Abstract # 206

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CMV Replication During Primary HIV Infection is Associated with T-cell Dysfunction

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Background

- HIV-infected men who have sex with men (MSM) are nearly universally co-infected with CMV.
- Subclinical CMV replication is associated with T cell dysfunction and higher levels of HIV RNA transcription.

Objective

- **To determine the effect of persistent CMV exposure during primary HIV infection on viral specific immune responses and immune exhaustion.**

Methods

- **Study Cohort**: 53 ART-naïve early HIV-infected, CMV seropositive MSM and 19 'at-risk' HIV uninfected, CMV seropositive adults.
- **Data generated:**
  - Intracellular Interferon (INF)-γ and Granzyme B expression after stimulation with inactivated CMV and HIV lysates (by flow cytometry).
  - PD-1 expression on $CD4^+$ and $CD8^+$ T cells (by flow cytometry).
  - Seminal CMV DNA (by Real Time-PCR).

Figure 1: Early HIV-**infected vs 'at Risk' HIV negatives**

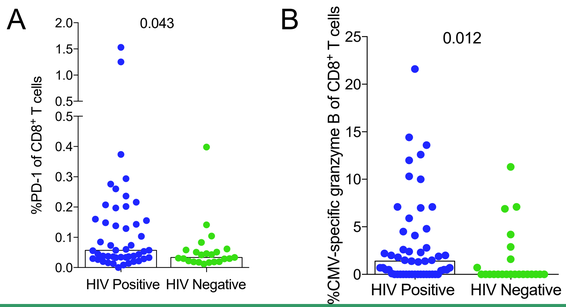


Figure 1. HIV+ individuals have higher PD-1 expression (Panel A) and higher CMV-specific Granzyme production on $CD8^+$ T cells (Panel B).

Table 1: Characteristics of Study Participants

	HIV-infected CMV Shedder (n=31)	HIV-infected CMV Non-Shedder (n=22)	At-Risk HIV Negatives (n=19)	p-value
Age (years), median [IQR][1]	43.6 [35 – 52]	46.6 [38-53]	38.5 [30-41]	0.046
Race (%)[3]			ND	ND
White	20 (67%)	12 (55%)		
Black	1 (3%)	2 (9%)		
Hispanic	4 (13%)	5 (23%)		
Asian	1 (3%)	1 (5%)		
Other	4 (13%)	2 (9%)		
CD4 Count (cells/uL), median [IQR][3]	548 [451.3 – 689.5]	515.5 [365.6-714.8]	ND	0.79
CD4/CD8 Ratio, median [IQR][3]	0.44 [0.32-0.82]	0.48 [0.12 – 0.77]	ND	0.95
Plasma HIV Viral Load (log_{10}copies/uL), mean [IQR][3]	5.00 [4.40-5.53]	4.87 [4.34 – 5.63]	NA	0.89
Seminal CMV level (log_{10}copies/uL), mean [IQR][2]	4.80 [3.95 – 5.63]	nd	2.36 [0 – 0]	<0.001

[1]P-value for Age determined by One way ANOVA.[2]When values were 0, values were set to 0.1 prior to log transformation. P-value for seminal CMV viral load determined by Kruskal-Wallis test. [3]P-value otherwise determined by Wilcoxon Rank test. nd: not detectable.

Figure 2: CMV Shedders vs Non-Shedders

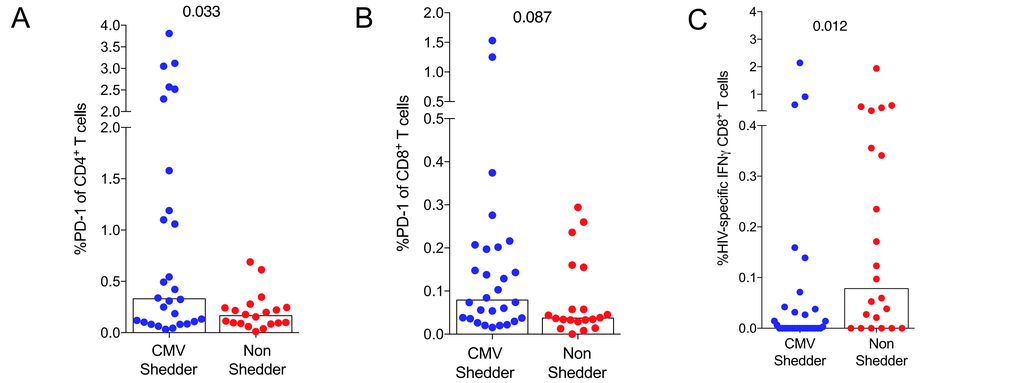


Figure 2. Compared to non-CMV shedders, HIV-infected CMV-shedders have higher PD-1 expression on $CD4^+$ T cells (Panel A), higher PD-1 expression on $CD8^+$ T cells (Panel B) and significantly reduced IFN-γ production on $CD8^+$ T cells following stimulation with inactivated HIV virions (Panel C).

Results

- CMV DNA was detected more often in HIV-positive compared to HIV-negative individuals (58% versus 10.5%, P<0.001).
- Compared to no HIV, early HIV-infected participants have:
  - Increased PD-1 expression on $CD8^+$ (P=0.043).
  - Greater Granzyme B production by $CD8^+$ after *ex vivo* stimulation with CMV lysate (P=0.012)
  - No difference in CMV- specific immune response measured by IFNg.
- Among HIV-positives, shedding of CMV DNA is associated with:
  - Increased PD-1 expression on $CD4^+$ T cells (P=0.033).
  - Increased PD-1 expression on $CD8^+$ T cells (P=0.087).
  - Reduced HIV-specific $CD8^+$ T cells response (P=0.012).
  - No differences in CMV-specific immune response.
- HIV-infected individuals with no CMV shedding had similar (or lower levels) of PD-1 on $CD8^+$ compared to HIV-uninfected.

Conclusions

- Subclinical CMV replication during early HIV-infection (but not HIV infection alone) is associated with T cell exhaustion and with impaired HIV-specific $CD8^+$ T cell responses**.**
- CMV may be the "smoking gun" further perturbing immune responses during Primary HIV infection.
- These observations might explain the connections between CMV replication and higher levels of seminal HIV shedding, increased peripheral HIV DNA levels and faster HIV disease progression previously described by our group and others.

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