiom.2020.102853](https://doi.org/10.1016/j.ebiom.2020.102853).
- [8] Andrade VM, Mavian C, Babic D, Cordeiro T, Sharkey M, Barrios L, et al. A minor population of macrophage-tropic HIV-1 variants is identified in recrudescing viremia following analytic treatment interruption. *PNAS* 2020;117:9981–90. doi: [10.1073/pnas.1917034117](https://doi.org/10.1073/pnas.1917034117).
- [9] Darcis G, Kootstra NA, Hooibrink B, van Montfort T, Maurer I, Groen K, et al. CD32+CD4+ T cells are highly enriched for HIV DNA and can support transcriptional latency. *Cell Rep* 2020;30:2284–2296.e3. doi: [10.1016/j.celrep.2020.01.071](https://doi.org/10.1016/j.celrep.2020.01.071).
- [10] Shan L, Deng K, Shroff NS, Durand CM, Rabi SA, Yang H-C, et al. Stimulation of HIV-1-specific cytolytic T lymphocytes facilitates elimination of latent viral reservoir after virus reactivation. *Immunity* 2012;36:491–501. doi: [10.1016/j.immuni.2012.01.014](https://doi.org/10.1016/j.immuni.2012.01.014).