Persistence of HIV-RNA in Autopsy Tissue Samples From Persons With HIV With Suppressed Viral Loads

00498

Hiromi Imamichi[1], Ven Natarajan[2], Francesca Scrimieri[2], Mindy Smith[1], Yunden Badralmaa[2], Marjorie Bosche[2], Jack Hensien[1], Thomas Buerkert[1], Weizhong Chang[2], Brad Sherman[2], Kanal Singh[1], H. Clifford Lane[1]

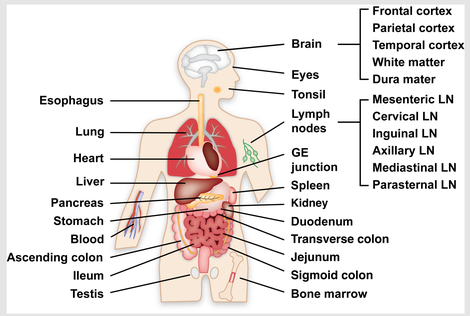
[1]National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, USA; [2]Frederick national Laboratory for Cancer Research, Frederick, MD, USA

BACKGROUND

The rapid viral rebound observed following treatment interruption, despite prolonged time on ART with plasma HIV-RNA levels <40 copies/ml (1), suggests persistent HIV-1 reservoirs outside of the blood. However, the relative contribution of different anatomical compartments to the HIV-1 reservoir is not well understood.

METHODS

Autopsy specimens were collected from 10 donors: 3 with active HIV-1 replication (blood HIV-RNA levels ≥5 copies/1 µg host-genomic RNA)("Active") and 7 with suppressed HIV-1 replication (blood HIV-RNA levels <5 copies/1 µg host-genomic RNA)("Suppressed") at the time of death. Specimens were collected from 31 different tissue compartments including blood as shown below.



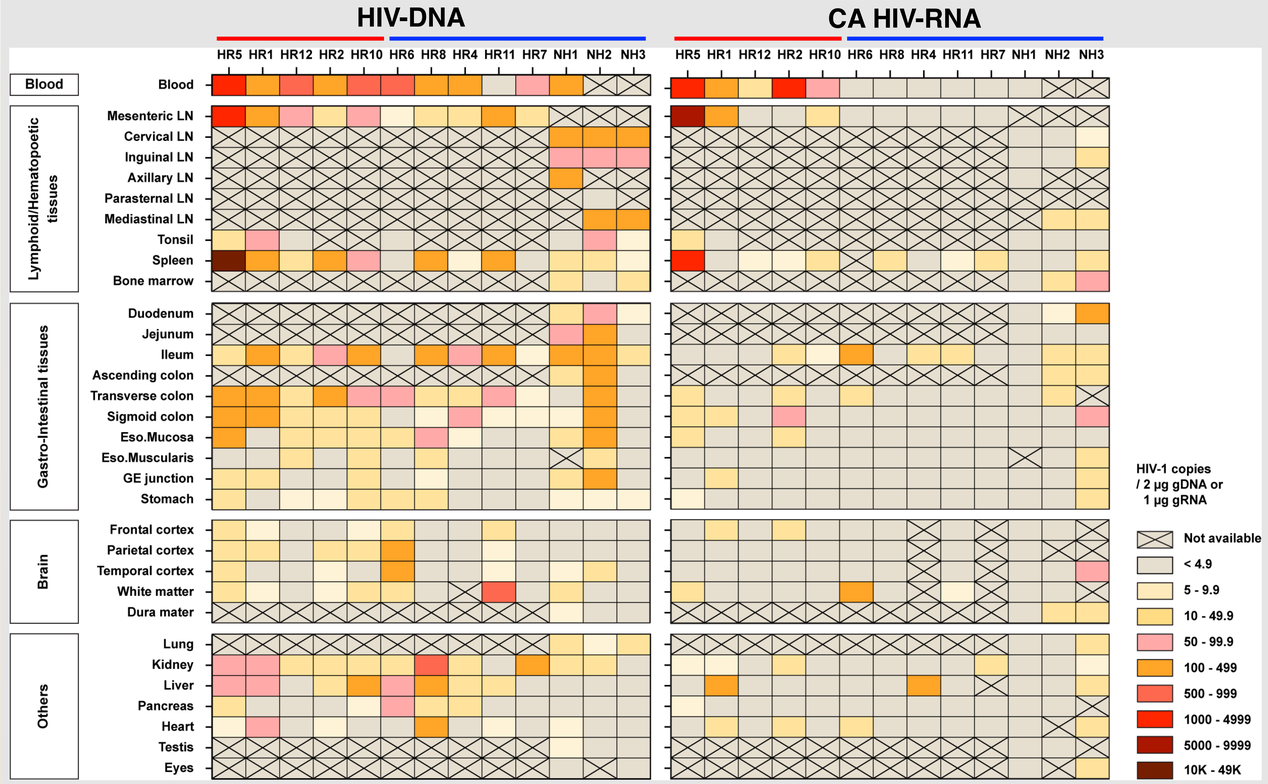
Levels of HIV-DNA and HIV-RNA were determined using quantitative PCR. HIV-1 proviruses were analyzed by 5'LTR-to-3'LTR PCR single-genome amplification of near full-length HIV-1 (9 kb in size) and direct amplicon sequencing as previously described (2). A total of 1,902 HIV-1 sequences derived from the 10 donors (median: 128, range: 42 - 697 sequences per donor) were obtained and used for analyses.

REFERENCES

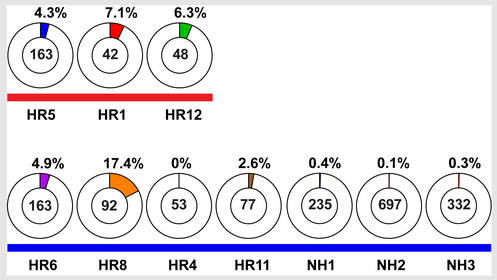
(1) Davey et al., 1999, PNAS 96(26): 15109-15114
(2) Imamichi et al., 2016, PNAS 113(31): 8783-8788

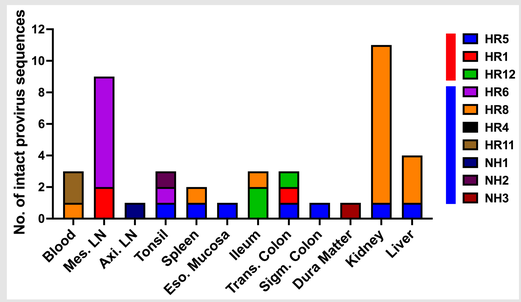
Hiromi Imamichi, Ph.D.
CMRS, LIR, NIAID, NIH
E-mail: himamichi@nih.gov

RESULTS



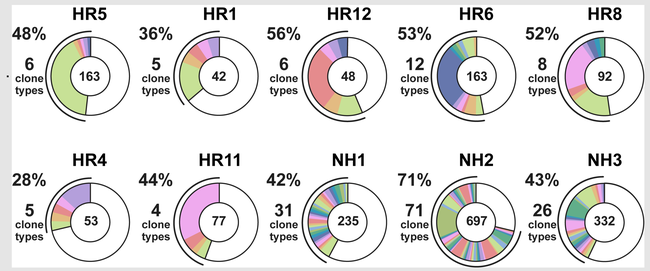
HIV-DNA and CA HIV-RNA species were detected in all 10 donors in 31 different tissue compartments. No statistically significant differences were noted between the Active (under the red bars) and Suppressed (under the blue bars) groups. Higher levels of HIV-DNA (above the overall median) were noted in lymphoid tissues, the intestine, the spleen, the kidney, and the liver.



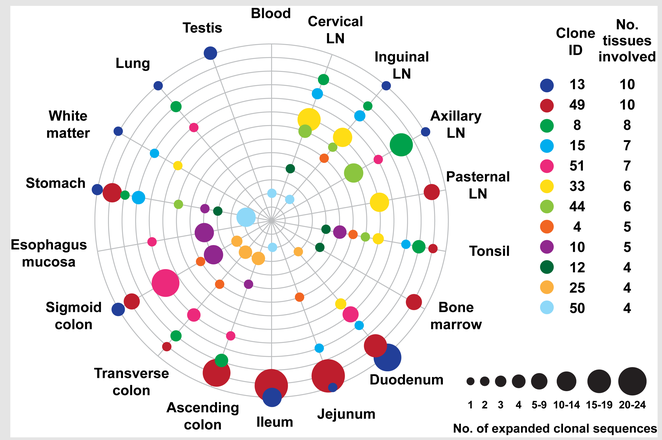


On average, 5.9% (13/253) of proviruses in the Active; and 3.7% (29/1649) of proviruses in the Suppressed groups were intact. No difference (p=0.18) was seen between the two groups. Of the 16 intact proviruses in HR8 (Suppressed group), 15 were found to be in expanded clones. Tissue specific enrichment of intact proviruses was not observed.

RESULTS



Expanded HIV-1 provirus clones were found essentially in each person with HIV-1 infection. On average, 47.4% of proviruses (120/253, n=3) in the Active; and 56.0% (923/1649, n=7) of proviruses in the Suppressed groups were found in expanded clones. No significant difference (p>0.99) was seen between the two groups.



The expanded provirus clones were distributed across many different tissues. A representative pattern seen in NH2 (Suppressed group) involving 12 different expanded clone types is shown.

SUMMARY

Similar levels of HIV-DNA and HIV-RNA expression were noted in autopsy samples from PWH with either Active or Suppressed HIV-1, implying a substantial seeding of multiple tissues with cells harboring proviral DNA during HIV-1 infection that is independent of treatment status. Overall, 54.8% of proviruses detected were in the context of clonal expansions, suggesting that cellular proliferation is a crucial driver of in vivo viral persistence. The absence of a common tissue sanctuary for intact proviruses highlights one of the potential challenges in designing effective HIV-1 cure strategies.