EVALUATING BIOMARKERS FOR HIV REBOUND DURING TREATMENT INTERRUPTION

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BACKGROUND

Validated biomarkers to evaluate HIV-1 cure strategies are currently lacking, therefore requiring analytical treatment interruption (ATI) in study participants, potentially impacting their health.

We assessed these patients safety concerns by evaluating viral reservoir size in blood and inflammatory levels in the brain.

Furthermore, restriction factor (RF) expression levels and cell-associated (CA) HIV-1 RNA transcripts were assessed as potential biomarkers for predicting viral rebound

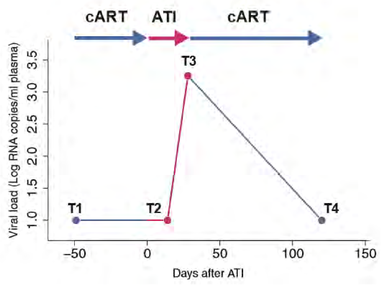


Figure 1. Schematic overview of the study set-up. PBMCs were collected at 4 different time points (T1-T2-T3-T4). CSF was collected at two time points (T1-T3). T1 represents the sampling under cART (baseline; undetectable VL); ATI occurs at D0; T2 represents 7-15 days after ATI (undetectable VL); At T3 viral rebound occurs (detectable VL); T4 represents a time point after restart cART (approximately 3 months; undetectable VL).

METHODS

In the HIV-STAR study (NCT02641756), we collected peripheral blood mononuclear cells (PBMC), plasma and cerebrospinal fluid (CSF) from 11 participants at 4 time-points on-and off-treatment. Total and integrated HIV-1 DNA, CA HIV-1 RNA transcripts and restriction factors (RF) expression were measured. Markers of neuro-inflammation and neuronal injury were measured in CSF and immune activation was assessed in plasma and CSF.

Monitored ATI are safe in terms of HIV-1 reservoir stability and neuro-inflammation.

Expression of restriction factors and HIV RNA transcripts after ATI might serve as a biomarker for viral rebound.

1. Measure the stability and dynamics of the HIV-1 reservoir.
2. Measure expression of RF, Interferon stimulating genes (ISGs) and co-factors.
3. Study neuro-inflammation on ART and at viral rebound in CSF and plasma.

- Total and integrated HIV-1 DNA and RNA transcripts were measured in PBMCs at T1->T4
- Quantitative real-time PCR was performed on RNA extracted from PBMCs at T1-> T4. RF APOBEC3G, SLFN11, SAMHD1, MX2, BST2, TRIM5 and PAF-1, ISGS IFIT and MX1 and co-factors NLRX1 and PSIP1 were measured
- NfL is a sensitive indicator of CNS injury and was measured in CSF at T1 and T3.
- YKL-40 is secreted by activated macrophages and is a marker for neuro-inflammation. It was measured in CSF at T1 and T3.
- Neopterin, Kynurenine and Kynurenine/Tryptophan ratio were measured as markers for immune activation in plasma.

RESULTS

- Reservoir markers such as total HIV-1 DNA, integrated HIV-1 DNA and CA viral RNA transcripts did not differ pre- and post-ATI (T1-T4) (Figure 2).
- No significant increase of neuronal injury (NfL) or inflammation (YKL-40) in CSF was observe between baseline and viral rebound. Markers of immune activation in plasma did not increase during ATI (data not shown).
- RF SLFN11 and APOBEC3G increased after ATI before viral rebound was observed (Figure 3).
- Tat-Rev transcripts were increased preceding viral rebound after interruption (Figure 3).

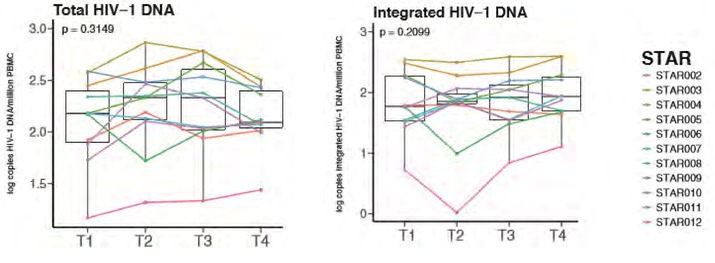


Figure 2: No significant difference in total and integrated HIV-1 DNA measurements in PBMCs between T1 and T4 was observed (p-value = 0.2061), indicating the HIV-1 reservoir remains stable after ATI.

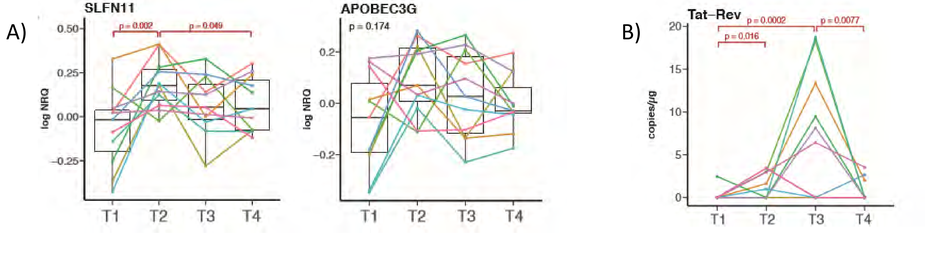


Figure 3: A) Expression of RF SLFN11 and APOBEC3G: There was a significant (SLFN11) or borderline significant (APOBEC3G) increase in expression of these RF between T1 and T2; B) Tat-Rev transcripts also increased significantly between T1 and T2 and before viral rebound, which occurred at T3. This is in contrast to other viral RNA transcripts measured (TAR, long LTR, PolyA, Pol (data not shown)). Legend as represented in Figure 2.

CONCLUSIONS

ATI did not increase viral reservoir size, nor did it reveal signs of increased neuronal injury or inflammation, suggesting that these well-monitored ATIs are safe. Elevation of Tat-Rev transcription and induced expression of RF SLFN11 and APOBEC3G after ATI prior to viral rebound indicates that these markers could be used as potential biomarkers predicting viral rebound.

ADDITIONAL KEY INFORMATION

Published data:

Description of the cohort and source of viral rebound: doi: 10.1016/j.chom.2019.08.003

Data presented in this poster: doi:10.1093/jac/dkaa003

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