# Impact of Partner HIV Status on Immune Activation and Inflammation during Chronic HIV Infection

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## Introduction

In response to pathogen challenge, humans generally experience persistent, low-grade, periodic immune activation and inflammation, which reflects that anti-microbial immunity has been mounted and should be beneficial. Although these immune processes are generally considered to be protective to the host during most other infections, this paradoxically also exacerbates pathogenesis during HIV infections by resulting in a constant supply of activated HIV target cells and studies have demonstrated that the level of systemic T-cell activation predicted worse disease course for those infected.

The infection and depletion of CD4⁺ T-cells characterize the most influential event in the pathogenesis of HIV infection, with the main cellular target during the established infection being activated CCR5⁺CD4⁺ T-cells. Low density of the HIV co-receptor CCR5 expressed on T-cells was found to be a determining factor in resistance to HIV infection. Persistently elevated levels of systemic immune activation represent the main driver of disease progression in HIV pathogenesis and plays a bigger role than the actual CD4⁺ T-cell depletion in determining disease course.

A network of pro-inflammatory, regulatory and haematopoetic cytokines has been shown to affect virtually every step of the life cycle of HIV, from entry into new cells to budding of new progeny. These systemic cytokines are also thought to be responsible for localised and systemic inflammatory responses, including the recruitment of potential HIV target cells at point of infection. IL-1β, IL-6, and TNF-α, either alone or synergistically, have been shown to act on HIV-infected cells to up-regulate HIV replication.

Initiation of systemic inflammation during HIV infection and chronic establishment of this state, driven by the replication of HIV in blood and mucosal compartments, have detrimental and far-reaching consequences to human health during chronic infection. The aim of this study was to evaluate the impact of stable sexual partner status on the extent of systemic immune activation and inflammatory cytokine production in HIV+ individuals during the chronic stages of HIV infection.

## Methods

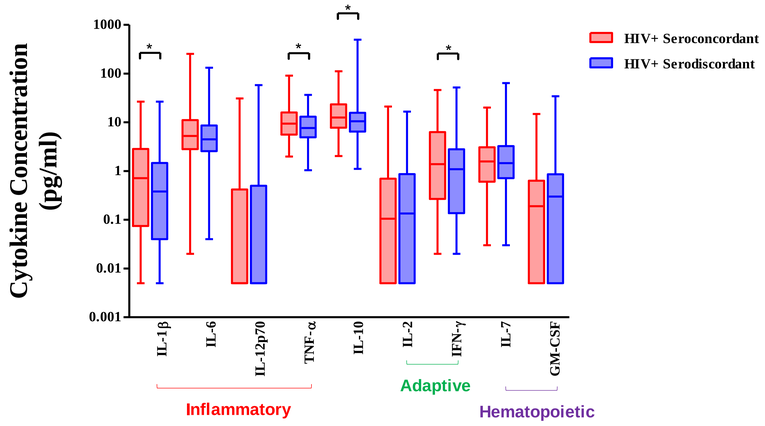
A total of 262 HIV positive individuals were included for this part of the study, of which 118/262 were in a relationship with an HIV negative partner (HIV Serodiscordant) and 144/262 were in a relationship with an HIV positive partner (HIV Seroconcordant). This study had a cross sectional design and at the clinic, sociodemographic and sexual behaviour interviews were conducted prior to collection of a blood sample and cervical cytobrush sample from women. After isolation of peripheral mononuclear cells from blood, systemic immune activation was determined by flow cytometry for the markers CD38, HLA-DR, Ki67 and CCR5. Plasma samples were assayed for the presence of 9 cytokines namely IL-1β, TNF-α, IL-6, IL-12p70, IFN-γ, IL-2, GM-CSF, IL-7 and IL-10.

## Results

More women were in a serodiscordant relationship than men. This bgender bias was unintended and was merely a reflection of the feminisation of HIV in Sub-Saharan Africa. Significantly more participants in the seroconcordant group had plasma HIV loads > 1500 cps/ml than the serodiscordant group. HIV serodiscordant individuals also reported significantly higher frequency of condom usage than concordant individuals.

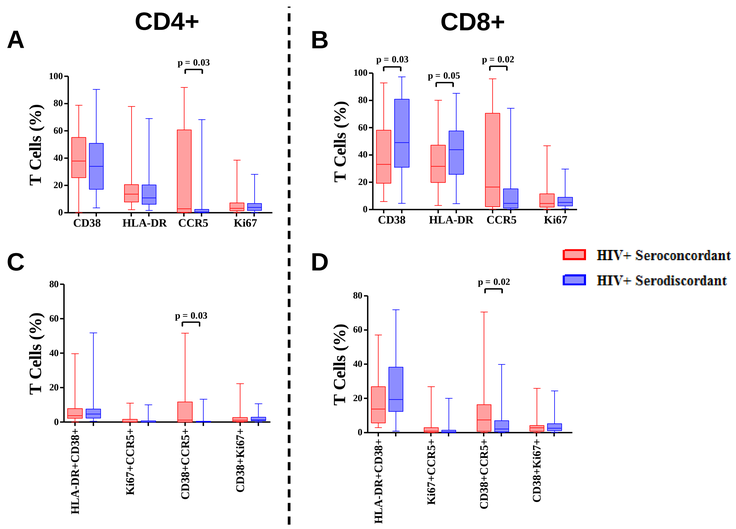
| Characteristics | HIV Seroconcordant | HIV Serodiscordant | P-value |
|---|---|---|---|
| N | 144 | 118 | |
| Male [%] | 53 | 32 | **0.004** |
| Age [yr; median (IQR)] | 37 (32-42) | 38 (32-45) | 0.4 |
| Blood CD4% [median (IQR)] | 45 (24-65) | 38 (21-64) | 0.5 |
| Plasma HIV load > 1500 cps/ml [%] | 89 | 58 | **0.003** |
| Condom usage [%] | 58 | 74 | **0.009** |
| Sex acts in last month [median, (IQR)] | 3 (1.5-6) | 3 (1.25-5) | 0.3 |

## BLOOD CYTOKINE CONCENTRATIONS



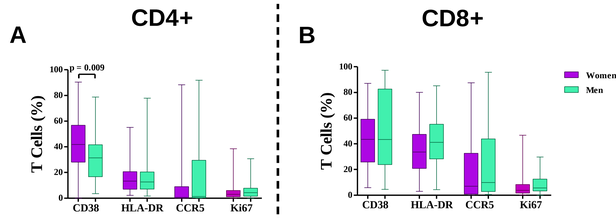

Plasma concentrations of IL-1β (p=0.04), TNF-α (p=0.03), IL-10 (0.02) and IFN-γ (p=0.05) were significantly higher in HIV seroconcordant compared to serodiscordant individuals.

## SYSTEMIC IMMUNE ACTIVATION



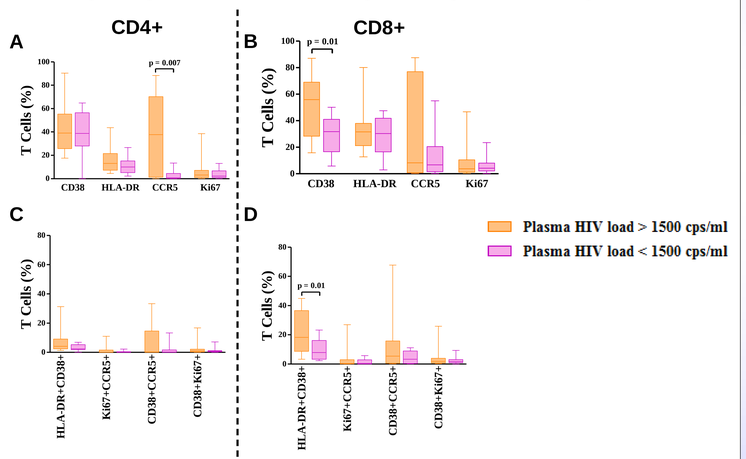

CCR5 expression on both CD4⁺ and CD8⁺ T-cells were elevated in HIV seroconcordant compared to the serodiscordant individuals. The frequency of activated target cells (CD38⁺CCR5⁺) on both CD4⁺ and CD8⁺ T-cell subsets were significantly higher in seroconcordant than serodiscordant individuals. Individual expression of CD38 and HLA-DR was higher in CD8⁺ T-cell subset of serodiscordant than seroconcordant individuals.

## IMPACT OF GENDER ON ACTIVATION




Frequencies of markers of activation were generally similar in men and women for both CD4⁺ and CD8⁺ T-cells. CD4⁺CD38⁺ frequencies were significantly elevated in women compared to men

## IMPACT OF VIREMIA ON ACTIVATION




HIV+ individuals with plasma viral loads >1500 cps/ml had significantly higher frequencies of CD4⁺ T-cells expressing CCR5 than those with viral loads <1500 cps/ml. CD38 expression was significantly higher on CD8+ T-cells of seroconcordant than serodiscordant individuals. Significantly higher frequencies of CD8⁺ T-cells from these individuals expressed CD38 in combination with HLA-DR compared to those with lower viral loads.

## Conclusions

In conclusion, this study suggests that continuous immune hyperactivation in the event of chronic HIV infection may lead to continuous activation and differentiation of T-cells in a cycle involving systemic immune activation, inflammation and constant replication of HIV. This could be accelerating the depletion of the naïve T-cell pool, and this could be exacerbated by the limited regenerative capacity in replacing lost naïve T-cells in adults While no causative relationship can be establish between seroconcordant individuals' higher expression of CCR5 and their potentially higher susceptibility to HIV infection prior to seroconversion (since this is a cross sectional study and cause and effect can only be inferred in longitudinal studies where biological markers are measured pre- and post-infection), we can speculate that continuous exposure to HIV in a concordant couple situation may lead to increased immune activation (compared to sex with an uninfected partner in a discordant couple situation), and also potentially increase the likelihood of superinfection.

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