Children with Perinatal HIV Exhibit High GDF15 Levels Despite Antiretroviral Therapy

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Introduction

Growth differentiation factor-15 (GDF15) is a cytokine member of the TGFB superfamily broadly expressed in tissue and secreted in response to cellular stress[1,2]. Circulating levels of GDF15 increase during chronic inflammation, mitochondrial dysfunction, obesity and cardiac diseases[1,2]. GDF15 has emerged as a biomarker for cardiovascular disease (CVD) indicating cardiac cellular apoptosis, with higher levels after cardiac events and correlations with the severity of heart failure[3].

Adults living with HIV on antiretroviral treatment (ART) have high levels of GDF15 that have been linked with CVD and left ventricular dysfunction[4,5]. In children with perinatal HIV (CPHIV) >5 years old, GDF15 levels correlated with echocardiographic abnormalities[6]. A recent study revealed an association of serum GDF15 levels with mitochondrial dysfunction in CPHIV with a median age >8.7 years old[7]. There is limited data in younger CPHIV. We investigated plasma levels of GDF15 in CPHIV ages 2 months to 20 years and their correlations with clinical parameters and markers of immune activation and intestinal barrier damage.

Methods

We quantified GDF15 plasma levels in 232 Kenyan children who were HIV unexposed (HIV-) or CPHIV and treatment naïve (ART-) or virally suppressed on treatment (ART+) aged 0-5 years (0-5y) and 5-20 years (5-20y). We assessed correlations between GDF15 and HIV viral load, CD4%, monocyte (sCD14), T cell (CD38+HLA-DR+ CD4 and CD8 T cells) and systemic (CRP) activation markers and gut mucosal damage (intestinal fatty acid binding protein, IFABP). Plasma biomarkers (GDF15, sCD14, CRP, IFABP) were measured by ELISA and T cell activation by flow cytometry. Statistical analysis was performed with GraphPad Prism using the Kruskall-Wallis test corrected for multiple comparisons by controlling the False Discovery Rate with the Benjamini, Krieger and Yekutieli method and Spearman's correlation.

Table 1a: 0-5y Participant Characteristics

	HIV-	ART-	ART+	p
n	36	30	30	
Age (y)	2.6 (1.3-3.6)	2.0 (1.0-3.2)	3.1 (2.2-3.5)	0.04[a]
#Female	20 (56%)	17 (57%)	12 (40%)	ns[b]
% CD4	33 (28-39)	23 (15-32)	32 (27-35)	0.0004 [a]
CD4:CD8	1.9 (1.2-2.5)	0.5 (0.3-1.1)	1.3 (0.9-1.6)	<0.0001[a]
HIV log copies/ml		5.2 (3.9-5.8)	2.0 (2.0-2.7)	<0.0001[c]

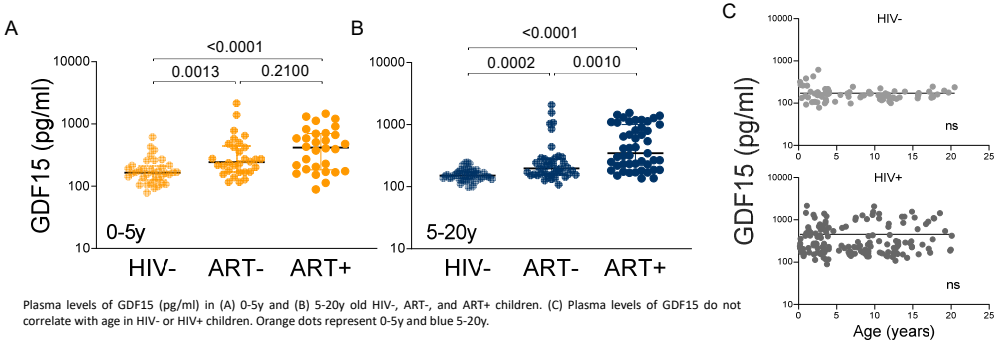
Table 1b: 5-20y Participant Characteristics

	HIV-	ART-	ART+	p
n	46	43	47	
Age (y)	11.7 (9.4-15.7)	10.6 (8.5-13.7)	12.5 (9.2-15.2)	ns[a]
#Female	19 (41%)	24 (56%)	24 (51%)	ns[b]
% CD4	38 (33-42)	24 (14-28)	30 (15-35)	<0.0001 [a]
CD4:CD8	1.7 (1.2-2.3)	0.5 (0.3-0.9)	0.7 (0.3-1.3)	<0.0001[a]
HIV log copies/ml		4.8 (4.2-5.2)	2.0 (2.0-4.0)	<0.0001[b]

Data are presented as Median values with interquartile range or #number and percentage. (a) Kruskal-Wallis; (b) Chi-Square; (c) Mann-Whitney

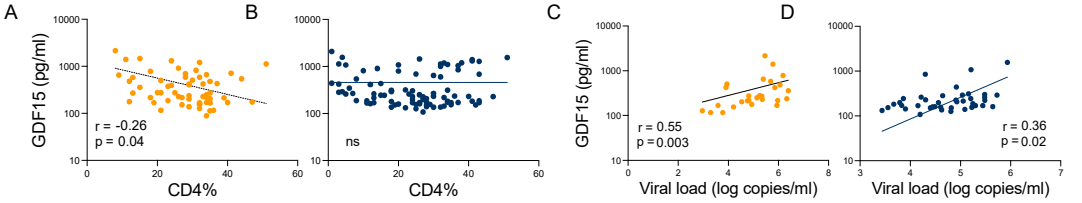
Results

Fig 1: High GDF15 levels in CPHIV regardless of age and treatment



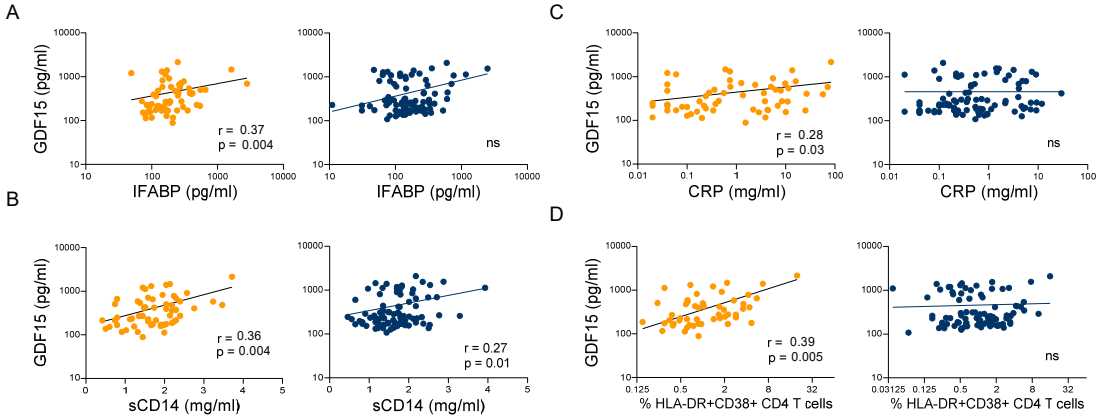
Plasma levels of GDF15 (pg/ml) in (A) 0-5y and (B) 5-20y old HIV-, ART-, and ART+ children. (C) Plasma levels of GDF15 do not correlate with age in HIV- or HIV+ children. Orange dots represent 0-5y and blue 5-20y.

Fig 2: Elevated GDF15 levels correlate with disease severity



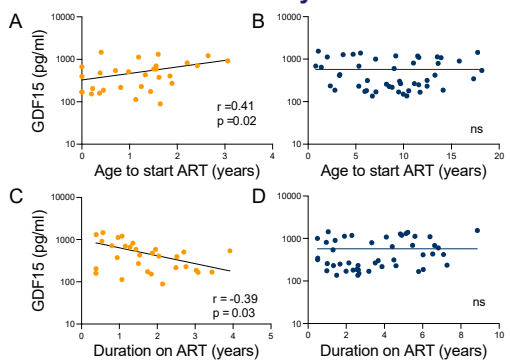
Plasma levels of GDF15 (pg/ml) inversely correlate with (A) %CD4 T cells in 0-5y old CPHIV, but not (B) 5-20y old CPHIV, and directly correlate with (C-D) HIV viral load (log RNA copies/ml) in ART-CPHIV. Orange dots represent 0-5y and blue 5-20y.

Fig 3: GDF15 levels, gut mucosal disruption, inflammation and T cell activation in CPHIV



Plasma levels of GDF15 (pg/ml) directly correlate with plasma levels of (A) IFABP, (B) sCD14 and (C) CRP and (D) the frequency of HLA-DR+CD38+ CD4 T cells in peripheral blood mononuclear cells in 0-5y old (orange), but not 5-20y (blue) old CPHIV except for sCD14.

Fig 4: Lower GDF15 levels correlate with earlier ART initiation and longer ART duration in 0-5y CPHIV



Plasma GDF15 levels correlated (A) positively with age at ART initiation and (B) inversely with duration of ART in 0-5y CPHIV, but not in (C, D) 5-20y CPHIV. Orange dots represent 0-5y and blue 5-20y.

Conclusions

CPHIV have elevated GDF15 levels compared with HIV- children starting in early childhood regardless of age and treatment.

- In 0-5y CPHIV, high GDF15 levels linked with advancing HIV, global inflammation, gut mucosal disruption and age of ART initiation and duration of treatment.
- 5-20y CPHIV have high GDF15 levels that are higher in ART+ compared to ART- and associate with viral loads, but are independent of inflammatory and gut mucosa markers.

Myocardial inflammation may begin early in perinatal HIV and continue despite successful ART with viral suppression in older children. Starting ART at younger ages may mitigate and reverse cardiovascular comorbidities from HIV in CPHIV. Our study is limited to biomarker analysis and further study is needed with corresponding clinical measures of cardiac function.

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