Long-Term Effect of Temporary ART During Primary HIV Infection on the Viral Reservoir

Alexander O. Pasternak[1], Jan M. Prins[2], and Ben Berkhout[1]

[1]Laboratory of Experimental Virology, Department of Medical Microbiology, Academic Medical Center of the University of Amsterdam (AMC), Amsterdam, Netherlands, and
[2]Department of Internal Medicine, Division of Infectious Diseases, Tropical Medicine and AIDS, AMC, Amsterdam, Netherlands

a.o.pasternak@amc.uva.nl

Background

Initiation of antiretroviral therapy (ART) during primary HIV-1 infection (PHI) has been proposed to limit the formation of viral reservoirs. However, it remains unknown whether temporary ART during PHI has a long-term effect on the viral reservoir during ART initiated subsequently at chronic HIV infection (CHI).

Study design and results

Levels of cell-associated (CA) HIV-1 unspliced RNA (usRNA) and total CA viral DNA (vDNA) were analyzed in 49 HIV-infected patients who had participated in a randomized controlled trial of 24 or 60 weeks of temporary ART versus no treatment during PHI (1). All 11 patients randomized to the no-treatment arm at PHI, and 19 of 38 patients randomized to receive ART at PHI, subsequently (re)started ART during CHI after a median period of 86 weeks without treatment. HIV nucleic acids were longitudinally quantified in PBMC at ART baseline time points and every 12 weeks thereafter up to week 60 of both PHI and CHI ART (Fig. 1) by seminested real-time PCR (2, 3). We used mixed modeling to compare the variables between groups and Spearman tests for correlation analyses.

Levels of usRNA and usRNA/vDNA ratios at PHI strongly predicted the viral setpoint upon early therapy interruption (p=0.0001 and p=0.00004, respectively), and the slope of the CD4 count decline in the untreated period after interruption of early ART (p=0.009 and p=0.003) (Fig. 2). The predictive power of CA RNA for both viral setpoint and CD4 count decline was stronger than that of the plasma viremia. Levels of both usRNA (p=0.009) and vDNA (p=0.03) during PHI ART were significantly lower than levels of corresponding markers during CHI ART in patients who were not treated with early ART. However, no significant difference was found in the levels of any marker between the early and chronic therapy periods in the same patients, and strong correlations for all the markers between the two therapy periods were observed (usRNA: p=0.002; vDNA: p=0.0001, usRNA/vDNA: p=0.003) (Fig. 3). Finally, level of usRNA, measured during CHI ART, was significantly lower in patients who had been pre-treated during PHI than in patients who had not been pre-treated (p=0.018) (Fig. 4).

Conclusions

Level of CA HIV RNA at PHI strongly predicted the CD4 count decline, suggesting that the viral reservoir, established early after infection, influences the disease progression for years afterwards. We observed a long-term suppressive effect of temporary early ART on the viral reservoir during ART initiated subsequently at CHI.

Literature

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2. Pasternak AO, et al. Highly sensitive methods based on seminested real-time reverse transcription-PCR for quantitation of human immunodeficiency virus type 1 unspliced and multiply spliced RNA and proviral DNA. J Clin Microbiol 2008;46:2206-11.
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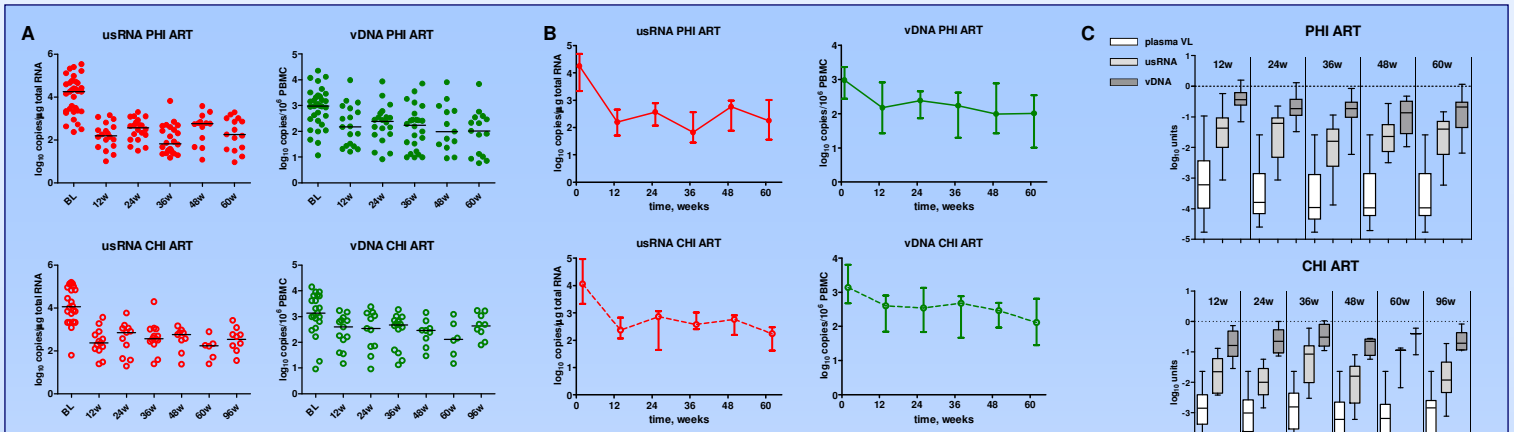


Figure 1. Levels (A), longitudinal trends (B), and decreases from baseline (C) of cell-associated HIV RNA and DNA during early and chronic therapy periods.

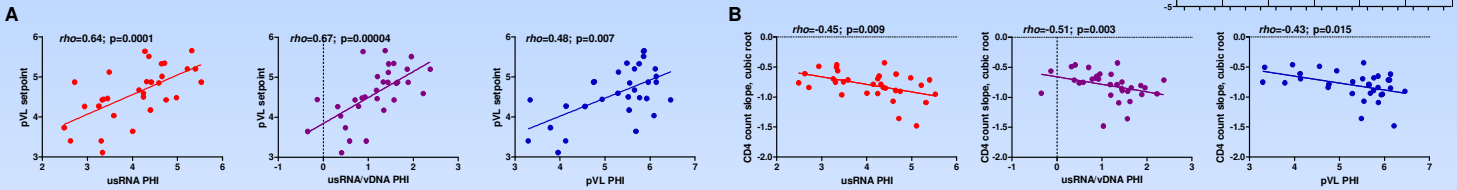


Figure 2. Predictive power of usRNA, usRNA/vDNA ratio, and plasma viral load at PHI for plasma viral load setpoint (A), and CD4 count slope (B) after interruption of early therapy.

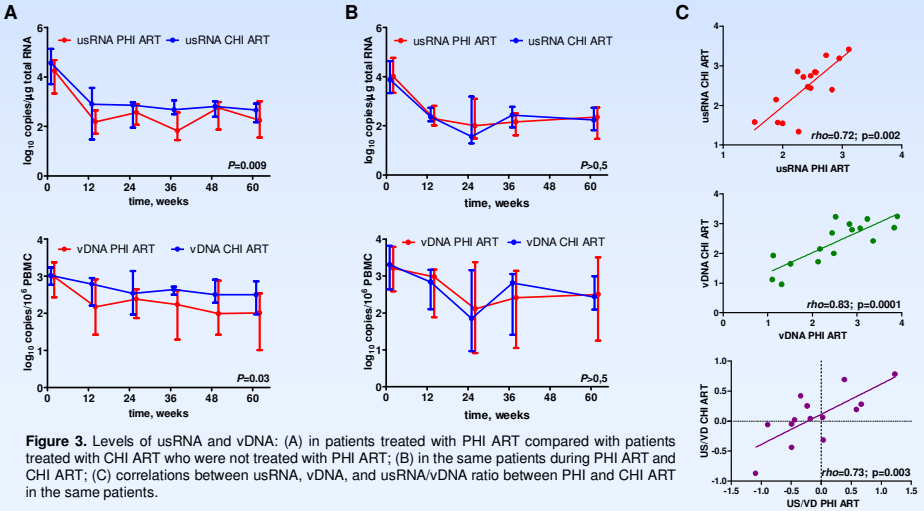


Figure 3. Levels of usRNA and vDNA: (A) in patients treated with PHI ART compared with patients treated with CHI ART who were not treated with PHI ART; (B) in the same patients during PHI ART and CHI ART; (C) correlations between usRNA, vDNA, and usRNA/vDNA ratio between PHI and CHI ART in the same patients.

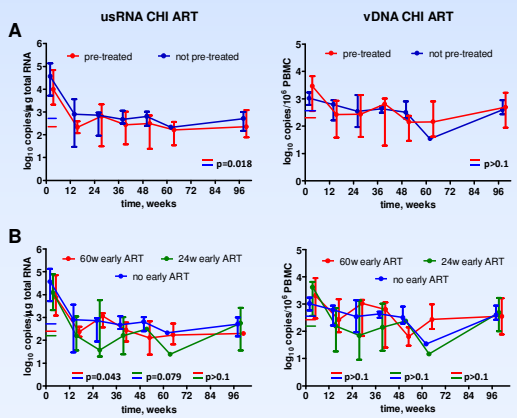


Figure 4. Levels of usRNA (A) and vDNA (B) during chronic therapy periods in patients pre-treated and not pre-treated (A) and pre-treated for 60 or 24 weeks or not pre-treated (B) with early ART.

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