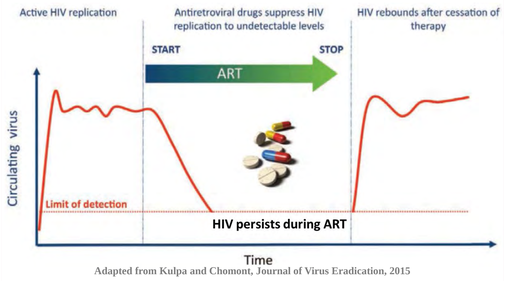
The Impact of ART Duration on the Infection of T cells within Anatomic Sites

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Introduction



Adapted from Kulpa and Chomont, Journal of Virus Eradication, 2015

ART is not curative. HIV-1 persists during effective therapy and HIV-1 rebounds to pre-treatment levels when ART is stopped. Thus, it is important to determine the following:

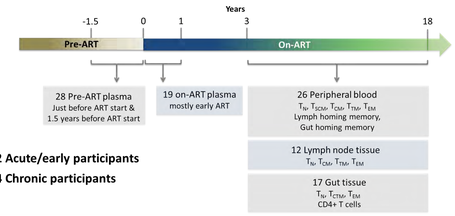
- **The cellular mechanisms contributing to HIV-1 persistence during therapy**
- **The anatomic and cellular sources that can contribute to HIV-1 viremia during ART and viral rebound when ART is stopped.**

Questions to be addressed

1) **What is the impact of treatment duration on the intracellular HIV-1 reservoir?**
2) **What cellular mechanisms contribute to the maintenance of the HIV-1 reservoir in cells?**
3) **What is the anatomic and the cellular source of plasma virus during effective antiretroviral therapy (ART)?**

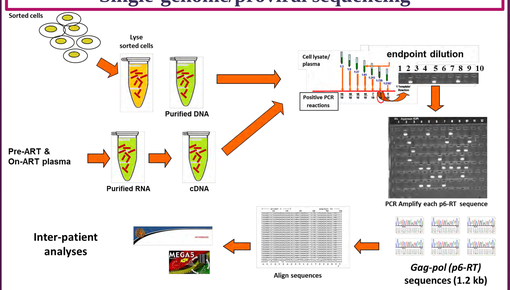
Materials/Methods

Clinical samples

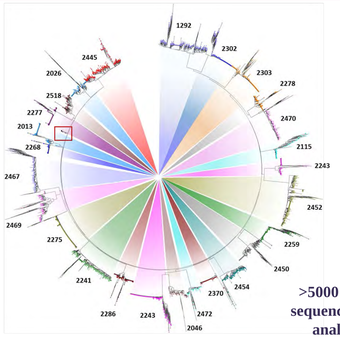


12 Acute/early participants
14 Chronic participants

Single-genome/proviral sequencing



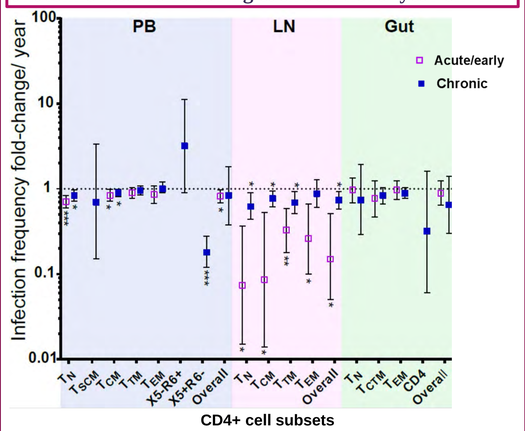
Total number of HIV-1 sequences obtained



>5000 HIV-1 sequences were analysed

Results

Dynamics of infection frequency in cellular and anatomic reservoirs during each additional year on ART



The changes of infection frequencies are indicated as a fold-change per year, where a fold-change greater than 1 indicates an increase and less than 1 indicates a decrease in the frequency of HIV-1 infected cells during each additional year on ART.

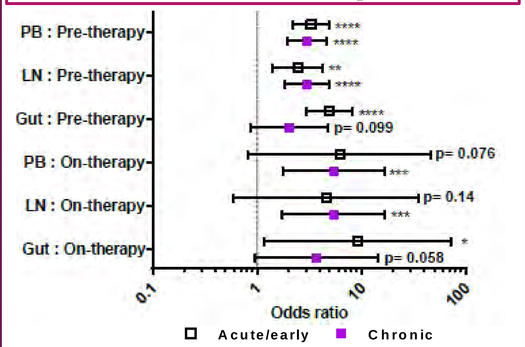
T_{EM} derived from peripheral blood (PB) obtained from participants who initiated ART during chronic infection:

Infection frequency fold-change = 1.0 per year
95% Confidence intervals= 0.9-1.2

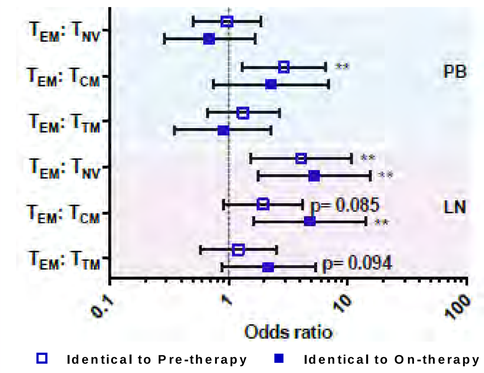
Overall, 5-fold decrease of infection frequencies in lymph node (LN) of participants treated during acute/early infection compared to those treated during chronic infection.

2 to 11 fold decrease in infection frequencies in LN-derived CD4+ T cells of participants treated during acute/early infection compared to those treated during chronic infection.

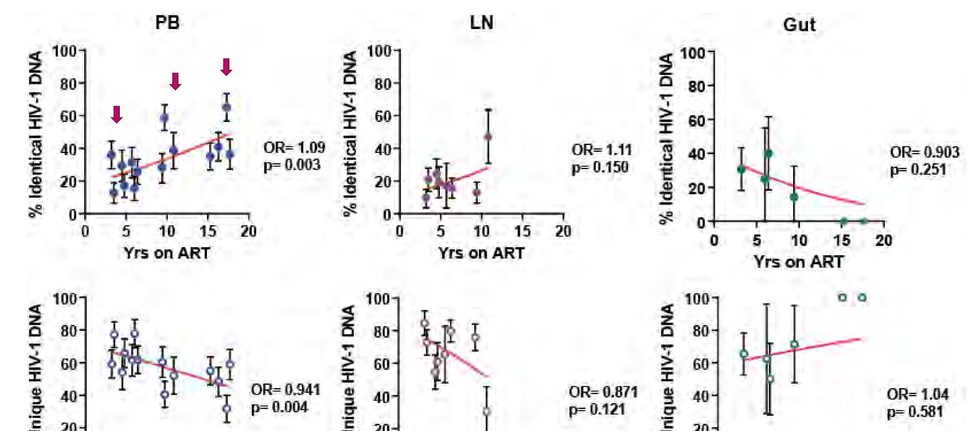
Pre- and on-therapy plasma samples contain few defective HIV-1 RNA sequences

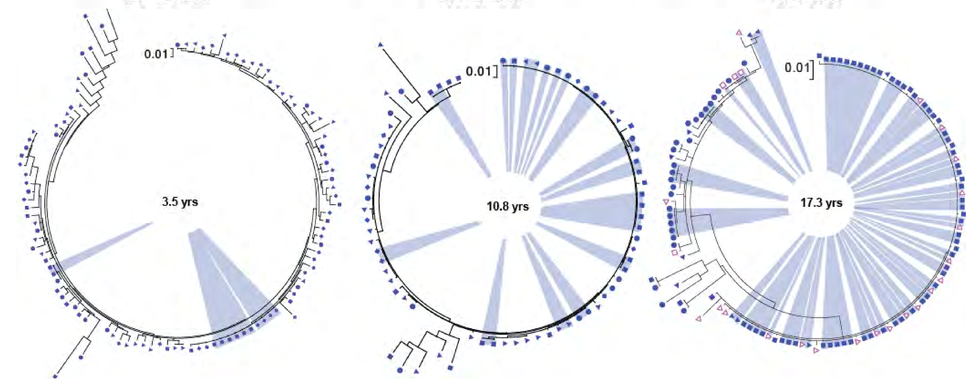


HIV-1 sequences from LN-derived T_{EM} cells more often genetically identical to pre- and on-therapy plasma viral sequences



The impact of ART duration on genetically identical and unique HIV-1 DNA sequences in anatomic regions



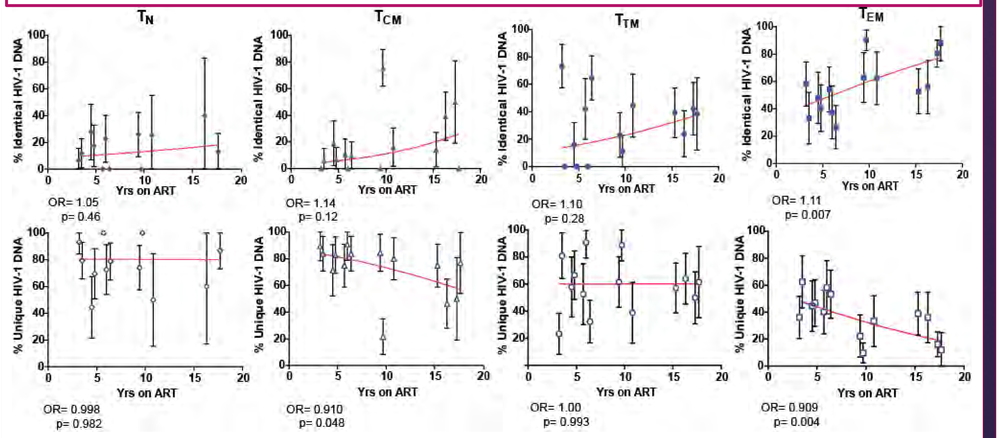


Expansions of identical HIV-1 DNA sequences increased but the proportion of unique HIV-1 DNA sequences decreased in PB during each additional year of ART.

The odds that an HIV-1 DNA sequence was from an identical sequence expansion increased where as the odds that a viral sequence was genetically unique decreased in PB during each additional year on ART.

The phylogenetic analysis of HIV-1 DNA sequences derived from PB showed increasing expansions of identical HIV-1 DNA sequences as ART duration increases.
The phylogenetic trees of 3 time points, indicated by red arrows in the top left panel, are shown.

The impact of ART duration on genetically identical and unique HIV-1 DNA sequences in PB-derived CD4+ cell subsets



Expansions of identical sequences increased but the proportion of unique HIV-1 DNA sequences decreased in T_{EM} during each additional year of ART.

Conclusions

- **Proliferation of HIV-infected T cells increased the proportion of identical HIV DNA sequences within peripheral blood over 3-18 years of therapy, and the EM cells were the main contributor.**
  - This did not increase the HIV reservoir size in EM cells, indicating these cells are regulated by strict homeostasis with the clonal expansion of particular EM cells containing identical HIV-1 sequences (possibly in response to an antigen) and the reduction/extinction of EM cells containing unique HIV-1 sequences.
- **The reservoir size in the LN decreased in participants who started ART during acute infection.**
  - This indicates that early ART initiation promotes T cell reconstitution in the LN.
  - **Pre-ART and early on-ART plasma samples more often contained genetically intact HIV sequences than peripheral blood and tissues.**
- **HIV sequences from effector memory CD4+ T cells derived from lymph node were genetically similar to pre-ART and early on-ART plasma.**
  - Indicating that effector memory CD4+ T cells derived from lymph node are capable of encoding infectious virus.

Acknowledgments

We acknowledge with gratitude the participants of this study.

ARCHE amfAR Research Consortium on HIV Eradication

Delaney AIDS Research Enterprise DARE to find a cure

Australian Government
National Health and Medical Research Council

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