Cell-Associated HIV RNA Predicts Post-Treatment HIV Control and CD4+ T-cell Loss

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Background

For the improved design of strategies towards HIV-1 functional cure, it is important to identify biomarkers that could predict the duration of post-treatment virological control and subsequent disease progression (the rate of CD4+ T-cell loss).

Study design and results

We studied 45 patients that received 24 or 60 weeks of temporary ART initiated at primary HIV infection (PHI) as part of a randomized trial (Primo-SHM study). Patients were treated with a quadruple triple-class ART regimen. Cell-associated (CA) HIV nucleic acids (unspliced (US)-gag and multiply spliced (MS)-tat/rev HIV RNA and total HIV DNA) were longitudinally quantified by seminested qPCR every 12 weeks during ART and at the virological setpoint (36 weeks after discontinuation of ART).

All patients experienced virological rebound (VR) (plasma viremia >50 copies/ml) within 9 months after therapy interruption. We first assessed the predictive power of the last measurements of the CA HIV biomarkers, CD4+ count, and CD4/CD8 ratio on ART before the therapy interruption, as well as of the duration of temporary ART, for the time to VR (the duration of post-treatment control). US RNA was the only significant predictor of the time to VR (HR=0.29 for patients with US RNA levels below vs. above the median, 95% CI, 0.10-0.83, p=0.021, log-rank test). Subsequently, we have assessed the predictive power of the same biomarkers and plasma viremia, measured at the virological setpoint, for the time to reach the CD4+ count of 350 cells/mm^3 in the absence of treatment. Among the virological markers, MS RNA was the strongest predictor of disease progression, whereas US RNA was not predictive. The median times to 350 cells/mm^3 in patients with MS RNA levels below and above the median were 1180 and 283 days, respectively (p=0.0002, log-rank test). In multivariate Cox regression analysis, CD4+ count (p=0.0004) and MS RNA level (p=0.011) were the only two significant predictors of disease progression.

Conclusions

Cell-associated HIV-1 US RNA was the sole predictor of the duration of post-treatment virological control after the interruption of early ART, whereas MS RNA independently predicted subsequent CD4+ T-cell loss. This suggests that reactivation of HIV and CD4+ T-cell loss after ART interruption could be driven by different mechanisms. Further exploration of the predictive potential of these biomarkers in large-scale clinical trials aimed at HIV functional cure is warranted.

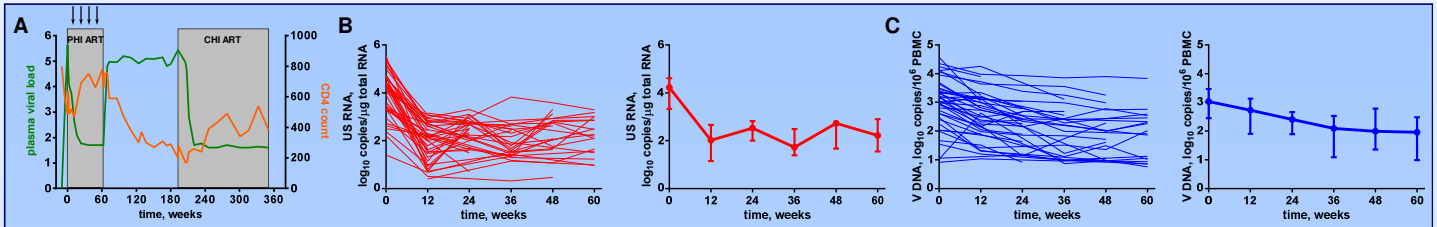

Figure 1. (A) Cell-associated (CA) HIV nucleic acids were quantified in PBMC at primary HIV infection (PHI) and every 12 weeks thereafter during early ART. (B, C) Individual and median time trends of CA HIV RNA (B) and DNA (C) during early ART.

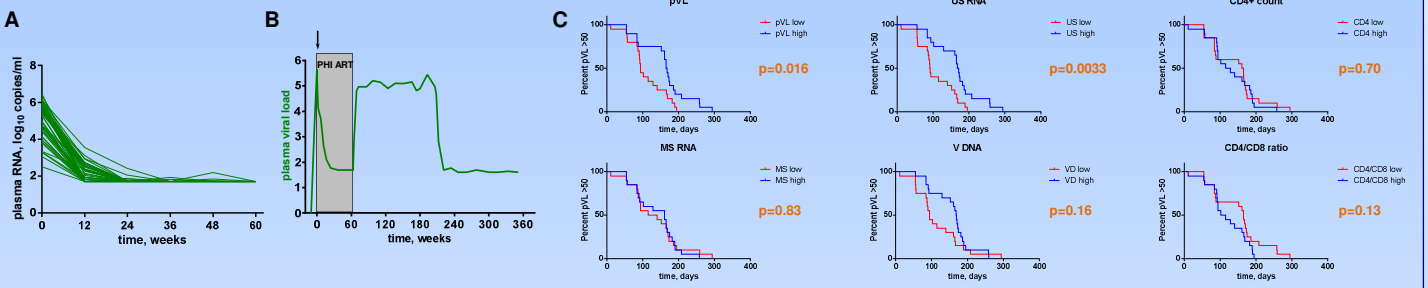

Figure 2. (A) Individual time trends of plasma viral load after early ART initiation. (B) Plasma viral load, CD4+ count, CD4/CD8 ratio, and CA HIV nucleic acids were quantified in PBMC at PHI. (C) Kaplan-Meier plots for prediction of the time to plasma viral load suppression after initiation of early ART. All potential predictors were dichotomized according to the median values.

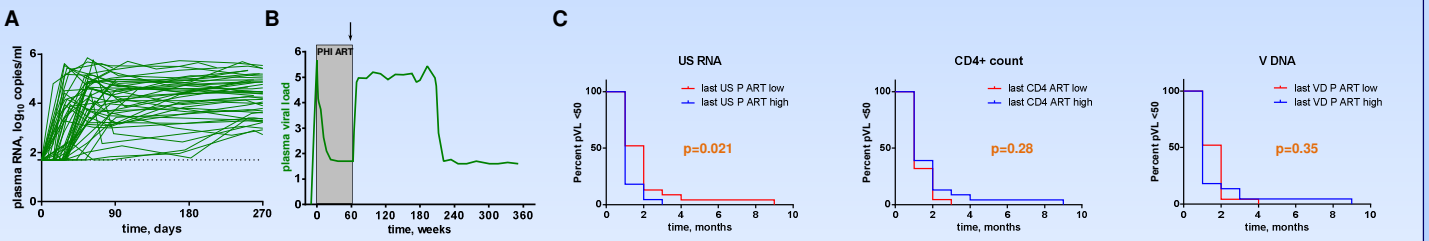

Figure 3. (A) Individual time trends of plasma viral load after early ART interruption. (B) CD4+ count and CA HIV nucleic acids were quantified in PBMC at early ART interruption. (C) Kaplan-Meier plots for prediction of the time to plasma viral load rebound after interruption of early ART. All potential predictors were dichotomized according to the median values.

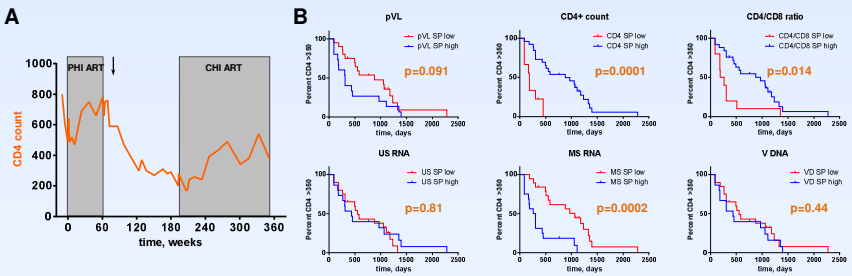

Figure 4. (A) Plasma viral load, CD4+ count, CD4/CD8 ratio, and CA HIV nucleic acids were quantified in PBMC at the virological setpoint (36 weeks after ART interruption). (B) Kaplan-Meier plots for prediction of the disease progression (time for the CD4+ count to reach 350 cells/mm^3). All potential predictors were dichotomized according to the median values.



Total reservoir (HIV DNA+)

Active reservoir (HIV DNA+ US-RNA+)

Hyperactive reservoir (HIV DNA+ US-RNA+ MS-RNA^{high})

Figure 5. A model of HIV reservoirs.

CA HIV DNA: a marker of total proviral reservoir (mostly defective).

CA HIV unspliced RNA: a marker of active reservoir (cells transcribing viral RNA); it overestimates but might correlate with functional reservoir (cells that can become reactivated to produce replication-competent virus upon latency reversal).

CA HIV multiply spliced RNA: a marker of "hyperactive reservoir" (a subset of active reservoir, containing cells with high MS-RNA levels); the relative size of this "hyperactive reservoir" may drive HIV pathogenesis, determining the rate of CD4+ T-cell loss).

Poster nr. 286

This study was supported by the research grant 2011020 from the Dutch AIDS Fonds