The impact of HIV and ART on markers of inflammation, vascular injury and disordered thrombogenesis in African children; a sub-study of the CHAPAS 3 Trial

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BACKGROUND

Studies of biomarkers reflecting inflammation and cardiovascular damage in HIV-infected individuals have consistently shown increased levels of D-dimer, IL-6 and CRP in HIV-infected adults; elevated levels are associated with a risk of disease progression, cardiovascular disease and all cause mortality (1). In paediatric cohorts a range of abnormalities in biomarkers have been demonstrated (2, 3) however, few data are available from young African HIV-infected and uninfected children and longitudinal data in HIV infected children are sparse.

OBJECTIVES

To assess the impact of HIV and ART on a panel of biomarkers reflecting inflammation, vascular injury and disordered thrombogeneisis in a large longitudinal study of young African HIV-infected children – both ART naïve and experienced.

METHODS

HIV-infected children who were either ART-naïve or ART-experienced (on stavudine + lamivudine + nevirapine or efavirenz for >2years, virologically suppressed at enrolment) had biomarkers measured at baseline, 48 and 96 weeks within the CHAPAS-3 trial which evaluated stavudine vs zidovudine vs abacavir based first-line ART in Uganda/Zambia (4). ART was commenced at baseline for the ART naïve children.

ART naïve and ART experienced (on d4T+3TC+NNRTI for >2 years, virologically suppressed) children from the CHAPAS-3 trial in Uganda/Zambia were included, with a single baseline assessment of age-matched controls. A panel of 19 biomarkers to assess inflammation, vascular injury and disordered thrombogeneis were measured at baseline in all children and repeated at 48 and 96 weeks in the HIV-infected children. Associations between change in log10 biomarkers from week 0 to 96 and baseline VL and age, and VL suppression at week 96, were estimated using normal linear regression.

RESULTS

208 ART naïve (group 1), 74 ART experienced (group 2) and 209 / 75 HIV-uninfected controls age matched to group 1 / 2 were recruited. Groups were well matched by age and sex. However there were significant differences between ART naïve/experienced and controls in weight (p<0.001/=0.03), height (p<0.001/=0.005) and between naïve/controls in CD4 percentage (p<0.001) - table 1.

BASELINE RESULTS

	Group 1 HIV infected ART naïve	HIV uninfected matched to group 1	Group 2 HIV infected ART experienced	HIV uninfected matched to group 2
Number	208	209	74	75
Male (%)	108 (52)	99 (47)	40 (54)	39 (52)
	p = 0.35		p = 0.80	
Median age yrs (IQR) Range	2.9 (1.7-4.4) 0.3 – 13.6	3.0 (2.1 – 4.1) 0.1 – 12.8	6.9 (5.9 – 8.5) 5.1 – 12.3	6.7 (5.6 – 8.6) 3.9 – 11.8
	p = 0.21		p = 0.60	
CD4 percentage (SD) Range	17 (8) 0 – 47	37 (8) 12 – 56	34 (10) 10 – 53	36 (8) 13 – 54
	p < 0.001		p = 0.11	
Weight for age z Mean (SD)	-2.4 (1.8)	-0.7 (1.8)	-1.5 (1.1)	-1.0 (1.3)
	p < 0.001		p = 0.03	
Height for age z Mean (SD)	-2.5 (1.7)	-0.9 (2.9)	-1.9 (1.0)	-1.2 (1.6)
	p < 0.001		p = 0.005	

Table 1. Baseline characteristics of the groups

6 Pro-inflammatory markers: *IL-1Ra,CRP, TNFa, IL-10,IL-6,IL-8*

•ART naïve vs controls: all 6 markers had higher values in ART naïve (p<0.001)

•ART naïve vs experienced: all 6 higher in ART naïve (p<0.001)

•ART experienced vs controls: 4/6 higher (p≤0.04), TNFa lower (p=0.02) in ART experienced, IL-1Ra comparable levels.

11 Markers of cardiovascular injury: *MCP-1, angiopoietin (Ang) 1+2, E-selectin, P-selectin, ICAM-3, thrombomodulin (TM), serum amyloid A (SAA), sICAM-1, VCAM, VEGF.*

•ART naïve vs controls: 9/11 higher (p≤0.03), Ang-2 lower (p=0.0001) in ART naïve, TM comparable levels.

•ART naïve v experienced: 10/11 higher in ART naïve (p<0.001), Ang-1 comparable levels.

•ART experienced v controls: 6/11 higher (p≤0.04), Ang-2, E-selectin, TM (p≤0.02) lower in ART experienced. SAA, sICAM-1 comparable levels.

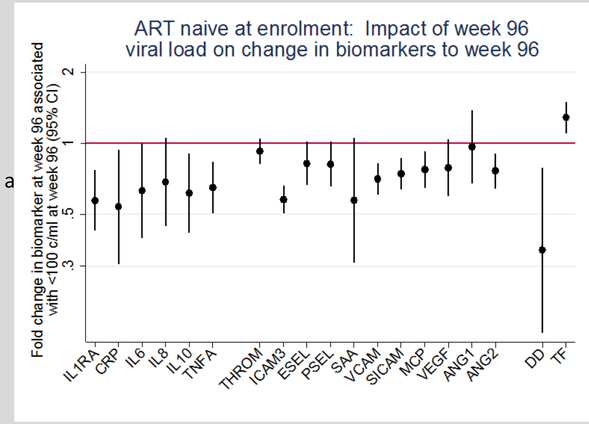
2 Markers of disordered thrombogenesis: *d-dimer, soluble tissue factor (TF).*

•ART naïve v controls: D-dimer higher in ART naïve (p<0.001), TM comparable levels

•ART naïve v experienced: D-dimer higher (p=0.0002) and TF lower (p=0.003) in ART naïve

•ART experienced v controls: D-dimer and TF higher in ART experienced (p<0.001)

LONGITUDINAL RESULTS



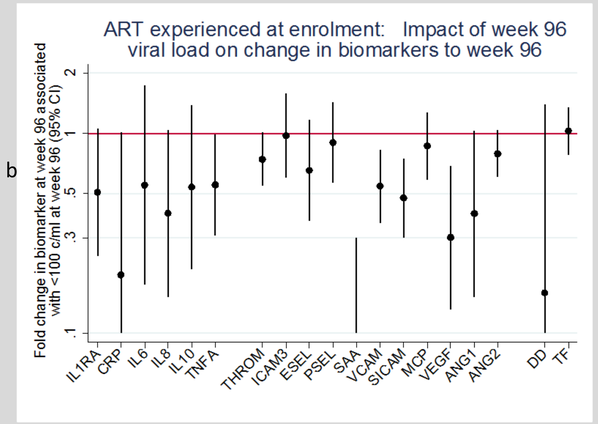


Figure 1. Graph to show impact of virological suppression on change in biomarkers from baseline in week 96 in (a) ART naïve children commencing ART (b) ART experienced children randomised to one of 3 ART regimens.

By week 96, all biomarkers had significantly declined excepting SAA, Ang-1 and 2 in the ART naïve group and P-selectin in the ART experienced group.

In naïve children, the only biomarkers for which declines to week 96 were not greater in children with VL<100 c/ml at week 96 compared to those >100 c/ml were TM, Ang-1 and TF (p>0.1) (Figure 1).

LONGITUDINAL RESULTS

For IL-10, TNFa, MCP, SAA, VCAM, VEGF, Ang-2 declines to week 96 were independently greater in older children (p<0.1). Fewer biomarker declines were associated with week 96 VL<100 c/ml in experienced children. There was no independent effect of baseline VL on week 96 declines in any biomarker (p>0.1).

CONCLUSIONS

All biomarkers tended to start high and showed ongoing normalization with progressive treatment, even in experienced children already on ART for ~4 years and with undetectable viral load at trial enrolment. Of particular interest, the continuing improvement in vascular biomarkers with treatment is compatible with the beneficial effects of ART on markers of cardiovascular structure and function in this cohort.

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