# Viral and Immune Characteristics of HIV Post-Treatment Controllers in ACTG Studies

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## Background

- HIV post-treatment controllers (PTCs) are individuals who can maintain low levels of viremia after ART discontinuation
- Little is known about PTCs who were treated during chronic infection
- Understanding the mechanisms of HIV control has implications for the design of novel strategies for HIV remission

## Objectives

1. **To identify PTCs in prior ACTG ATI trials**
2. **To assess the virologic and immunologic predictors of post-treatment control**

## Methods

### Data Sources, Study, and Subject Selection

- 8 ACTG ATI studies - 497 total participants with virologic suppression underwent analytic treatment interruption (ATI)
- Identified participants who maintained virologic suppression (≤400 copies/mL) for ≥24 weeks (short-term viral blips not exclusionary)
- 16 total participants are PTCs (3.2% of entire cohort)
  - 6/91 (6.6%) treated during acute infection
  - 10/406 (2.5%) treated during chronic infection

**Table 1: Time Points**

| PTCs | Non-PTC Controls |
|---|---|
| Baseline (pre-ATI) | Baseline (pre-ATI) |
| Early ATI (within 12 weeks) | Early ATI (after viral rebound, median 4 weeks post-ATI) |
| Late ATI (median 96 weeks) | Late ATI (Only in a subset, ~12-16 weeks post-ATI) |

- Total HIV DNA and usCA-RNA measured in PBMCs by qPCR
  - Total cell numbers evaluated with CCR5 qPCR
  - RNA integrity evaluated by total RNA and IPO8 RNA quantification
  - Samples below the LOD analyzed with an inferred value of ½ LOD
- T cell ICS assay
  - 1M PBMC cells were stimulated with 2 µg/ml Gag peptide pool for 14hours (overlapping 15- to 20-mer peptides spanning the entire clade B consensus sequence of the HIV-1 *gag* sequence)
- NK cell ICS assay
  - 1M PBMC cells were stimulated with K562 cells at E:T ratio =5:1 for 6 hours

### Statistical Analysis

- Exact Cochran-Mantel-Haenszel test stratified by acute/chronic treatment for categorical variables
- Separate analysis of acute/chronic-treated groups by Exact Wilcoxon rank sum or signed-rank tests

## Results

**Table 2: Participant Characteristics**

| | Early-Treated PTCs (N=6) | Early-Treated Controls (N=16) | Chronic-Treated PTCs (N=10) | Chronic-Treated Controls (N=20) | All PTCs (N=16) | All Controls (N=36) |
|---|---|---|---|---|---|---|
| Male, % | 83% | 94% | 70% | 70% | 75% | 82% |
| Age, median | 35 | 36 | 42 | 44 | 42 | 41 |
| Baseline CD4+ count | 871 | 818 | 942 | 795 | 894 | 795 |
| Years on ART | 1.0 | 1.0 | 5.5 | 5.5 | 4.3 | 2.5 |
| Race | | | | | | |
| White, % | 83% | 75% | 50% | 55% | 63% | 66% |
| Black, % | 17% | 6% | 30% | 25% | 25% | 16% |
| Hispanic, % | | 19% | 20% | 20% | 13% | 18% |

**Figure 1: VLs of PTC and Non-PTC Controls**

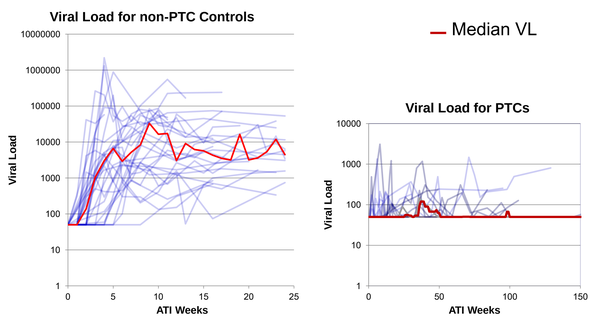
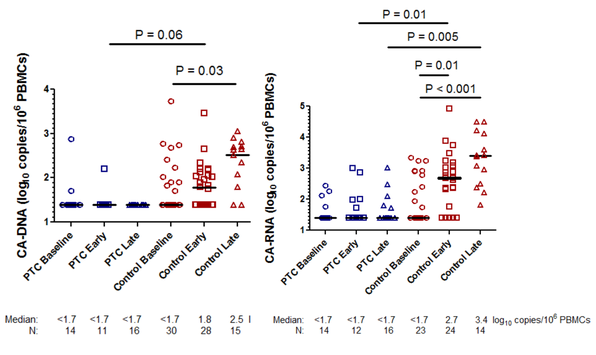
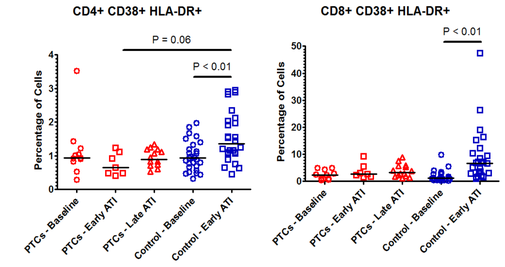



**Figure 2: CA-DNA and CA-RNA (All Participants)**



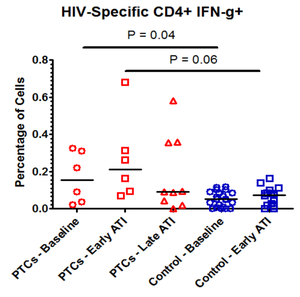

- Detectable CA-RNA and DNA does not preclude post-treatment control (Figure 2)
- Increase in post-ATI CA-RNA and DNA levels in non-PTC control participants, but not in PTCs

**Figure 3: CD4+ and CD8+ Cell Activation**



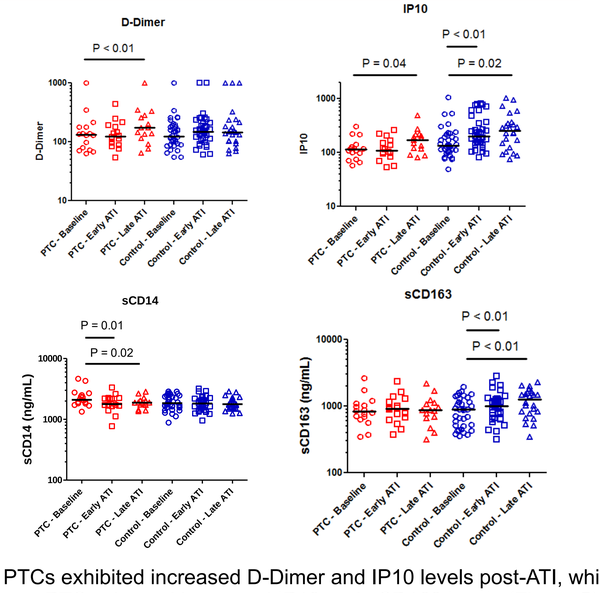

- No baseline differences in T cell activation between PTCs and non-PTCs, but non-PTCs show significantly increased cellular activation after ATI (Figure 3)

**Figure 4: HIV-Specific CD4+ Cell Activity**



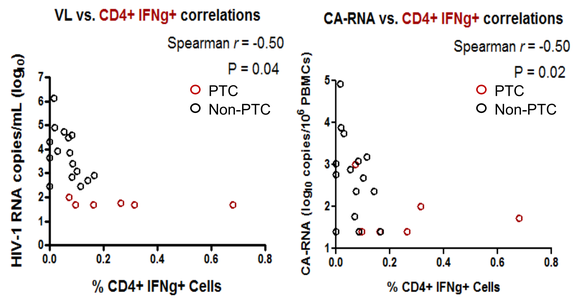

- Higher levels of HIV-specific CD4+ IFN-g-producing cells in PTCs at baseline (Figure 4)

**Figure 5: Soluble Markers of Inflammation**




- PTCs exhibited increased D-Dimer and IP10 levels post-ATI, while non-PTCs showed increased IP10 and sCD163 levels (Figure 5)

**Figure 6: Factors Correlated with Early post-ATI CA-RNA and VL**




- Post-ATI VL and CA-RNA levels inversely correlated with HIV-specific CD4+ IFN-g activity (Figure 6).

## Conclusions

- PTCs may be more frequently found in participants treated during acute infection, but can be identified in those treated during chronic infection
- Detection of CA-RNA and DNA pre-ATI does not preclude post-treatment control
- In contrast to non-PTCs, no significant change in CA-RNA and DNA HIV in PTCs after ATI
- Higher levels of baseline HIV-specific CD4+ IFN-g-producing cells in PTCs
- CD4+ IFN-g-producing cells after ATI associated with VL and CA-RNA levels
- Increases in IP10 and D-Dimer levels in PTCs after ATI
- Increases in IP10 and sCD163 levels in non-PTCs after ATI

## Implications

- PTCs can be identified in patients treated during both acute and chronic infection
- Detectable HIV expression and viremia in PTCs point to immune-mediated control and/or inefficient viral replication
- HIV-specific CD4+ IFN-g-production may contribute to viral control post-ATI

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