Key cytokines mediating chronic inflammation and accelerating aging (inflammaging) in subjects with stable HIV disease

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ABSTRACT

Introduction: In subjects on antiretroviral therapy with stable HIV disease, there is increased evidence that they are at risk of chronic diseases and mortality when compared to healthy controls. The underlying pathophysiology is a state of chronic inflammation and accelerated aging referred to as "inflammaging". Inflammatory mediators in the systemic circulation may worsen chronic conditions such as cardiovascular, respiratory, neurologic, renal, metabolic, and liver diseases.
The objective of this study was to define key inflammatory mediators that are present in the systemic circulation in subjects with well-controlled HIV disease.
Methods: This was a secondary data analysis of the ongoing study titled Impact of Oxidative Stress on HIV-Induced Lung Disease study database. The Luminex High Sensitivity multiplex assay was used to measure picogram levels of the following cytokines in plasma: TNF-α, MIP-3α, MIP-1β, MIP-1α, ITAC, IL-23, IL-21, IL-17A, IL-13, IL-12 (p70), IL-10, IL-8, IL-7, IL-6, IL-5, IL-4, IL-2, IL-1β, IFNγ, GM-CSF, and Fractalkine. Subjects with well-controlled HIV disease were compared to healthy controls.
Results: A total of 54 subjects were included in the analysis, 28 with HIV disease and 26 healthy controls. A significant increase was documented in 8 of the 21 cytokines evaluated (IL-1β, TNF-α, IFNγ, IL-12 (p70), IL-10, MIP-1β, MIP-3α, and ITAC).
Conclusions: This study demonstrates that a systemic inflammatory response is present in subjects with well-controlled HIV disease. We documented 8 key cytokines that are significantly elevated when compared to healthy controls. Targeting these mediators may control inflammaging and improve outcomes in patients with well-controlled HIV disease.

INTRODUCTION

In the middle of the 1990s highly active antiretroviral therapy was introduced, since then human immunodeficiency virus (HIV) infection became a chronic infection. Despite the control over the HIV replication in plasma and the decrease in overall mortality, there is increase in prevalence of non-AIDS defining illnesses, including cardiovascular, respiratory, neurological, metabolic, renal and liver disease, along with different types of solid and hematologic cancers(1-5). Most of these conditions are linked to a state of chronic inflammation , which exhibits great resemblance to immune-senescence or immune exhaustion(2,4,5). This has been confirmed by the improvement in chronic inflammation biomarkers which didn't normalize. (16)

The objective of this study was to define key inflammatory mediators that are present in the systemic circulation in subjects with well-controlled HIV disease.

METHODS

- This was a secondary data analysis of the ongoing study titled Impact of Oxidative Stress on HIV-Induced Lung Disease study database.
- Venous blood was collected using sodium citrate Vacutainer tubes. Following centrifugation at 300 x g for 10 min, the plasma was separated by aspiration, aliquoted and stored frozen at -80oC until assayed.
- The concentrations of 21 different cytokines and chemokines (TNF-α, MIP-3α, MIP-1β, MIP-1α, ITAC, IL-23, IL-21, IL-17A, IL-13, IL-12 (p70), IL-10, IL-8, IL-7, IL-6, IL-5, IL-4, IL-2, IL-1β, IFNγ, GM-CSF, and Fractalkine) in plasma were determined using Milliplex MAP Multiplex kits (EMD Millipore, Billerica, MA) according to the manufacturer's instructions. Subjects with well-controlled HIV disease were compared to healthy controls.

RESULTS

Table 1 patient characteristics

Variable	HIV Positive	HIV Negative	P-value
Age at enrollment, Median (IQR)	50.5 (8.2)	52 (22)	0.862
NA, Median (IQR)	50.5 (8.2)	52 (22)	0.862
Current Smoker, n (%)	24 (75)	34 (87)	0.227
Male Sex, n (%)	24 (75)	17 (44)	0.009
Cirrhosis, n (%)	2 (6)	0 (0)	0.193
Chronic Kidney Disease, n (%)	3 (9)	0 (0)	0.087
COPD, n (%)	11 (34)	20 (51)	0.229
Diabetes Mellitus, n (%)	1 (3)	7 (18)	0.063
Hepatitis B Positive, n (%)	4 (12)	0 (0)	0.037
Hepatitis C Positive, n (%)	8 (25)	3 (8)	0.055
Hypertension, n (%)	14 (44)	15 (39)	0.809
Any Alcohol Use in the Last 6 Months, n (%)	15 (47)	17 (44)	0.814
CD4 Absolute, Mean, (SD)	545 (467)		
CD4 Percent Mean, (SD)	24.6 (15.0)		
Viral Load, Mean, (SD)	102 (7165)		

- A total of 54 subjects were included in the analysis, 28 with HIV disease and 26 healthy controls patient characteristics are depicted in table 1.
- A significant increase was documented in 8 of the 21 plasma cytokines evaluated (IL-1β, TNF-α, IFNγ, IL-12 (p70), IL-10, MIP-1β, MIP-3α, and ITAC), as seen in figure 1.
- The primary function of the elevated cytokines in HIV patients are depicted in table 2.

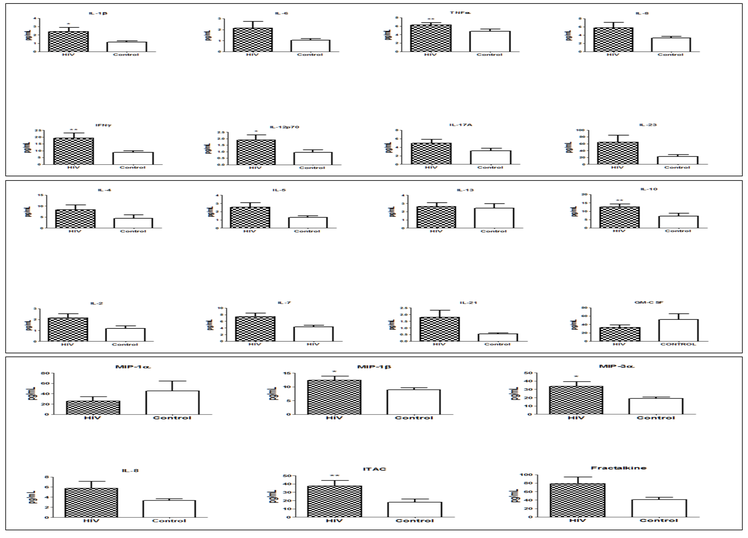

Figure 1 cytokine level in HIV vs non HIV controls

RESULTS

Table 2 function of elevated cytokines

Cytokine	Produced by	Function
TNF- α	White blood cells (WBCs)	Apoptosis
MIP-3α	Epithelial cells	WBC Chemotactic
MIP-1α	Macrophages	WBC Chemotactic
MIP-1β	Macrophages	WBC Chemotactic
ITAC	White blood cells (WBCs)	Chemotactic for activated Tcells
Fractaline	Endothelial cells	WBC adhesion molecule and chemotactic
IL-1β	Macrophages	cell proliferation, differentiation and apoptosis
IL-10	monocytes	anti-inflammatory cytokine
IL-12 (p70)	Antigen presenting cells (APCs)	T cell-stimulating factor
IFN-γ	White blood cells (WBCs)	Immunity mainly against viruses , also against some bacteria

TNF: Tumor necrosis factor, **MIP**: Macrophage Inflammatory protein, **ITAC**: Interferon-inducible T-cell alpha chemoattractant, **IL**: Interleukin, **IFN-γ**: interferon gamma

CONCLUSIONS

- This study demonstrates that a systemic inflammatory response is present in subjects with well-controlled HIV disease. We documented 8 key cytokines that are significantly elevated when compared to healthy controls.
- Translocation of microbial products from intestinal lumen and respiratory mucosa to the systemic circulation may, drives a local and systemic inflammatory state, this may be due to the profound alteration in gut-associated lymphoid tissue (GALT) caused by viral replication.
- Targeting these mediators identified in our may control inflammaging and improve outcomes in patients with well-controlled HIV disease.
- Tetracycline adjunction to ART is a promising future direction, from the perspective of being immunomodulatory agent acting through inhibition of Matrix Metalloproteinases(MMPs).

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