Poster Session # P-F2
Abstract # 508

21th Conference on Retroviruses and Opportunistic Infections

March 3- 6, 2014
Boston, MA, USA

Seminal CMV Replication, Immune Activation and Higher Proviral HIV DNA during Suppressive ART

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Background

CMV replication is:

- Frequent in the genital tract of HIV infected men
- Associated with increased immune activation and HIV disease progression.

Objective

To determine if CMV-associated immune activation influences the size of the HIV DNA reservoir during suppressive antiretroviral therapy (ART).

Methods

- Paired blood and semen samples from 53 HIV infected men who have sex with men on long-term ART were studied.
- Levels of CMV DNA were measured in seminal plasma by RT-PCR.
- Total HIV DNA (pol), 2-long terminal repeat (2-LTR), and cellular HIV RNA (unspliced gag and multiply-spliced encoding for tat/rev) were measured in peripheral blood mononuclear cells (PBMC) by droplet digital PCR.
- Levels of CD4$^+$ and CD8$^+$ T-cell immune activation (CD38$^+$HLA-DR$^+$) and proliferation (Ki67$^+$) were determined from frozen PBMC by multicolor flow-cytometry.
- Associations between levels of proviral HIV DNA, cellular HIV RNA, immune activation and proliferation in blood, time on ART, CD4$^+$ T-cells counts and the presence of CMV replication in semen were investigated using univariate and multivariate parametric and non-parametric statistics.

Results

- CMV DNA was detected in 44% of seminal samples
- Compared with no CMV, detectable CMV DNA in semen was associated with the following levels in peripheral blood:
  - Increased CD4$^+$ T-cell proliferation (Ki67$^+$) (P=0.01) FIGURE 1A
  - Increased CD4$^+$ T-cell activation (CD38$^+$HLA-DR$^+$) (P<0.01) FIGURE 1B
  - Higher levels of proviral HIV DNA (2.84 versus 2.11 $\log_{10}$ copies/million CD4$^+$, P<0.05) FIGURE 1C
  - Higher levels of cellular multiply-spliced HIV RNA (P=0.04)
- Levels of unspliced HIV RNA, 2-LTR, average cellular transcription (i.e. cellular HIV RNA/DNA ratio) and CD8$^+$ T-cell activation were not different between men with and without seminal CMV.
- A trend towards a correlation was found between seminal CMV DNA and CD4-associated HIV DNA levels in peripheral blood (P=0.06, r= 0.26).
- Among subjects with detectable CMV in semen, significant correlations were found between HIV DNA levels and frequency of activated (P<0.01, r=0.6) and proliferating peripheral blood CD4+ T-cells (P<0.01, r=0.64). FIGURE 2A-2B
- In multivariate analysis, presence of seminal CMV (P=0.04), and detectable 2-LTR (P<0.01) were independently correlated with higher HIV DNA in PBMC.

Figure 1: Differences in CD4 T-cell Proliferation, Activation and HIV DNA Reservoir, between Subjects with and without Seminal CMV

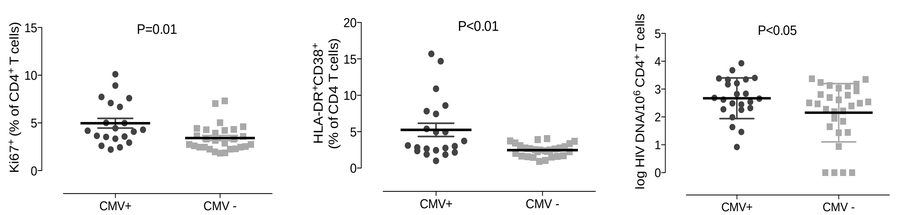
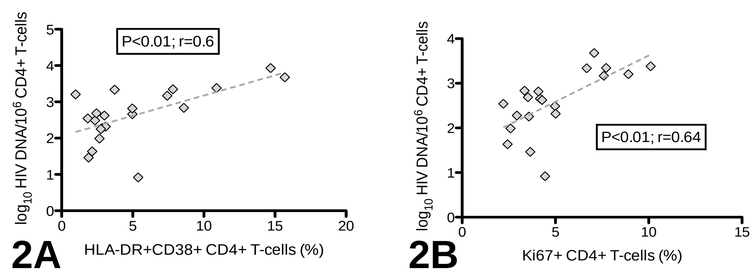


Figure 2: Association between CMV DNA and % of Activated and Proliferating CD4+ T-cells (among CMV shedders)



Conclusions

- **Asymptomatic seminal CMV replication is associated with higher levels of systemic CD4+T-cell immune activation and proliferation and with a greater size of the HIV DNA reservoir.**
- **No difference in average HIV transcription was found between subjects with and without seminal CMV DNA shedding, suggesting that CMV is not directly associated with low-level HIV replication but more likely with homeostatic proliferation of HIV-infected CD4+ T-cells.**
- **Interventions aimed at reducing seminal CMV replication and associated immune activation could be important for HIV curative strategies.**

Acknowledgments

This work was supported by the Department of Veterans Affairs, the James Pendleton Charitable Trust; amfAR grant 108537 with support from FAIR, the US National Institutes of Health (NIH) awards 7UM1AI068636-07, AI090970 (IAVI), AI69432, AI096113, AI043638, MH62512, MH083552, AI100665, AI077304, AI36214, AI047745, AI74621, GM093939AI080353, AI306214 (CFAR), AI27670 (ACTU), and AI064086 (K24 to RHH), AI43638; by a grant from the National Institutes of Health, University of California, San Francisco-Gladstone Institute of Virology & Immunology Center for AIDS Research, P30-AI027763; the California HIV/ AIDS Research Program RN07-SD-702, MC08-SD-700 and EI-11-SD-005; the National Center for Advancing Translational Sciences through UCLA CTSI Grant UL1TR000124 and the National Institute of General Medical Sciences grant GM093939; the Interdisciplinary Research Fellowship in NeuroAIDS R25-MH081482.