sCD163, T Cell Activation, and HIV Progression in Perinatally-Infected HIV+ Children

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Introduction

CD163 is a hemoglobin scavenger receptor expressed primarily on monocytes and macrophages that endocytoses haptoglobin-hemoglobin complexes[1,2]. It also plays a role in erythroblast adhesion and immune sensing of bacteria[1]. When exposed to pro-inflammatory stimuli such as lipopolysaccharide (LPS), Fcγ receptor crosslinking, or oxidative stress, CD163 sheds via proteinase-mediated cleavage as soluble CD163 (sCD163)[1]. Thus, plasma levels of sCD163 reflect non-specific monocyte and macrophage activation[2,3].

In HIV infection, chronic inflammation in the innate and adaptive immune systems is associated with disease progression. HIV+ adults have high plasma sCD163 levels that persist despite antitretroviral treatment (ART)[3]. Elevated plasma sCD163 levels in HIV+ adults have been linked to non-AIDS morbidities including cardiovascular disease and neurocognitive dysfunction[2,3,6]. Moreover, sCD163 predicts all-cause mortality in adults[3]. With each milligram per liter increase in plasma sCD163 levels, the incidence of death increases by 6%[3].

In children, persistent inflammation during development leads to additional long-term comorbidities such as cognitive developmental delay and early onset cardiovascular disease[7-10]. There is limited data on plasma sCD163 levels in children[11,12]. We investigated plasma sCD163 levels in HIV+ children and their correlations with HIV disease progression, T cell activation and intestinal mucosal damage.

Methods

We studied a Kenyan cohort of 77 perinatally-infected HIV+ children, comprising 44 untreated (ART-) and 33 on antiretroviral therapy (ART+), and 45 HIV uninfected-unexposed controls (HIV-) between ages 5-20 years old. sCD163 and intestinal fatty acid binding protein (I-FABP) levels were measured in plasma, diluted 1:100 and 1:1500 respectively, by ELISA according to manufacturer protocol (R&D Systems). T cell activation and proliferation were evaluated by flow cytometry on cryopreserved peripheral blood mononuclear cells with the surface markers CD3, CD4, CD8, CD45RO, CD38, HLA-DR and intracellular antibodies Ki67 and cytokine IL-2. Statistical analysis was performed on GraphPad Prism software. Comparisons between multiple groups were performed with the Kruskal-Wallis followed by the two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli to correct for multiple comparisons by controlling the False Discovery Rate, multiple time points were evaluated with Wilcoxon matched-pairs signed-rank test. Correlations were assessed with the Spearman rank test. Threshold of significance for all tests was 0.05.

Table 1: Subject Characteristics

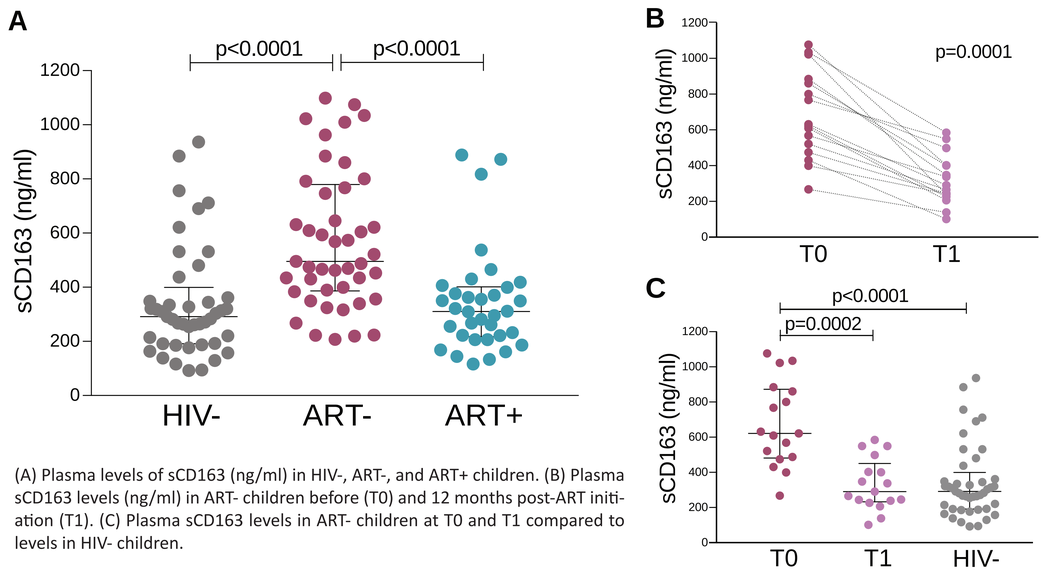
	HIV-	HIV+ ART-	HIV+ ART+	p
n	45	44	33	
Age*	12 (9-16)	11 (9-14)	12 (8-13)	NS[a]
Female	18 (40%)	25 (57%)	20 (60%)	NS[b]
%CD4*	38 (33-42)	24 (13-28)	32 (26-40)	p<0.0001[a]
HIV log copies/ml*		4.8 (4.2-5.2)	2 (2.0-2.0)	p<0.0001[c]

Median values with upper and lower quartile range

(a) Kruskal-Wallis test; (b) Chi-Square test; (c) two-sided Mann-Whitney test

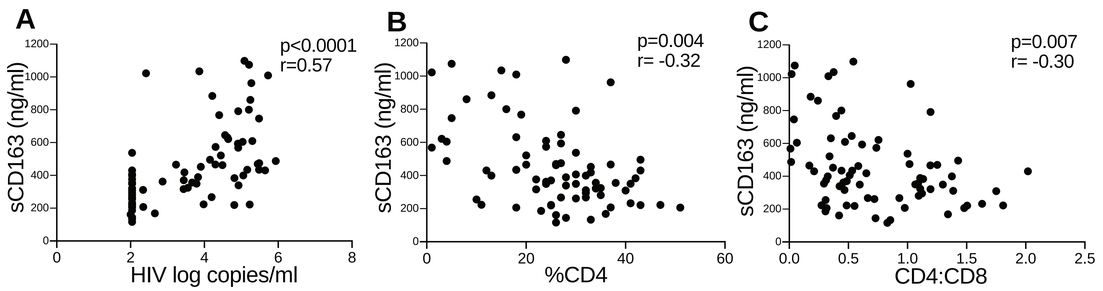
Results

Fig. 1: High plasma sCD163 levels in untreated HIV+ children normalize with treatment



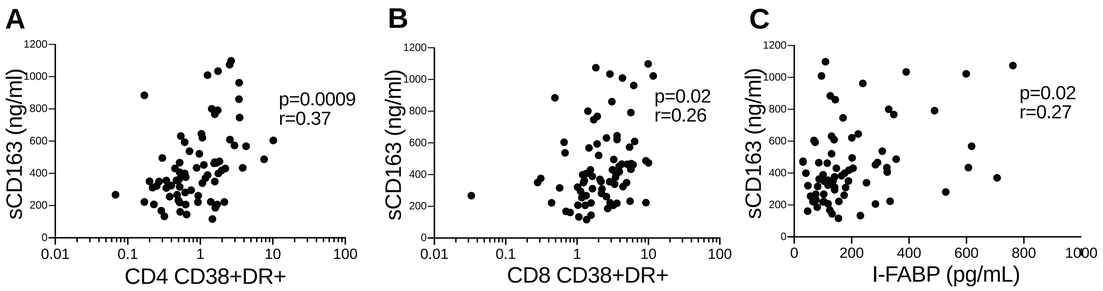
(A) Plasma levels of sCD163 (ng/ml) in HIV-, ART-, and ART+ children. (B) Plasma sCD163 levels (ng/ml) in ART- children before (T0) and 12 months post-ART initiation (T1). (C) Plasma sCD163 levels in ART- children at T0 and T1 compared to levels in HIV- children.

Fig. 2: Elevated plasma sCD163 levels correlate with HIV disease progression



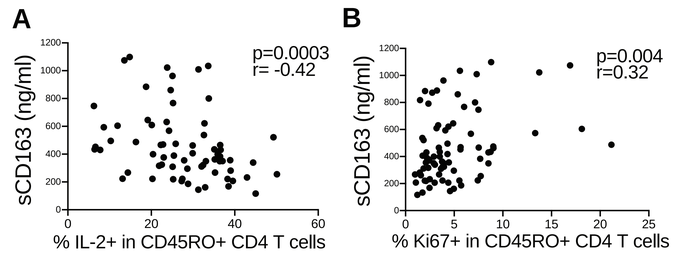
The plasma levels of soluble CD163 (ng/ml) (A) directly correlate with HIV viral load (log RNA copies/ml), and inversely correlate with (B) %CD4 T cells and (C) CD4:CD8 ratio.

Fig. 3: Plasma sCD163 levels correlate with T cell activation and gut mucosal disruption



The plasma levels of sCD163 (ng/ml) directly correlate with frequencies of CD38+HLA-DR+ (A) CD4 and (B) CD8 T cells. (C) Correlations between sCD163 levels and intestinal fatty acid binding protein (I-FABP).

Fig. 4: Plasma sCD163 levels and CD4 T cell proliferation



(A) The plasma levels of sCD163 (ng/mL) correlate inversely with levels of IL-2+ RO+ memory CD4 T cells. (B) Plasma levels of sCD163 (ng/mL) directly correlate with levels of Ki67 in memory CD4 T cells.

Conclusions

Treatment naïve HIV+ children have higher levels of plasma sCD163 compared to HIV- and ART+ children. Within one year of antiretroviral therapy, plasma sCD163 levels normalize to levels similar to HIV- children. sCD163 correlates with HIV disease progression, marked by increasing viral load and T cell activation and decreasing %CD4 and CD4:CD8 ratios in children. Compromised gut barriers and microbial translocation may trigger monocyte activation and sCD163 release, as sCD163 directly associates with I-FABP. Thus sCD163 is linked to inflammation in the innate and adaptive immune systems. Interestingly, sCD163 plasma levels correlated directly with Ki67 and inversely with IL-2 in memory CD4 T cells, suggesting sCD163 may potentiate activated CD4 T cell proliferation and have a potential inhibitory role on homeostatic CD4 T cell proliferation. In summary, high plasma sCD163 levels in HIV+ children are associated with HIV disease progression, T cell activation, and gut mucosal disruption, and may serve as a biomarker of advancing HIV status.

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