Of HIV and men

Christina K Psomas

European Hospital, Marseille, France

The history of people living with HIV seems relatively long so far, and even if the best is yet to come, we should not forget how far we have come. In the era of the post-Berlin patient, we have accumulated much knowledge regarding the mechanisms of establishment of the latent HIV-1 reservoir, which are thoroughly described in Vanhamel *et al*. in this issue [1].

Although ART suppresses HIV-1 replication below the threshold of conventional methods of measurement of plasma viremia, it does not eradicate the virus; HIV-1 is capable of residual replication [2,3] and/or viral production under ART [4,5] and, according to some authors, it is actively present in tissues even while a person is on ART [6]. It almost always rebounds after analytical treatment interruption (ATI). The latent HIV-1 reservoir is thought to be largely responsible for this rebound, because the reservoir size not only undermines clinical progression in people living with HIV who are under treatment [7], but also predicts time to viral rebound [8]. Among these reservoirs, each T cell subset contributes differently to the pool of HIV integrated reservoirs [9,10]. Furthermore, cellular reservoirs that are preferentially studied in routine practice in peripheral blood mononuclear cells give us an inexact estimate of the total HIV-1 burden because the localisation of infected cells in lymphoid tissues accounts for a disproportionately large proportion of infected cells in the body: more than 98% of the total HIV-1 burden in some studies [11,12]. Although we are aware of the fact that some forms of persistent provirus (transcription- or translation-competent proviruses) [13] may impact the health of individuals living with HIV via products of abortive viral infections that create persistent immune activation [14], only replication-competent proviruses are capable of viral rebound after ART cessation and therefore constitute the main barrier to HIV-1 cure.

In the quest for a sterilising or functional cure it seems necessary to determine the size of persistent reservoirs in order to comparatively evaluate efficacy of cure strategies and predict post-treatment viral control. Measuring the HIV-1 latent reservoir is challenging because of the extreme paucity (1/100,000–1/1,000,000 of peripheral blood CD4+ lymphocytes although it is thought to be somewhat higher in tissues) and heterogeneity of latently infected cells [15], as well as the fact that the latter are undistinguishable from uninfected cells. Quantitative PCR-based assays used to measure the HIV-1 DNA latent reservoir globally overestimate its size owing to their inability to distinguish between defective and replicative provirus. In comparison, the quantitative viral outgrowth assay (QVOA), which is considered the reference standard to measure the replication-competent fraction of the HIV-1 reservoir, provides a minimal estimate of the reservoir size because it does not take into account intact integrated proviruses that can be induced by additional rounds of T cell activation [16–18]. Therefore, despite major advances in the HIV-1 reservoir research field, the size and biological properties of its different fractions still remain elusive.

The timing of ART intervention remains important, but although we have thought that 'earlier is never early enough', a recent study by Colby *et al.* [19] has demonstrated that in the RV411 Thai study, all patients experienced rapid viral rebound after ATI even if they were first treated while in Fiebig I, probably because Fiebig I is too early for HIV-1-specific immunity to develop. No matter what method is used to quantitively assess the HIV-1 latent reservoir, insights gained from the ANRS Visconti [20] and the SPARTAC cohorts [7] demonstrated that post-treatment controllers are preferentially patients with a lower HIV reservoir. This is why strategies for cure are based on the endeavour to decrease the HIV reservoir below an arbitrary threshold using latency-reversal agents (LRAs) ('shock and kill' strategies) that induce HIV provirus reactivation. However, even if activating latent virus may be a necessary step in many HIV cure strategies, LRAs alone do not seem sufficient to confer remission off ART. Indeed, in 2012, the Siliciano group proved that HIV cure should include HIV reactivation combined with immune stimulation [21], leading to researchers from all over the world adopting the 'kick and kill' approach. In this context, the RIVER (Research In Viral Eradication of HIV Reservoirs) trial is the first randomised controlled trial of the kick and kill approach studying total proviral DNA in CD4+ T cells in individuals with defined primary HIV infection undetectable after 6 months of immediate standard ART, who were either maintained on ART for 18 or more weeks, or put on ART intensified by vorinostat and a prime-boost HIV-1 vaccine. Unfortunately, no significant difference was observed in total HIV DNA copies/million CD4+ T cells or in QVOA by study arm [22]. However, we keep advancing towards an HIV cure and we maintain hope. As Lao Tzu said: 'A journey of a thousand miles begins with a single step'. And we have already taken more than one step since the beginning of the HIV story.

Corresponding author: Christina K Psomas, Department of Infectious Diseases and Internal Medicine, European Hospital, Marseille, France
Email: kcpsomas@gmail.com

References

1. Vanhamel J, Bruggemans A, Debyser Z. Establishment of latent HIV-1 reservoirs: what do we really know? *J Virus Erad* 2019; **5**: 3–9.
2. Buzon MJ, Massanella M, Llibre JM *et al.* HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects. *Nat Med* 2010; **16**: 460-465.
3. Hatano H, Jain V, Hunt PW *et al.* Cell-based measures of viral persistence are associated with immune activation and programmed cell death protein 1 (PD-1)-expressing CD4+ T cells. *J Infect Dis* 2013; **208**: 50-56.
4. Maldarelli F, Palmer S, King MS *et al.* ART suppresses plasma HIV-1 RNA to a stable set point predicted by pretherapy viremia. *PLoS Pathog* 2007; **3**: e46.
5. Palmer S, Maldarelli F, Wiegand A *et al.* Low-level viremia persists for at least 7 years in patients on suppressive antiretroviral therapy. *Proc Natl Acad Sci U S A* 2008; **105**: 3879-3884.
6. Chun TW, Nickle DC, Justement JS *et al.* Persistence of HIV in gut-associated lymphoid tissue despite long-term antiretroviral therapy. *J Infect Dis* 2008; **197**: 714-720.
7. Williams JP, Hurst J, Stohr W *et al.* HIV-1 DNA predicts disease progression and post-treatment virological control. *Elife* 2014; **3**: e03821.
8. Li JZ, Etemad B, Ahmed H *et al.* The size of the expressed HIV reservoir predicts timing of viral rebound after treatment interruption. *Aids* 2016; **30**: 343-353.
9. Chomont N, El-Far M, Ancuta P *et al.* HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation. *Nat Med* 2009; **15**: 893-900.
10. Jaafoura S, de Goer de Herve MG, Hernandez-Vargas EA *et al.* Progressive contraction of the latent HIV reservoir around a core of less-differentiated CD4(+) memory T Cells. *Nat Commun* 2014; **5**: 5407.
11. Estes JD, Kityo C, Ssali F *et al.* Defining total-body AIDS-virus burden with implications for curative strategies. *Nat Med* 2017; **23**: 1271-1276.
12. Deleage C, Chan CN, Busman-Sahay K, Estes JD. Next-generation in situ hybridization approaches to define and quantify HIV and SIV reservoirs in tissue microenvironments. *Retrovirology* 2018; **15**: 4.
13. Baxter AE, O'Doherty U, Kaufmann DE. Beyond the replication-competent HIV reservoir: transcription and translation-competent reservoirs. *Retrovirology* 2018; **15**: 18.
14. Doitsh G, Galloway NL, Geng X *et al.* Cell death by pyroptosis drives CD4 T-cell depletion in HIV-1 infection. *Nature* 2014; **505**: 509-514.
15. Kulpa DA, Chomont N. HIV persistence in the setting of antiretroviral therapy: when, where and how does HIV hide? *J Virus Erad* 2015; **1**: 59-66.

16. Siliciano JD, Siliciano RF. Assays to Measure Latency, Reservoirs, and Reactivation. *Curr Top Microbiol Immunol* 2018; **417**: 23-41.
17. Wang Z, Simonetti FR, Siliciano RF, Laird GM. Measuring replication competent HIV-1: advances and challenges in defining the latent reservoir. *Retrovirology* 2018; **15**: 21.
18. Pinzone MR, O'Doherty U. Measuring integrated HIV DNA ex vivo and in vitro provides insights about how reservoirs are formed and maintained. *Retrovirology* 2018; **15**: 22.
19. Colby DJ, Trautmann L, Pinyakorn S *et al.* Rapid HIV RNA rebound after antiretroviral treatment interruption in persons durably suppressed in Fiebig I acute HIV infection. *Nat Med* 2018; **24**: 923-926.
20. Saez-Cirion A, Bacchus C, Hocqueloux L *et al.* Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. *PLoS Pathog* 2013; **9**: e1003211.
21. Shan L, Deng K, Shroff NS *et al.* Stimulation of HIV-1-specific cytolytic T lymphocytes facilitates elimination of latent viral reservoir after virus reactivation. *Immunity* 2012; **36**: 491-501.
22. Fidler S, Stohr W, Pace M *et al.* A randomised controlled trial comparing the impact of antiretroviral therapy (ART) with a 'kick-and-Kill' approach to ART alone on HIV reservoirs in individuals with primary HIV infection (PHI); RIVER trial. *AIDS 2018*. July 2018. Amsterdam, the Netherlands. Abstract TUAA0202LB.