Cell-associated HIV-1 unspliced RNA level predicts both time to virological suppression and duration of post-treatment virological control in patients treated with temporary early ART

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Disclosure of speaker's interests

No conflict of interest

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PLoS MEDICINE

No Treatment versus 24 or 60 Weeks of Antiretroviral Treatment during Primary HIV Infection: The Randomized Primo-SHM Trial

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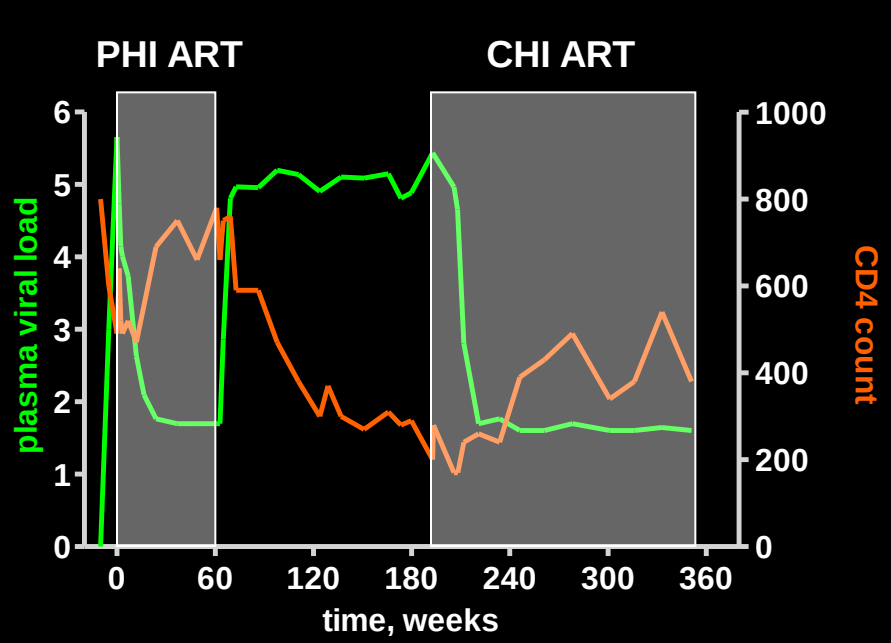
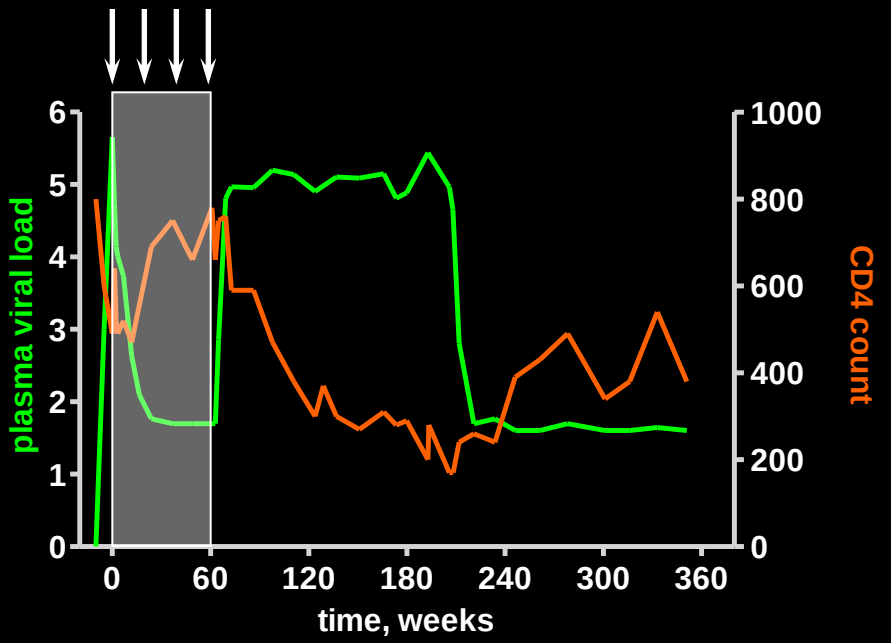
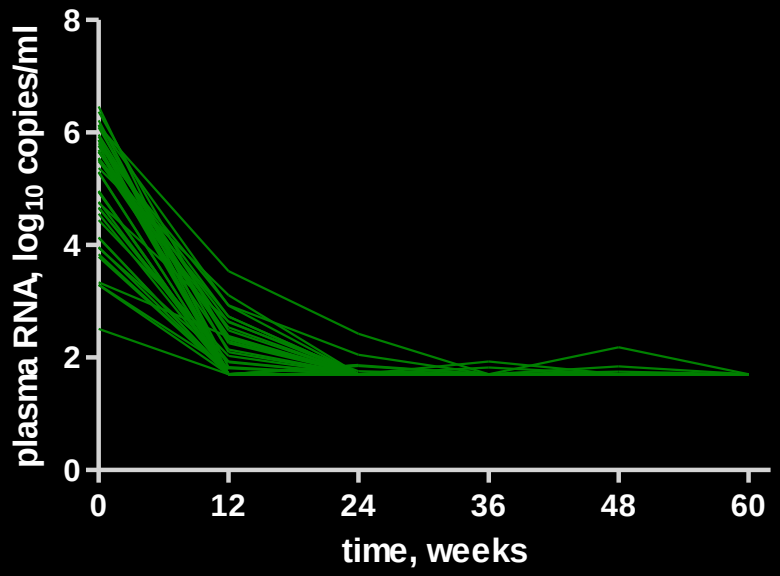
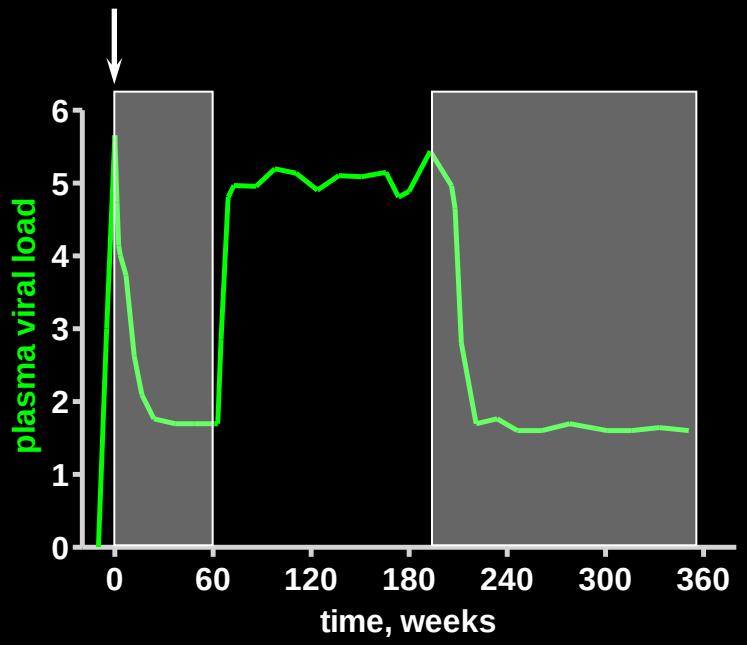
Cell-associated HIV nucleic acids were quantified in PBMC at PHI and every 12 weeks thereafter during early ART



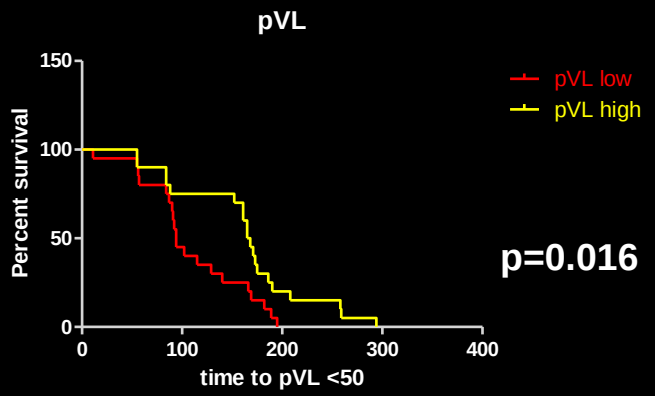


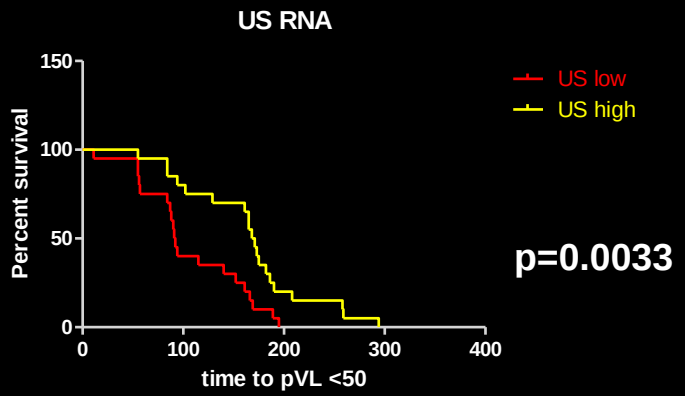
What determines the rate of virological suppression after ART initiation?

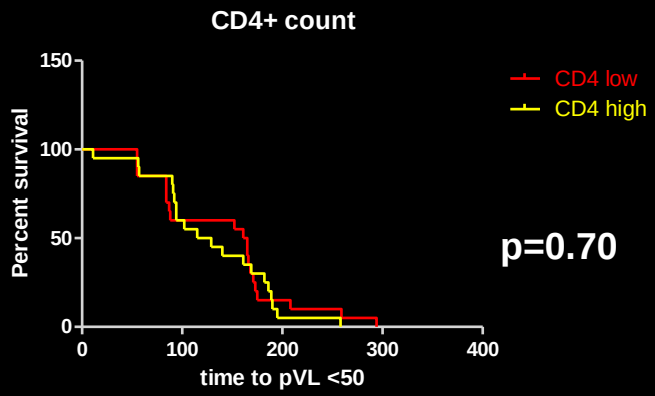


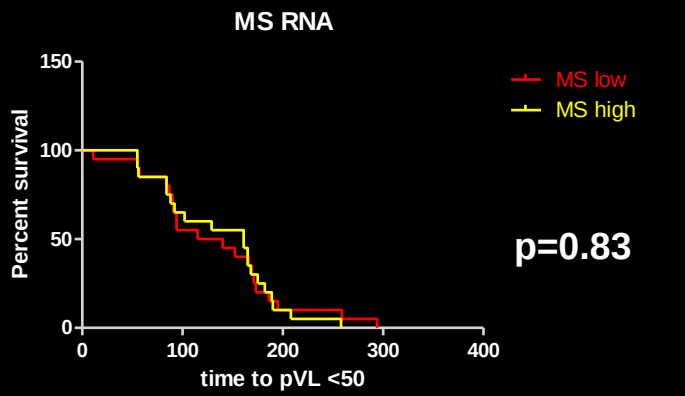


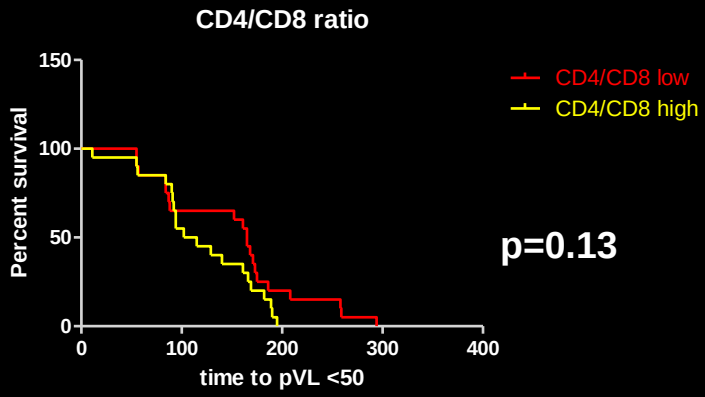
Plasma viral load, CD4+ count, CD4/CD8 ratio, unspliced RNA, multiply spliced RNA, and total viral DNA were measured at PHI

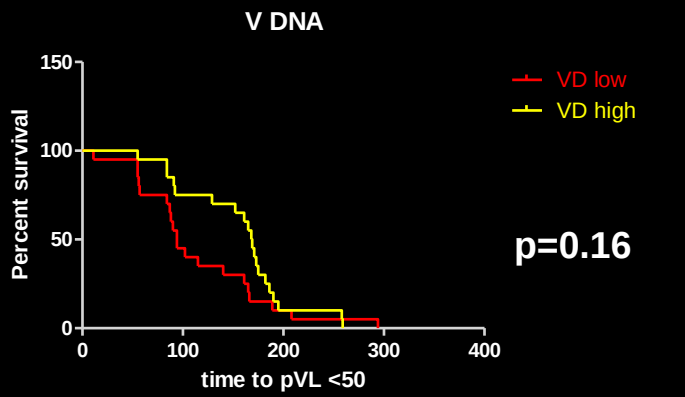






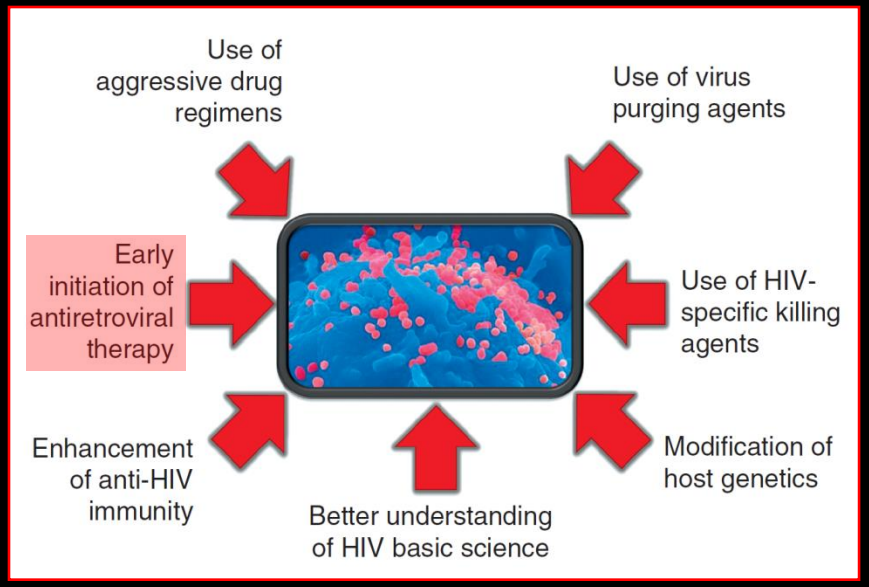






In the multivariate Cox regression, US RNA at PHI was the only significant predictor of the time to virological suppression (HR=0.65 per 1 $\log_{10}$ increase in US RNA, 95% CI, 0.48-0.87, p=0.0043).

Early initiation of ART is one of the most promising strategies for HIV cure



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Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

Asier Sáez-Cirión[1]*, Charline Bacchus[2], Laurent Hocqueloux[3], Véronique Avettand-Fenoel[4,5], Isabelle Girault[6], Camille Lecuroux[6], Valerie Potard[7,8], Pierre Versmisse[1], Adeline Melard[4], Thierry Prazuck[3], Benjamin Descours[2], Julien Guergnon[2], Jean-Paul Viard[5,9], Faroudy Boufassa[10], Olivier Lambotte[6,11], Cécile Goujard[10,11], Laurence Meyer[10,12], Dominique Costagliola[7,8,13], Alain Venet[6], Gianfranco Pancino[1], Brigitte Autran[2], Christine Rouzioux[4,5]*, the ANRS VISCONTI Study Group[¤]

The NEW ENGLAND JOURNAL of MEDICINE

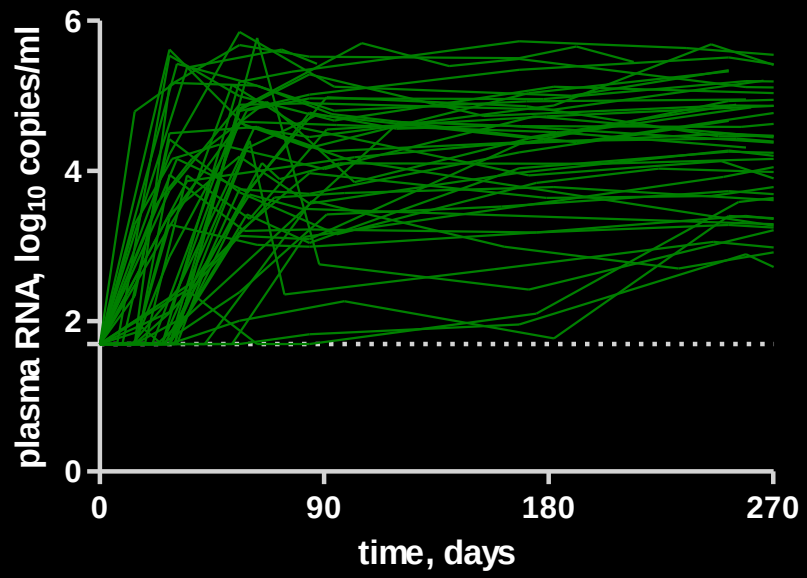
BRIEF REPORT

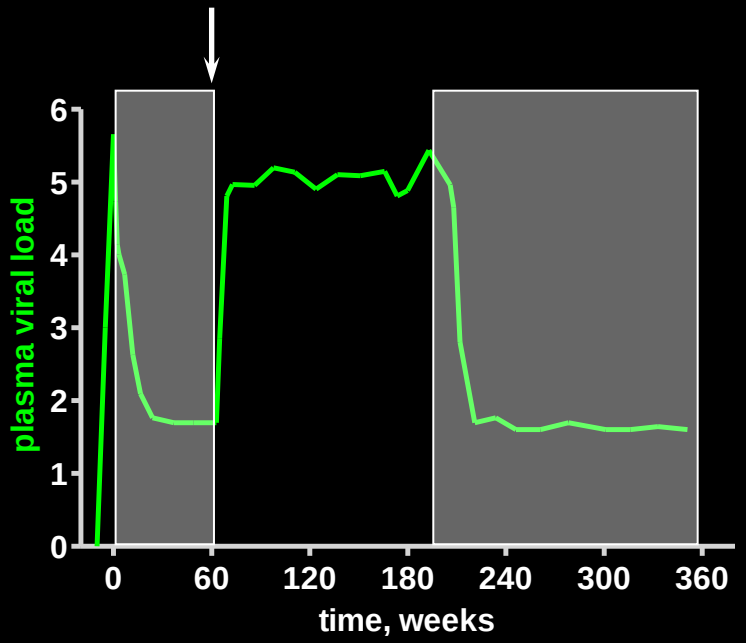
Absence of Detectable HIV-1 Viremia after Treatment Cessation in an Infant

Deborah Persaud, M.D., Hannah Gay, M.D., Carrie Ziemniak, M.S., Ya Hui Chen, B.A., Michael Piatak, Jr., Ph.D., Tae-Wook Chun, Ph.D., Matthew Strain, M.D., Ph.D., Douglas Richman, M.D., and Katherine Luzuriaga, M.D.

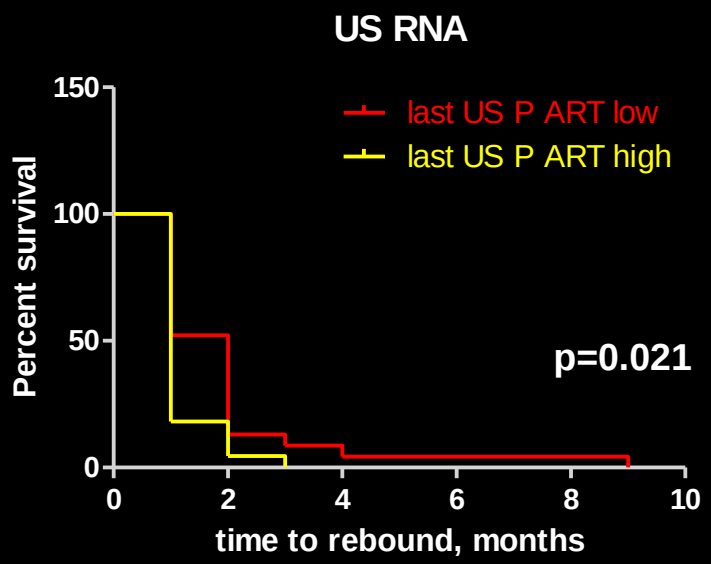
For the improved design of strategies towards HIV-1 functional cure, it is important to identify biomarkers that could predict the duration of post-treatment virological control (Visconti study, etc.)

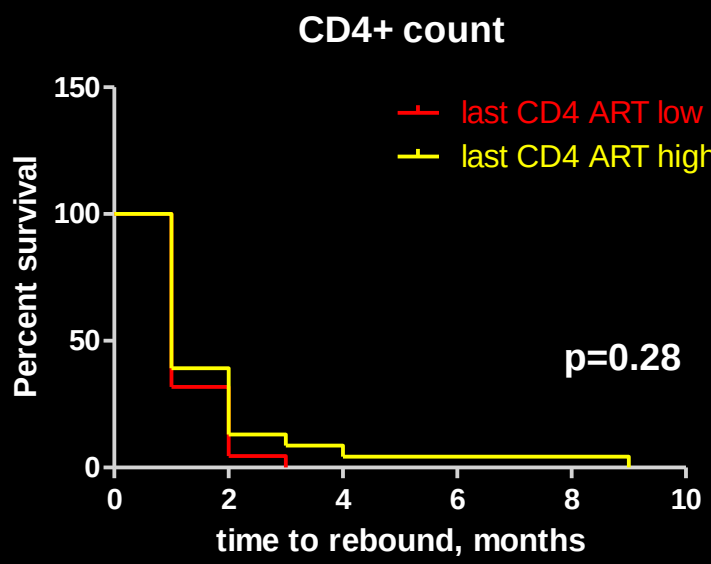
What determines the rate of virological rebound after ART interruption?



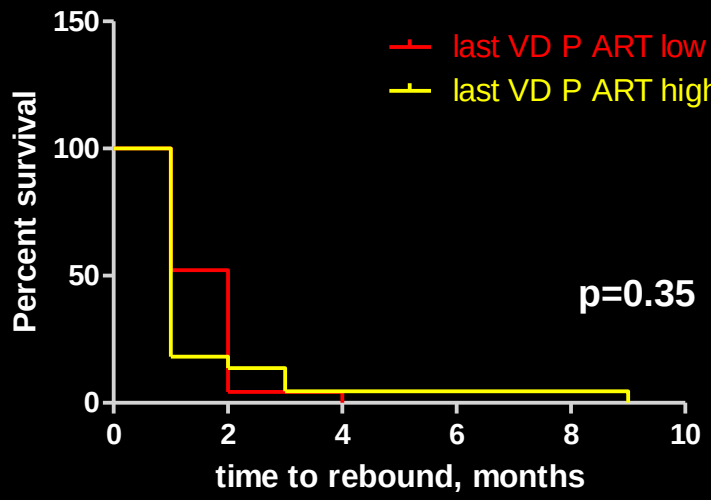


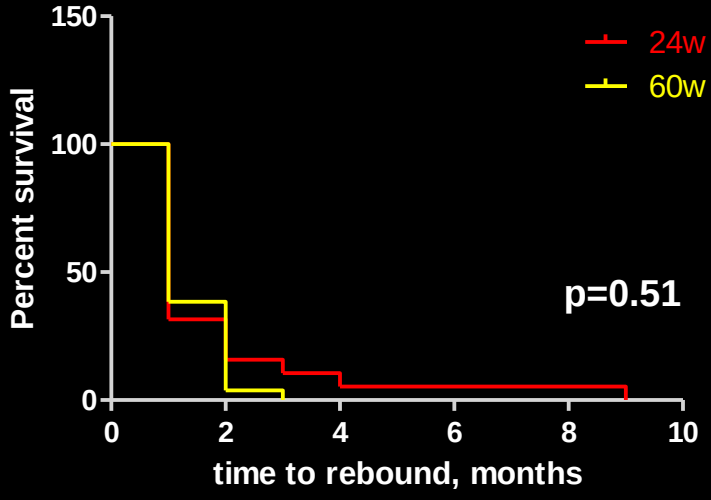
Unspliced RNA, total viral DNA, and CD4+ count were measured before interruption of early ART



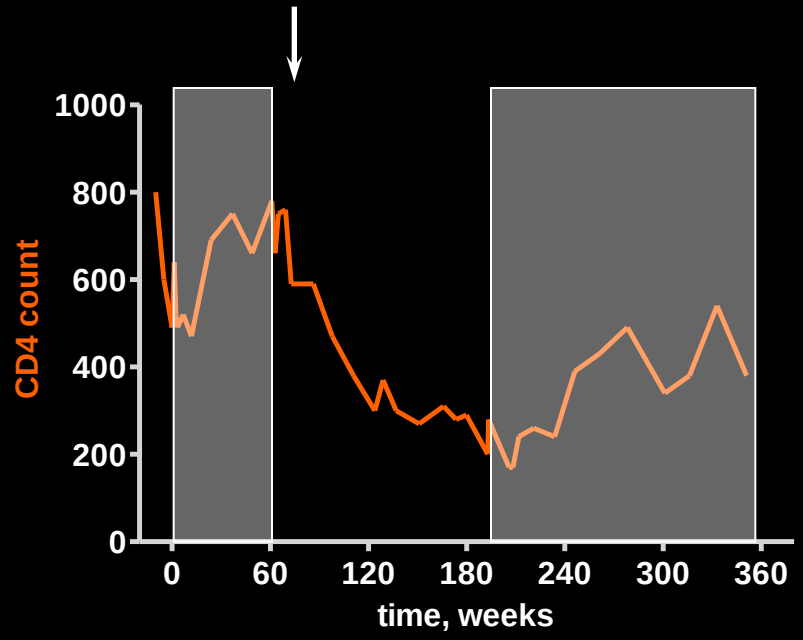


Further exploration of US RNA as a predictor of post-treatment control in large-scale clinical trials aimed at HIV functional cure is warranted

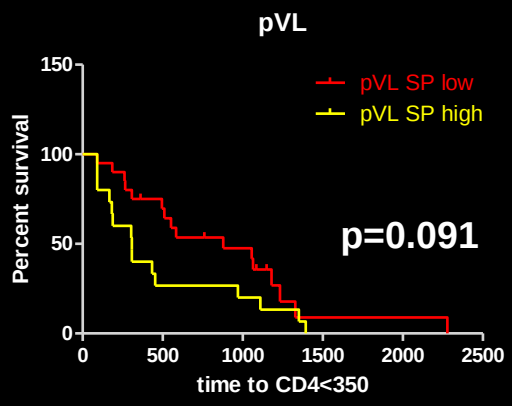


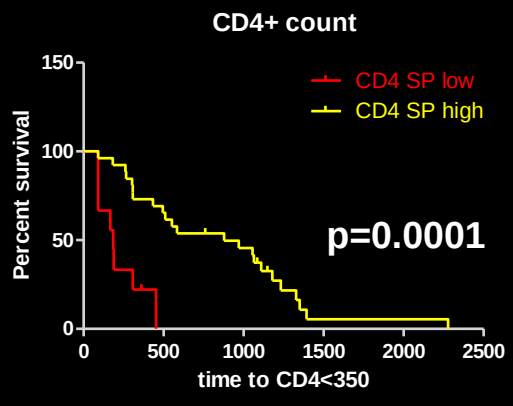


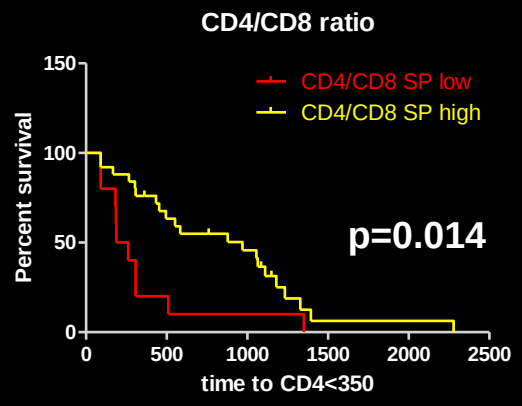
What determines the rate of disease progression (CD4+ T-cell loss) after interruption of early ART?

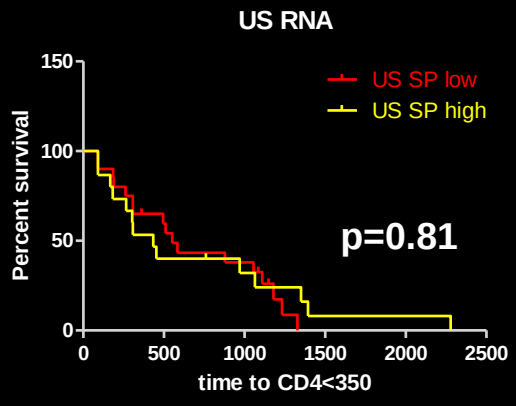


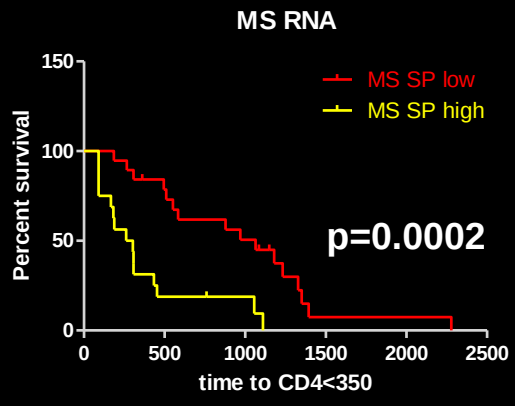
Plasma viral load, CD4+ count, CD4/CD8 ratio, unsplced RNA, multiply spliced RNA, and total viral DNA were measured at the virological setpoint (36 weeks after early ART interruption)

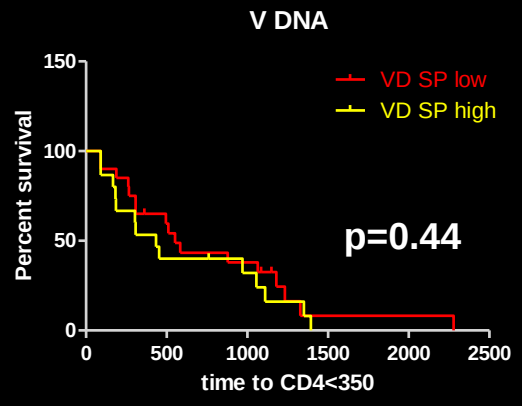












In the multivariate Cox regression analysis, CD4+ count (p=0.0004) and MS RNA level (p=0.011) were the only two significant predictors of disease progression.

Conclusions

Cell-associated HIV-1 unspliced RNA level independently predicted both time to virological suppression and time to virological rebound in patients treated with temporary early ART

Cell-associated HIV-1 multiply spliced RNA level independently predicted disease progression (CD4+ T-cell loss) after interruption of early ART, while unspliced RNA was not predictive

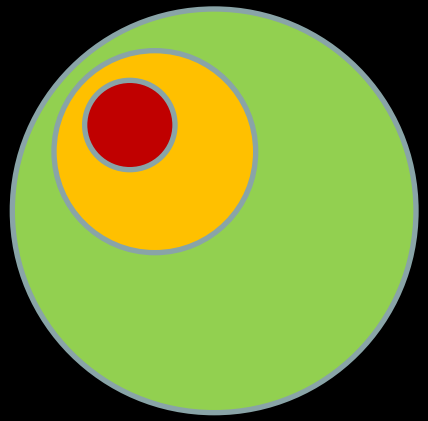
It looks like reactivation of HIV after therapy is interrupted and subsequent CD4+ T-cell loss are driven by different mechanisms

Reservoirs, reservoirs…

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

Unspliced RNA: a marker of active reservoir (cells transcribing viral RNA); overestimates but might correlate with functional reservoir (cells that produce virus or can become reactivated to do so upon latency reversal)

Multiply spliced RNA: a marker of “hyperactive reservoir” (cells with high MS RNA levels, a subset of active reservoir – the relative size of this “hyperactive reservoir” may drive HIV pathogenesis, determining the rate of CD4+ T-cell loss)



Total (DNA^+)

Active (DNA^+ US-RNA^+)

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

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HIV Reservoir: Finding the Right Needles in a Needlestack

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