Long-term Early Antiretroviral Therapy Limits the HIV-1 Reservoir Size as Compared to Later Treatment Initiation but not to Levels Found in Long-term Non-Progressors

Eva Malatinkova1, Ward De Spiegelaere2, Pawel Bonczkowski3, Maja Kiselinova2, Karen Vervisch4, Wim Trypsteen2, Margaret Johnson5, Chris Verhofstede2, Danny de Looze3, Charles Murray4, Sabine Kinloch-de Loes2, Linos Vandekerckhove4

a) HIV Translational Research Unit, Department of Internal Medicine, Faculty of Medicine and Health Sciences, Ghent University and Ghent University Hospital, Ghent, Belgium.

b) Division of Infection and Immunity, Royal Free Hospital, London NW3 2QG, United Kingdom.

c) AIDS Reference Laboratory, Department of Clinical Chemistry, Microbiology and Immunology, Ghent University, Ghent, Belgium.

d) Department of Gastroenterology, Ghent University Hospital, Ghent, Belgium.

e) Department of Gastroenterology, Royal Free Hospital, London NW3 2QG, United Kingdom.

Background

- Early initiation of long-term antiretroviral therapy (ART) may lead to viral control after treatment discontinuation.
- Recent evidence indicates that ART initiated within primary HIV-1 infection (PHI) limits the HIV-1 reservoir size.
- Insight into the reservoir in patients with different timings of ART, as well as those who can control HIV-1 without therapy, should further inform treatment strategies.

Materials and methods

- A cross-sectional study of HIV-1 DNA reservoir size (total and integrated HIV-1 DNA), ongoing viral replication (2-LTR circles) and viral transcription (cell associated HIV-1 unspliced RNA (usRNA)) was performed in peripheral blood mononuclear cells (PBMCs) of 84 patients and total HIV-1 DNA in rectal biopsies of 51 patients.
- Four patient cohorts were recruited in two clinical centers (London, UK and Ghent, BE): 1) long-term treated patients with ART initiated early, within seroconversion (SRCV on ART) or 2) later, during chronic infection (Chronic ART), 3) long-term non-progressors (LTNP) and 4) ART-naïve recent seroconverters (Recent SRCV).
- Acutely and chronically treated patients had undetectable VL for at least 4 years and median treatment time was 10 years.

Results

- Levels of usRNA in blood were significantly lower in early compared to chronically treated cohort, indicating a lower transcriptional activity in early treated patients and not different from levels found in LTNP.
- Levels of episomal 2-LTR circles in blood were low in ART-treated patients and LTNP and high in recent ART-naïve seroconverters, confirming high levels of ongoing replication in this cohort.
- Significantly lower levels of total and integrated HIV-1 DNA in blood were detected in early as compared to chronically treated patients. However, these levels were still higher when compared to LTNP, indicating a fast seeding of the HIV-1 reservoir during PHI.
- Early treated patients exhibited a higher CD4/CD8 ratio as compared to chronically treated patients, suggesting lower levels of residual immune activation and not different to that found in LTNP.
- Comparable total HIV-1 DNA levels in rectal biopsies were found in ART-treated patients and LTNP.

Conclusions

- Our data demonstrate that long-term early treated patients have smaller HIV-1 reservoir size in PBMCs as compared to patients treated during chronic infection, however, not reaching levels found in LTNP. Interestingly, the reservoir dynamics (2-LTR and usRNA) as well as the CD4/CD8 ratio in early treated patients are not different from LTNP.
- Our results support early ART initiation in terms of achieving low levels of viral reservoir, even though it is on its own not capable of reducing the reservoir size to the levels found in LTNP, suggesting that additional interventions will be needed to achieve a functional cure in the setting of early treatment.

Acknowledgements

- We thank the study participants for their essential contribution as well as the financial contributors: