Abstract # 335

# TCM CD4 T cell infection associates with immune failure and HIV persistence on ART


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## Introduction

- Morbidity and mortality especially from severe non-AIDS conditions are increased for individuals with persistently low CD4 T cell counts (immune non-responders, INR) and/or persistent immune activation despite virologic suppression on antiretroviral therapy (ART)
- Current treatments to increase CD4 T cell counts or reduce immune activation have been unable to reduce morbidity or mortality

- **Objective:** To determine if differential infection of CD4 T cell subsets could further explain divergent CD4 response to ART and maintenance of the latent HIV reservoir

## Methods

- 30 HIV-positive participants were enrolled in a cross-sectional cohort based upon their CD4 response to ART-mediated virologic suppression
- Immunologic responders (IR) were defined as having CD4 counts >500 cells/µL < 2 years after ART initiation
- INR were defined as having CD4 counts <350 cells/ µL > 2 years after ART initiation
- The frequency of peripheral blood mononuclear cells harboring total and integrated HIV DNA were measured in sorted naïve (N), central memory (CM), transitional memory (TM), and effector memory (EM) CD4 T cells for INR and compared to IR
- Immunological parameters - including frequencies of CD4 and CD8 T cells and of their N (CD45RA+CCR7+CD27+), CM (CD45RA-CCR7+CD27+), TM (CD45RA-CCR7-CD27+), and EM (CD45RA-CCR7-CD27-) subsets, their levels of activation/proliferation, and the expression of immune checkpoint molecules - were analyzed by flow cytometry

## Results

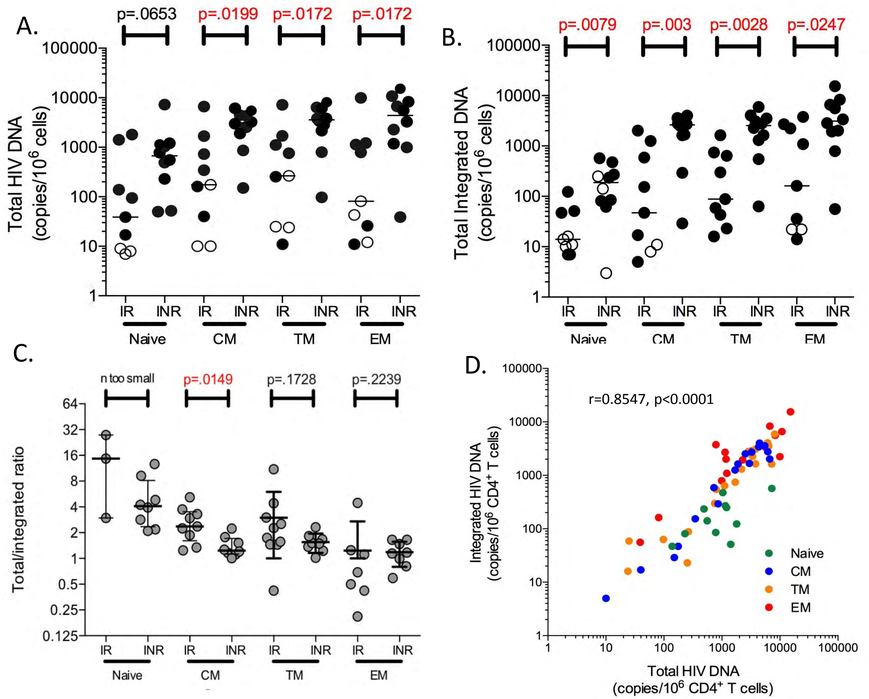
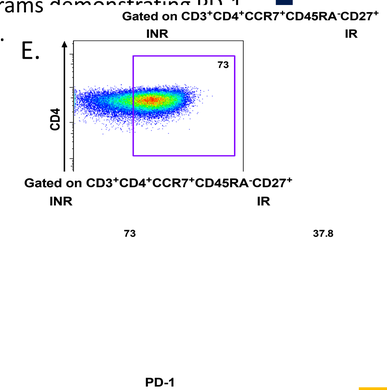



Figure 1. (A) Total HIV DNA, (B) integrated HIV DNA and (C) total/integrated HIV DNA ratio for immunologic responders (IR) and immunologic non-responders (INR) on antiretroviral therapy within naïve, central memory (CM), transitional memory (TM) and effector memory (EM) CD4 T cell subsets. (D) Correlations between Total and Integrated HIV DNA in the different CD4+ subsets. Open symbols depict undetectable HIV DNA. The limit of detection based on cell input is plotted. (E) Flow diagrams demonstrating PD-1 expression for CD4 cells gated on CD45RA-CCR7+CD27+ (CM).

Table 1. IR and INR Immunophenotyping.

| Measurement | IR Means ± SEM | INR Means ± SEM | P-value |
|---|---|---|---|
| Bulk CD4⁺ Ki-67⁺ | 1.363 ± 0.2089 | 2.438 ± 0.2726 | 0.0088 |
| CD4⁺ CM Ki-67⁺ | 1.700 | 2.910 | |
| CD4⁺ CD38+HLA-DR⁺ | 2.640 | 3.740 | |
| CD8⁺ CD38+HLA-DR⁺ | 5.410 | 10.30 | |
| Bulk CD4⁺ PD-1⁺ | 28.53 ± 2.543 | 47.55 ± 4.9 | |
| CD4⁺ CM PD-1⁺ | 22.50 | 53.70 | |
| Bulk CD4⁺ TIGIT⁺ | 4.943 ± 0.8347 | 8.354 ± 1.1 | |
| CD4⁺ CM TIGIT⁺ | 6.470 | 11.30 | |




## Key Findings

- Median age was 46 years, 90% were male, 82.8% were African-American
- The frequency of cells harboring total and integrated HIV DNA were lowest for N CD4 cells while the other subsets were equivalent
- Total and integrated HIV DNA levels were highly correlated (r=0.9240; P<0.0001) and significantly higher for INR than IR in all CD4 T cell subsets (nearly all with P<0.05)
- Total/integrated (T/I) HIV DNA ratio was lowest for EM CD4 cells and highest for N CD4 cells, consistent with a higher potential for HIV integration within EM CD4 T cells
- Interestingly the T/I ratio was significantly lower in INR than IR only for CM CD4 cells (p=0.0149)
- Levels of proliferation (Ki-67+) and expression of immune checkpoint molecules previously associated with HIV persistence (PD-1 and TIGIT) were significantly higher in both bulk and CM CD4 T cells of INR.

## Conclusions

- INR have higher levels of HIV DNA in all subsets when compared to IR, thus highlighting a link between the lack of immune reconstitution and viral persistence
- INR have twice the expression of PD-1 and TIGIT in CM cells

more, INR having a lower T/I ratio only in central
CD4 cells as compared to IR suggests a higher
l for proviral integration and productive infection of
ral memory CD4 cells as an important virologic
of INR


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