Abstract: 771

Pre-cART Pro-inflammatory milieu, Microbial Translocation (MT) and Risk of Disease Progression in HIV-infected Patients Starting Their First cART: Data from the Icona Foundation Cohort

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Objectives: Inflammation and MT persist despite suppressive cART and might be therapeutically targeted. We hereby investigated the predictive significance of pre-cART MT and pro-inflammatory markers on disease progression upon initiation of cART.
Methods: In a random sample of Icona patients with ≥1 stored pre-cART sample and new HIV diagnosis within max 24 months of cART start we tested pre-cART biomarkers (binary-above/below median; continuous-logescale: LPS(LAL), sCD14, EndoCab, hs-CRP (ELISA). Standard survival analysis (Kaplan-Meier, Cox regression) were used to investigate associations between biomarkers and 2 time to outcomes i) severe non-AIDS event (SNAE), AIDS-defining condition or death whichever occurred first; ii) SNAE or death. Follow-up accrued from the date of starting cART to the time of last available visit or at event. Analyses were repeated in patients starting cART with CD4< 350.
Results: We studied 486 patients (278 LPS, 477 sCD14, 375 h-CRP, 475 EndoCab measurements available). Median CD4, VL, age, time from HIV diagnosis at cART were: 256/mm3 (range:2-1180), 4.8Logcp/mL (IQR:4.1-5.2), 37 years (range:18-74), 1 month (IQR:0-23). Median(IQR) values: LPS 251pg/ml (152-393), sCD14 2.8ug/ml (2.2-3.9), EndoCab 36.5 MMu/ml (21.3-66.0), hs-CRP 1.51mg/L (0.6-4.1). 102 events were recorded: 36 (35%) AIDS, 47 (46%) non-AIDS and 19 (19%) death.
Hs-CRP was the only biomarker independently associated with endpoint
i) in the whole cohort (Table) and in the analysis restricted to patients with pre-cART CD4< 350/mmc (RH=1.98 per >1.51 vs.< =1.51, 95% CI 1.13-3.47, p=.017). Although weaker, this association occurred also for endpoint
ii) SNAE/death (RH=1.71 per >1.51 vs. < =1.51, 95% CI 0.96-3.05,p=.07).
Conclusion: Circulating pre-cART hs-CRP but not MT, seems associated with the risk of disease progression after cART initiation regardless of patients' pre-cART CD4, suggesting that pre-therapy HIV-driven pro-inflammatory *milieu* might overweight MT and its downstream immune-activation even after HIV-viremia suppression. This result should help guiding the design of interventional trials.

Table. RH of clinical progression defined as SNAE°, AIDS-defining condition or death whichever occurred first from fitting a Cox regression model

	Unadjusted and adjusted relative hazards of SNAE°, AIDS-defining events or death in total population					
	Unadjusted RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value	Adjusted** RH (95% CI)	p-value
(a) Biomarkers fitted as categorical variables						
LPS, pg/ml						
<=250.8	1.0		1.0		1.0	
>250.8	0.87 (0.51, 1.50)	0.618	0.81 (0.47, 1.42)	0.471	0.86 (0.48, 1.55)	0.625
not measured	1.20 (0.75, 1.91)	0.448	1.17 (0.72, 1.92)	0.531	1.22 (0.74, 2.04)	0.437
sCD14, ug/ml						
<=2.83	1.0		1.0		1.0	
>2.83	1.08 (0.72, 1.60)	0.718	0.90 (0.59, 1.38)	0.640	0.85 (0.55, 1.31)	0.470
not measured	2.25 (0.81, 6.27)	0.119	1.78 (0.62, 5.16)	0.286	2.80 (0.90, 8.71)	0.076
EndoCAb, pg/ml						
<=36.5	1.0		1.0		1.0	
>36.5	0.79 (0.53, 1.18)	0.246	0.91 (0.60, 1.39)	0.670	0.94 (0.61, 1.45)	0.790
not measured	0.63 (0.15, 2.60)	0.527	0.58 (0.14, 2.39)	0.448	0.60 (0.14, 2.63)	0.501
hs-CRP, mg/l						
<=1.51	1.0		1.0		1.0	
>1.51	1.79 (1.13, 2.85)	0.014	1.79 (1.10, 2.91)	0.019	2.03 (1.21, 3.39)	0.007
not measured	1.46 (0.85, 2.51)	0.168	1.62 (0.92, 2.85)	0.092	1.78 (0.99, 3.20)	0.053
(b) Biomarkers fitted as continuous variables in the $\log_e$ scale						
LPS, pg/ml						
per $\log_e$ higher	0.99 (0.70, 1.39)	0.945	0.89 (0.62, 1.26)	0.504	0.66 (0.39, 1.10)	0.113
sCD14, ug/ml						
per $\log_e$ higher	1.08 (0.74, 1.58)	0.697	0.83 (0.52, 1.32)	0.435	0.76 (0.36, 1.64)	0.488
EndoCAb, pg/ml						
per $\log_e$ higher	0.88 (0.70, 1.12)	0.300	0.96 (0.76, 1.23)	0.769	1.04 (0.65, 1.65)	0.874
hs-CRP, mg/l						
per $\log_e$ higher	1.16 (1.01, 1.33)	0.031	1.11 (0.97, 1.28)	0.130	1.12 (0.92, 1.36)	0.267

°SNAE (Severe non-AIDS Events): cardiac decompensation, IRC, liver diseases, MI, malignancies, pneumonia, renal disease and septic infection

*All models (a separate one for each biomarker) adjusted forage, CD4, VL, HCV/HBV, year of cART, duration of HIV infection at starting cART,type of cART started

**Further mutually adjusted for all biomarkers

[Table]