Abstract # WEPEB0534

TCM CD4 T cell infection extent before ART associated 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 prior to initiating ART could further explain divergent CD4 response to ART and maintenance of the latent HIV reservoir

Methods

- 30 HIV-positive participants were categorized into two groups based upon their CD4 response to ART-mediated virologic suppression and provided peripheral blood mononuclear cells (PBMCs) at time points before and after ART initiation. Median age of the cohort was 46; 90% were male, 82.8% were African-American
- 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 PBMCs 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 proliferation, and the expression of immune checkpoint molecules (ICM) - were analyzed by flow cytometry

Results

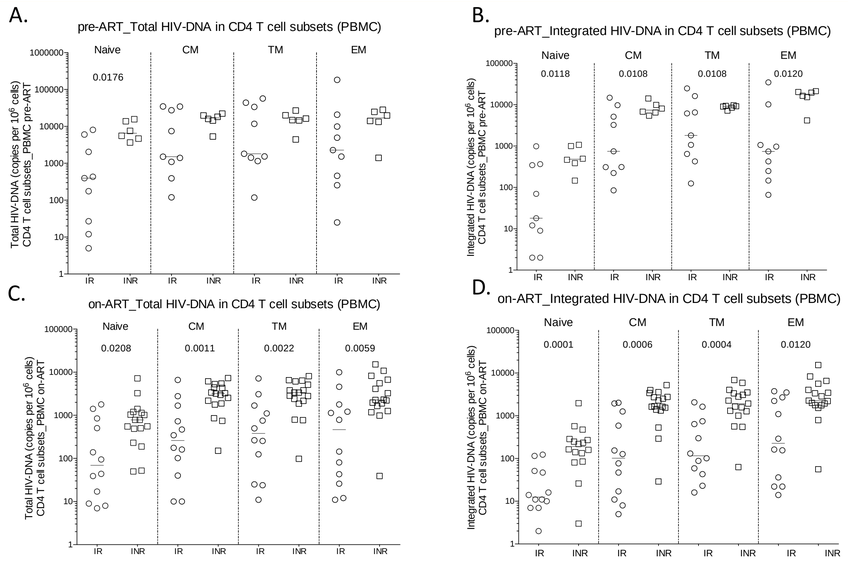

Figure 1. Total (A,C) and integrated (B,D) HIV DNA pre-ART (A,B) and on ART (C,D) for immunologic responders (IR) and immunologic non-responders (INR) within naïve, CM, TM and EM CD4 T cell subsets.

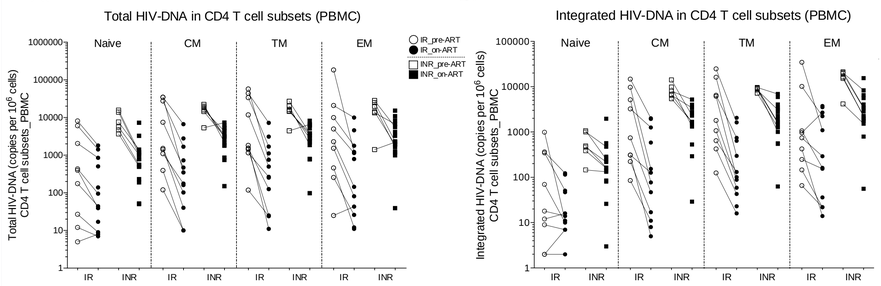

Figure 2. Total (A) and integrated (B) HIV DNA trajectories for IR pre-ART (open circles) and post-ART (shaded circles) compared to INR pre-ART (open squares) and post-ART (shaded squares) within naïve, CM, TM and EM CD4 T cell subsets.

- Total and Integrated HIV-DNA content in all CD4 T-cell subsets were significantly higher (P<0.01) prior to ART and on-ART in INR than IR (**Fig. 1**)
- HIV-DNA levels in IR were significantly reduced (P<0.01) on-ART compared to pre-ART in all CD4 T-cell subsets whereas levels were more stable in INR CM & TM cells between post-ART and pre-ART time points (**Fig. 2**). Thus, long-lived CM and TM cells with HIV-DNA persist longer in INR compared to IR on ART.

Results

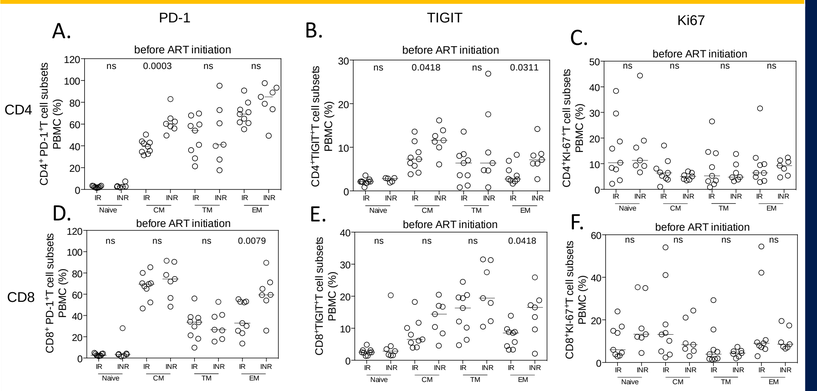

Figure 3. PD-1 (A,D), TIGIT (B,E), and Ki67 proliferation level (C,F) of blood CD4 (A-C) and CD8 (D-F) T cell subsets before ART initiation in IR and INR.

- Expression of ICM such as: PD-1 and TIGIT were significantly increased in memory CD4 T-cells (but not CD8) of INR (P<0.05) before ART (but not during ART, not shown), despite similar levels of proliferation

Conclusions

- Compared to IR, INR demonstrate higher levels of ICM expression (pre-ART) and viral burden (both prior to and on-ART) in all memory CD4 T cell subsets.
- **CM and TM CD4 T-cells harboring HIV-DNA persist longer during ART in INR.**
- These data link levels of CD4 T-cell infection prior to ART, particularly in long-lived CD4 T-cell subsets, with immune recovery and HIV persistence

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