JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

LETTER TO THE EDITOR

Longitudinal changes in HIV DNA in HIV controllers: what do they mean?

Denise C Hsu[1,2,3§] and John W Mellors[4]

[§]**Corresponding author:** Denise C Hsu, 315/6 Rajvithi Road, Phayathai, Bangkok 10400, Thailand. Tel: +66 91 047 1136. (hsudc@hiv-th.org)

Keywords: HIV controllers; HIV reservoir; HIV DNA; HIV cure

Received 21 December 2018; **Accepted** 29 January 2019

Copyright © 2019 The Authors. Journal of the International AIDS Society published by John Wiley & Sons Ltd on behalf of the International AIDS Society.
This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

The existence of the latent HIV reservoir is a major barrier to HIV cure [1]. Understanding what maintains the latent reservoir and how latently infected cells are eliminated will help advance HIV cure efforts.

For the majority of individuals living with HIV, levels of plasma genomic HIV RNA and cellular HIV DNA and mRNA rise rapidly and peak within the first month following infection, then plateau [2]. After antiretroviral therapy (ART) is initiated, HIV RNA levels decline rapidly (by 10,000-fold) and can become undetectable by clinical assays. HIV DNA levels also decline, but less impressively (10- to 20-fold) [2-4]. Modelling demonstrates that HIV DNA decay kinetics fit a 3-slope curve over three time intervals: zero to seven months, eight to thirty-two months and >32 months, with slopes of decay of −0.131, −0.016 and −0.0021 $\log_{10}$ copies/10^6 peripheral blood mononuclear cells (PBMC)/month over the respective time periods [5].

HIV controllers are a small group (approximately 1%) of individuals who are able to control viral replication without ART to very low or undetectable levels of HIV-1 RNA by clinical assays for long periods of time [6]. The mechanisms involved in their viral control likely include a combination of both viral and host factors [7]. The longitudinal kinetics of infected cell decay (i.e. of HIV DNA) in HIV controllers are less well described.

In their recent article in the *Journal of the International AIDS Society*, Avettand-Fenoel *et al.* described HIV DNA kinetics in 202 HIV controllers (defined as having HIV RNA <400 copies/mL without ART) from the ANRS-CODEX cohort [8]. The median HIV DNA was 1.5 $\log_{10}$copies/10^6 PBMC, which is much lower than the 3.3 $\log_{10}$ copies/10^6 PBMC in ART-naïve individuals during primary HIV infection in the ANRS-PRIMO cohort [9], but similar to the predicted 1.6 $\log_{10}$ copies/10^6 PBMCs after five years of uninterrupted ART in individuals started on ART within 15 days after HIV infection in the same cohort [5]. Mathematical modelling of HIV DNA dynamics in the ANRS-CODEX HIV controller cohort revealed a significant decline in 46% of participants. HLA-B*27/B*57 alleles and lower levels of plasma HIV RNA and HIV DNA at the entry visit into the cohort were independently associated with HIV DNA decline.

The authors postulated that intrinsic resistance of host cells to HIV infection, lower levels of immune activation leading to fewer potential target cells, lower residual HIV replication and a shorter half-life of infected cells may all have contributed to the observed decline in HIV DNA levels. By contrast, non-HLA-B*27/B*57 alleles or persistent HIV RNA ≥1 $\log_{10}$ copies/mL during follow-up were associated with increases in HIV DNA over time in the same controller cohort. Characterization of the HIV proviruses by DNA sequencing and analyses of clonal expansion of infected cells in the controllers could provide additional insight into the mechanisms behind the divergent HIV DNA dynamics that were observed [10]. Such analyses would differentiate clonal expansion of cells with identical proviruses from ongoing cycles of infection as the cause of rising HIV DNA levels.

Although a decline in HIV DNA levels in HIV controllers is intriguing, it does not necessarily imply a reduction in the latent but replication-competent (intact) proviral reservoir that can produce infectious virus and lead to viral rebound. This is because unintegrated linear and episomal DNAs, in addition to integrated proviruses, are also detected by total HIV DNA quantification, neither of which can produce infectious virus. HIV controllers have also been found to have a higher proportion of unintegrated DNA to total HIV DNA when compared to both treated and untreated non-controllers [11]. In addition, the vast majority of integrated proviral DNA is defective and cannot lead to the production of infectious virions [12]. Though assays designed to quantify replication-competent provirus may be able to provide a more accurate estimate of the latent reservoir, these assays are labour intensive and may lack the dynamic range to detect small fluctuations [13]. Newer PCR-based assays of intact provirus should provide further insight into whether the changes observed in HIV DNA levels in HIV controllers in the ANRS-CODEX cohort parallel those of the intact reservoir.

AUTHORS' AFFILIATIONS

[1]Department of Retrovirology, AFRIMS, Bangkok, Thailand; [2]US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA; [3]Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA; [4]Division of Infectious Diseases, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

COMPETING INTERESTS

JWM is a consultant to Gilead Sciences and Merck, and has share options in Co-Crystal Pharmaceuticals, Inc. DCH has no conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

DCH and JWM drafted the letter.

ACKNOWLEDGEMENT

FUNDING

DH receives support from a cooperative agreement W81XWH-18-2-0040 between the Henry M. Jackson Foundation for the Advancement of Military Medicine Inc. and the U.S. Department of the Army. JWM receives grant support from the Bill and Melinda Gates Foundation (OPP1115715 and OPP1115400), Gilead Sciences (GS-US-382-1450), Janssen Pharmaceutica NV (ICD #909694), the National Cancer Institute (HHSN261200800001E), and the National Institute of Allergy and Infectious Diseases, Division of AIDS (UM1AI068636 (AIDS Clinical Trials Group); UM1AI069494 (Pitt-Ohio State Clinical Trials Unit); UM1AI106707 (Microbicides Trials Network); UM1AI126603 (I4C Martin Delaney Collaboratory) and U01AI131285 (DC-04)).

DISCLAIMER

Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. The investigators have adhered to the policies for protection of human subjects as prescribed in AR 70–25.

REFERENCES

1. Katlama C, Deeks SG, Autran B, Martinez-Picado J, van Lunzen J, Rouzioux C, et al. Barriers to a cure for HIV: new ways to target and eradicate HIV-1 reservoirs. Lancet. 2013;381(9883):2109–17.
2. Ananworanich J, Chomont N, Eller LA, Kroon E, Tovanabutra S, Bose M, et al. HIV DNA set point is rapidly established in acute HIV infection and dramatically reduced by early ART. EBioMedicine. 2016;11:68–72.
3. Strain MC, Little SJ, Daar ES, Havlir DV, Gunthard HF, Lam RY, et al. Effect of treatment, during primary infection, on establishment and clearance of cellular reservoirs of HIV-1. J Infect Dis. 2005;191(9):1410–8.
4. Hocqueloux L, Avettand-Fenoel V, Jacquot S, Prazuck T, Legac E, Melard A, et al. Long-term antiretroviral therapy initiated during primary HIV-1 infection is key to achieving both low HIV reservoirs and normal T cell counts. J Antimicrob Chemother. 2013;68(5):1169–78.
5. Laanani M, Ghosn J, Essat A, Melard A, Seng R, Gousset M, et al. Impact of the timing of initiation of antiretroviral therapy during primary HIV-1 infection on the decay of cell-associated HIV-DNA. Clin Infect Dis. 2015;60(11):1715–21.
6. Olson AD, Meyer L, Prins M, Thiebaut R, Gurdasani D, Guiguet M, et al. An evaluation of HIV elite controller definitions within a large seroconverter cohort collaboration. PLoS ONE. 2014;9(1):e86719.
7. Walker BD, Yu XG. Unravelling the mechanisms of durable control of HIV-1. Nat Rev Immunol. 2013;13(7):487–98.
8. Avettand-Fenoel V, Bayan T, Gardiennet E, Boufassa F, Lopez P, Lecuroux C, et al. Dynamics in HIV-DNA levels over time in HIV controllers. J Int AIDS Soc. 2019;22(1):e25221.
9. Ghosn J, Deveau C, Chaix ML, Goujard C, Galimand J, Zitoun Y, et al. Despite being highly diverse, immunovirological status strongly correlates with clinical symptoms during primary HIV-1 infection: a cross-sectional study based on 674 patients enrolled in the ANRS CO 06 PRIMO cohort. J Antimicrob Chemother. 2010;65(4):741–8.
10. Boritz EA, Darko S, Swaszek L, Wolf G, Wells D, Wu X, et al. Multiple origins of virus persistence during natural control of HIV infection. Cell. 2016;166(4):1004–15.
11. Graf EH, Mexas AM, Yu JJ, Shaheen F, Liszewski MK, Di Mascio M, et al. Elite suppressors harbor low levels of integrated HIV DNA and high levels of 2-LTR circular HIV DNA compared to HIV+ patients on and off HAART. PLoS Pathog. 2011;7(2):e1001300.
12. Ho YC, Shan L, Hosmane NN, Wang J, Laskey SB, Rosenbloom DI, et al. Replication-competent noninduced proviruses in the latent reservoir increase barrier to HIV-1 cure. Cell. 2013;155(3):540–51.
13. Wang Z, Simonetti FR, Siliciano RF, Laird GM. Measuring replication competent HIV-1: advances and challenges in defining the latent reservoir. Retrovirology. 2018;15(1):21.