Characterizing HIV-1 transcriptional activity during frequent longitudinal sampling in aviremic patients on ART: Implications for HIV cure research

Steffen Leth\textsuperscript{1,3}, Rasmus Nymann\textsuperscript{1,3}, Sofie Jørgensen\textsuperscript{1,3}, Thomas Aagaard Rasmussen\textsuperscript{1}, Lars Østergaard\textsuperscript{1,3}, Paul Wesley Denton\textsuperscript{1,2,3}, Martin Tolstrup\textsuperscript{1,3}, Ole Schmeltz Søgaard\textsuperscript{1,3}

1. Department of Infectious Diseases, Aarhus University Hospital, Denmark
2. Aarhus Institute for Advanced Studies, Aarhus University, Denmark
3. Institute of Clinical Medicine, Aarhus University, Denmark

Correspondence: Steffen Leth, email: steffenleth@gmail.com

Introduction

Reversal of latency is currently being pursued in clinical trails as a component of HIV eradication efforts. Reversal of latency has been determined by increases in cell-associated unspliced HIV-1 RNA (CA-US HIV-RNA), but the natural longitudinal dynamics of HIV-1 transcriptional activity has not been fully characterized.

Materials and Methods

We conducted a longitudinal, observational cohort study enrolling 26 aviremic, HIV-1 patients with CD4\(^+\) T-cell count >200/µL and >2 year on ART. Table 1.

Monthly blood samples were collected over six consecutive months. HIV-1 transcription as measured by CA-US HIV-RNA and proviral load (total HIV-1 DNA) were quantified in unfractionated CD4\(^+\) T cells using digital droplet PCR. Data were analyzed by a linear regression model with random-effects to allow for repeated measurements for individuals.

Results

Data on CA-US HIV RNA were available on 26 patients and Total HIV DNA on 22 patients. Fig 1a, b, c.

Three outcome estimates were computed (Table 2):

1. Intra-individual contribution to the overall cohort variation in CA-US HIV RNA. Total HIV-DNA and RNA/DNA ratios. This indicates that the majority of the observed cohort variation was attributed to inter-individual differences.

2. 95% prediction intervals for the cohorts absolute level of CA-US HIV RNA and Total HIV-DNA. This estimates the range in which a new random sample or a median in absolute values would fall, if additional sampling from an individual from this cohort, or an individual matching this cohort, were performed.

3. 95% variation interval, estimates the variation around the median absolute level of CA-US HIV RNA, Total HIV-DNA and RNA/DNA ratios. For a single patient this was expressed as multiplication factors (fold change) over the course of 6 months. Hence, within a single individual we observed a 0.360 to 2.776 fold variation in the levels of CA-US HIV RNA measured over the course of 6 months.

Conclusion

HIV-1 transcriptional activity showed minor fluctuations during frequent sampling over a period of 6 months in aviremic, HIV-1 infected individuals on ART. These data provide the first insights into the natural occurring longitudinal variation of CA-US HIV-RNA, a primary outcome measure in HIV-1 latency reversal trails. These data provide a solid foundation for both design and interpretation of future latency reversal trials.