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Host Transcriptomic Determinants of HIV Persistence *in vivo*

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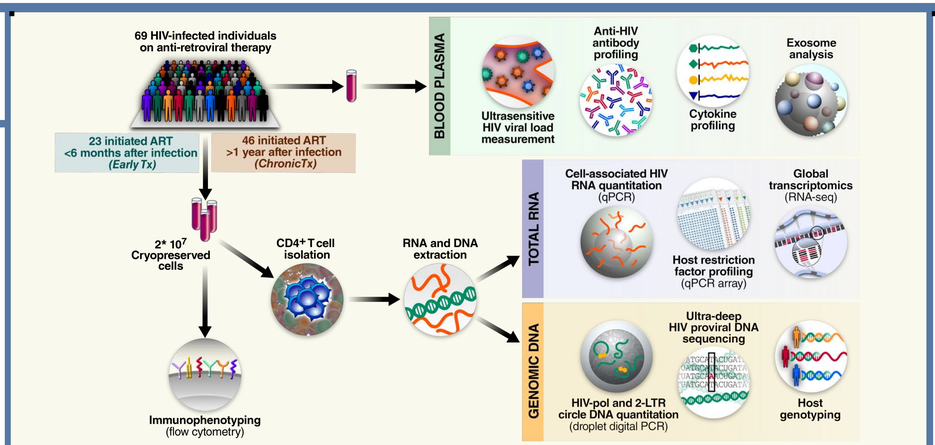
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BACKGROUND

- Data are limited describing the role of the host molecular and immunologic environment in governing HIV latency in the setting of antiretroviral therapy (ART).
- A comprehensive understanding of host and viral factors driving the formation and maintenance of the latent HIV reservoir will guide the development of effective curative strategies.
- We performed global transcriptomic profiling of CD4+ T cells from 69 HIV-infected individuals on suppressive ART to identify novel host determinants of HIV persistence.

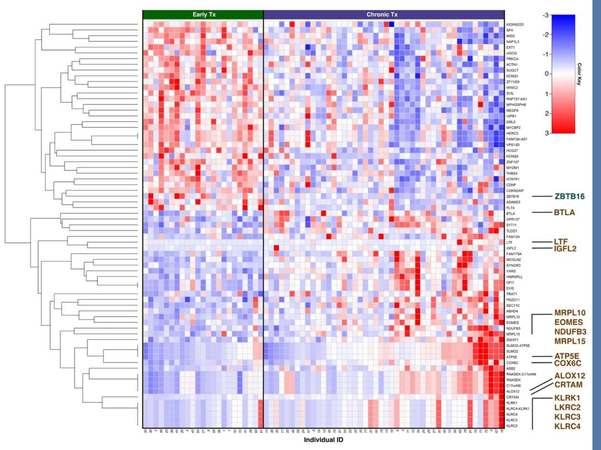


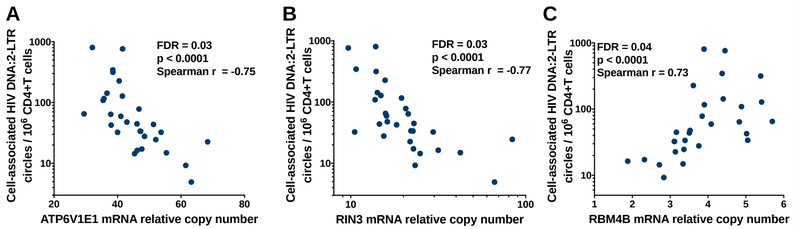
False discovery rate (FDR) was used to correct for multiple comparisons in statistical analyses

RESULTS

1) 71 host factors were differentially expressed in the setting of early ART administration.

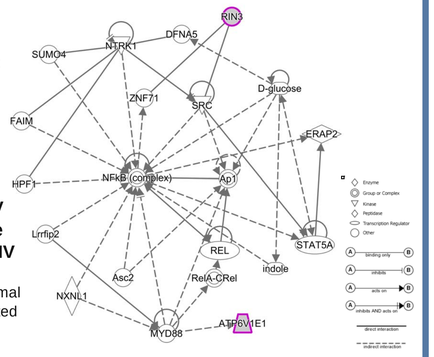
- ZBTB16/PLZF (Transcriptional modulator of innate T cell maturation) expression exhibited the most pronounced elevation in the Early Tx group.
- Elevated expression of several immune dysfunction and exhaustion markers was associated with Chronic Tx status.
- Notably, associations between ART initiation timing and cellular energy metabolism and oxidative stress responses were observed.

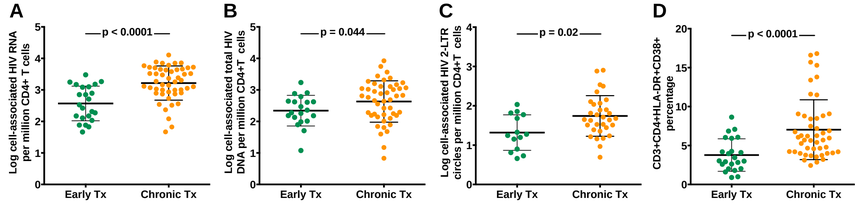




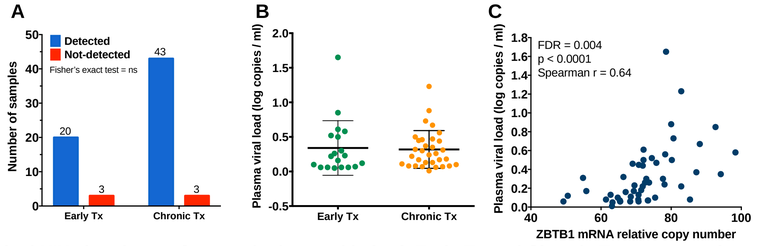
2) Select host factors were associated with levels of episomal HIV DNA during suppressive ART. Expression levels of three host factors in the Chronic Tx group were associated with levels of CD4+ T cell-associated HIV 2-LTR circles, a potential marker of ongoing replication, abortive integration, or cell proliferation.

3) Host genes associated with episomal HIV DNA levels are embedded in an interactome containing NF-κB and AP-1, regulators of HIV transcription. Integrative bioinformatic analysis revealed that two of three genes correlated with episomal HIV DNA levels (gray with purple borders) are connected with the NF-κB and AP-I transcription factors.





4) CD4+ T cell-associated HIV RNA and DNA levels and immune activation were significantly lower in individuals who initiated ART during early versus chronic infection.



5) Residual HIV viremia was frequently detected in both Early Tx and Chronic Tx groups and was significantly associated with expression of the host transcriptional modulator ZBTB1. The level of viremia was similar in those treated during early versus chronic infection, despite lower levels of immune activation and CD4+ T cell-associated HIV RNA and DNA levels in those treated early. Residual viremia was strongly correlated with expression of the host transcriptional mediator ZBTB1 in CD4+ T cells.

CONCLUSIONS

- Early ART initiation may be associated with maturation of innate T cells and prevention of immune dysfunction, providing another possible justification for universal early administration of ART.
- Delayed ART initiation may result in previously unrecognized alterations in cellular energy metabolism and mitochondrial function, affecting HIV persistence and immunopathogenesis.
- Select host factors are associated with episomal DNA levels during suppressive ART; their role in establishment and maintenance of latency should be explored.
- Transcriptional modulator ZBTB1 may be a determinant of residual viremia during ART.
- Comprehensive transcriptomic profiling of well-characterized cohorts yields valuable insights into determinants of viral persistence, providing potential targets for pharmacological manipulation.