IL-33/ST2 Axis as an Inflammatory and Gut Damage Marker in Primary HIV Infection

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INTRODUCTION

Interleukin-33 (IL-33) acts as an "alarmin" in response to cellular damage induced by infection or stress at barrier sites such as the skin, lungs and gut. Soluble ST2 (sST2) is an IL-33 decoy receptor, contributing to limit inflammation. Given that sST2 is elevated in inflammatory conditions and that it plays a role in T-cell activation as well as in epithelial tissue repair/damage, we assessed the plasma levels of IL-33 and sST2 in relation with the primary and chronic phases of HIV infection, influence of antiretroviral therapy (ART) initiation and the association with the level of T-cell activation and exhaustion, gut epithelial damage and microbial translocation.

METHODS

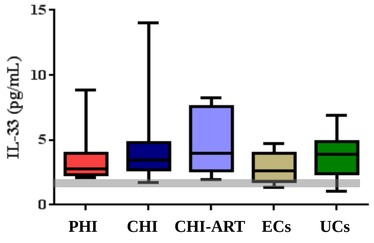
A total of 48 patients diagnosed during primary HIV infection (PHI) defined as being within 180 days of the estimated date of infection were followed: 24 remained untreated while 17 initiated early ART. We also assessed chronically infected patients (CHI) who were either untreated (n=61) or treated (n=23), elite controllers (ECs, n=21) and uninfected controls (UCs, n=20). IL-33 and sST2 plasma levels were measured by ELISA as well as the markers of gut epithelial damage, microbial translocation, inflammation and IDO enzyme immunosuppressive activity (Kynurenine/Tryptophan ratio). IL-33 mRNA was measured by qPCR. CD4 and CD8 T-cell activation (HLA-DRCD38) and exhaustion (PD-1) were assessed by FACS.

Table 1. Demographic and clinical characteristics of study participants (n=173)

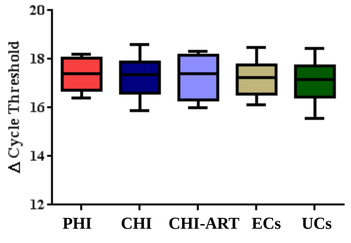
Characteristics	PHI n=48	CHI n=61	CHI-ART n=23	ECs n=21	UCs n=20
Age in years (Mean SD) Range	36.1 10.3 19-57	38.7 8.7 21-61	45.6 8.3 29-62	46.4 6.9 39-62	46.4 7.2 30-61
Gender Male, n (%) Female, n (%)	47 (97.9) 1 (2.1)	49 (80.3) 12 (19.7)	17 (73.9) 6 (26.1)	14 (66.7) 7 (33.3)	13 (65.0) 7 (35.0)
CD4 T-cell count (cells/µL, Mean SD) Range	544 269 220-1680	331 170 3-755	610 248 267-1177	678 246 440-1341	913 304 281-1559
CD8 T-cell count (cells/µL, Mean SD) Range	927 505 279-2590	858 503 272-3496	718 283 245-1381	582 339 162-1193	450 155 227-843
CD4:CD8 ratio (Mean SD) Range	0.70 0.47 0.16-2.76	0.46 0.30 0.01-1.20	0.92 0.34 0.44-1.55	1.34 0.64 0.69-2.72	2.23 0.86 0.38-3.97
VL, log_{10}copies/mL (Mean SD) Range	4.28 1.08 1.25-7.48	4.75 0.93 2.89-6.21	<1.7 NA	<1.7 NA	NA NA

RESULTS

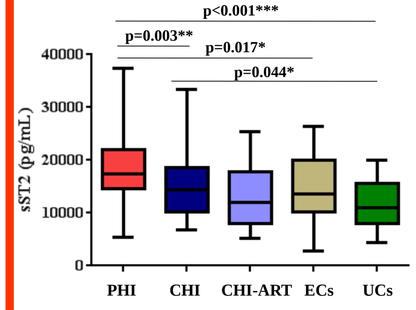
Plasma IL-33 levels during primary and chronic phases of HIV infection



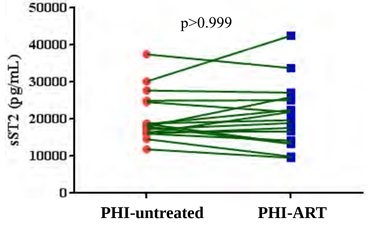
IL-33 mRNA expression during primary and chronic phases of HIV infection

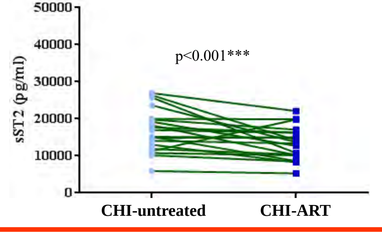


Plasma sST2 levels in the primary and chronic phases of HIV infection



Influence of ART initiation on plasma sST2 levels in primary and chronic phases of HIV infection



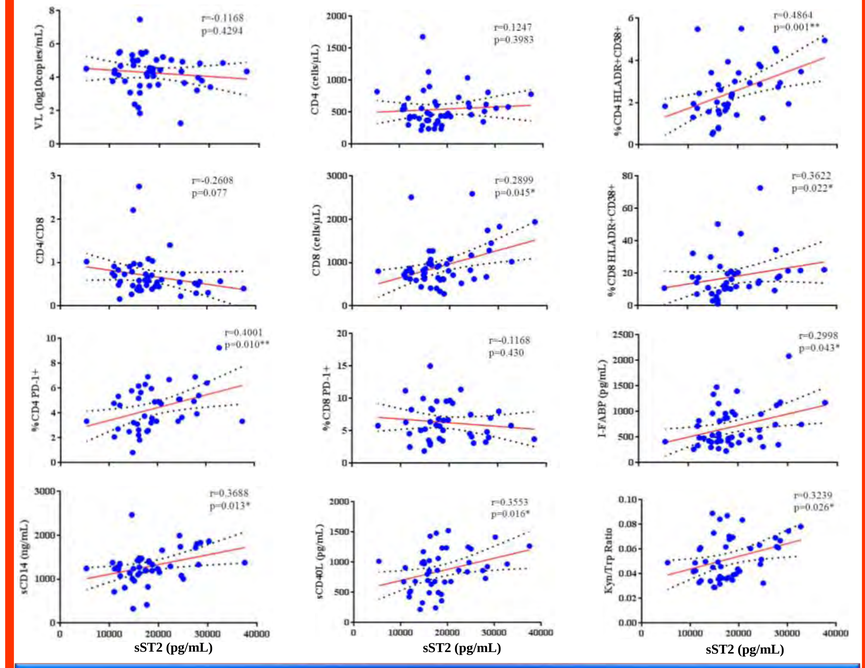


Abbreviations:

PHI: Primary HIV infection; CHI: Chronic HIV infection; ART: Antiretroviral therapy; ECs: Elite Controllers; UCs: Uninfected controls; p<0.05; **p<0.01; ***p<0.001; Δ Cycle Threshold (CT): CT of IL-33 minus CT of Actin;

Lower Limit of detection

Correlations of plasma sST2 levels with markers of disease progression, gut damage, inflammation and microbial translocation in primary HIV infection



CONCLUSION

Plasma sST2 levels were elevated in primary HIV infection and were correlated with CD8 T-cell count, immune activation and microbial translocation, sST2 may be a marker of gut damage and disease progression. The IL-33/ST2 axis may be a novel immunotherapeutic target for HIV infection.

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