EBioMedicine 66 (2021) 103305

Contents lists available at ScienceDirect

EBioMedicine

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

Commentary

The many faces of HIV elite control

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ARTICLE INFO

Article History:
Received 11 March 2021
Accepted 11 March 2021
Available online xxx

Elite controllers represent a rare phenotype (<1%) among people living with HIV (PLWH), who spontaneously suppress viral replication to undetectable levels (generally considered <50 RNA copies/ml) in the absence of antiretroviral therapy (ART)[1]. Serving as an important model for understanding what constitutes functional cure/remission, they hold clues to what virological, genetic and immunological features underlie sustained viral control.

In this article of *EBioMedicine*, Berg and colleagues describe the retrospective identification of a high frequency of potential elite controllers in the Democratic Republic of Congo (DRC) from 2017–2019 [2]. These individuals were identified as HIV-antibody positive/RNA-negative (Ab+/RNA-) on the basis of a single sample time point, hence defined as "potential". The authors systematically excluded other factors that could explain this high prevalence of elite controllers, which included collection site bias, false positive serology, compromised sample integrity, viral genetic diversity and undisclosed ART usage. Samples from the DRC from 1987 and 2001–2003 (ART drugs unavailable at the time) were also included, confirming the same trend of higher than expected numbers.

Potential elite controllers have been identified at Blood banks as Ab+/RNA- donations. In step with the progressive national rollout of ART and the increasing numbers of PLWH on ART in South Africa, a study conducted by the South African National Blood Service (SANBS), found the presence of ART drugs in increasingly larger proportions of donations between 2010 and 2016 (ranging from 38.5% to 76.1%) [3]. Approximately 60% in the Berg et al. study failed to disclose use of ART. Collectively, these findings highlight the unreliability of self-reporting of ART usage and underscore the importance of including ART drug testing in research studies enrolling elite controllers.

Estimates of potential elites (no ART) identified at the SANBS are consistent with global figures of <1% (0.7%) of PLWH [3], whereas those in the DRC (2.7%–4.3%) suggest a substantially higher representation of such individuals in this region[2]- highly plausible since HIV-1 first originated in human populations in West-central Africa through multiple independent introductions from simian immunodeficiency virus (SIV)-infected chimpanzees.

Africa, in particular sub-Saharan Africa, harbours the greatest burden of HIV-1 infection, and the greatest diversity of HIV-1. Many subtypes, circulating recombinant forms (CRFs) and unique recombinant forms are represented in West and Central Africa, dominated by a single CRF01_AG (2015–2020) [4]. By contrast, subtype *C* is dominant in South Africa and is the predominant subtype found worldwide. HIV-1 genetic variability, fuelled by unabated viral replication and spread, poses an ongoing challenge for diagnosis, treatment, vaccine and cure intervention strategies.

Globally, African populations are the most genetically diverse, yet this host genetic variability is highly understudied compared to other continents. Interestingly, a recent study of high-depth-sequenced African genomes suggested the likelihood that viral infections, including HIV-1, have sculpted the genomes of African populations [5]. In West-central Africa, the Biaka Western Pygmies, who resided within regions inhabited by chimpanzee species infected with SIV strains that were ancestral to HIV-1, have a higher representation of protective alleles or evidence of selection in select genes associated with HIV-1 infection or disease progression, when compared to populations residing outside such regions, which included the Mbuti Eastern Pygmies [6].

Elite controllers make up a heterogeneous group based on varying longitudinal clinical features of viral load and CD4 cell count. Some subphenotypes are distinguished by long-term sustained control, others with occasional "blips" or small increases in detectable virus, others experience progressive loss of CD4 cell counts despite maintaining viral control, while others rapidly lose viral control after a period of suppressing HIV-1. This variation is also evident when considering characteristics of the viral reservoir (HIV DNA quantity, provirus integration sites, induction/production of replication-competent virus, intact/defective provirus) [7] and immune response mechanisms [8]. Recent descriptions of exceptional elite controllers [9,10] have provided important insights into factors that may characterize this particular subphenotype. Different factors and varying combinations of factors are likely to play a role in different individuals, and as more in-depth studies are undertaken, and on larger numbers, it may become possible to have endotypes (a collection of viral/host biomarkers) that describe specific subphenotype groupings of elite controllers.

HIV-1 is a complex disease. It is important to study diverse populations of a similar phenotype, including in West-central Africa,

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2021.103258.
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https://doi.org/10.1016/j.ebiom.2021.103305

where as suggested by Berg et al., larger numbers of elite controllers may exist. Harnessing the population diversity of Africa will enhance genetic discovery, and importantly, relevant to the populations most in need of interventions for HIV prevention, treatment and cure.

Contributors

Dr Tiemessen wrote this commentary.

Declaration of Competing Interest

Dr Tiemessen has nothing to disclose.

Acknowledgments

The author is supported by the South African Research Chairs Initiative of the Department of Science and Innovation and National Research Foundation of South Africa (84177), and the Strategic Health Innovation Partnerships (SHIP) Unit of the South African Medical Research Council (a grantee of the Bill & Melinda Gates Foundation). The funders had no role in the writing of this commentary.

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