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IL-6 is a stronger predictor of clinical events than hsCRP or D-dimer in HIV disease

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BACKGROUND

- Higher plasma levels of interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP) and D-dimer have been linked to subsequent risk of anaemia[1], diabetes[2], progression to AIDS[3], cardiovascular disease[4,5], cancer[6] and death[7] during HIV infection.
- However, the strength of associations these biomarkers have with different types of clinical outcomes is not well understood.

METHODS

Study Design:

- Participants in the control arms of 2 HIV trials (SMART and ESPRIT) with biomarkers measured at baseline were followed from study entry to ascertain: 1) all-cause death, 2) non-AIDS and non-violent/accidental death, 3) fatal and non-fatal progression to AIDS, 4) fatal and non-fatal cardiovascular disease (CVD; defined as prior myocardial infarction, stroke or coronary artery disease requiring surgical procedure) and 5) fatal and non-fatal non-AIDS-defining malignancies (NADM; excluding basal and squamous cell skin cancers).
- Participants in the control arms received standard of care according to HIV guidelines and were to be continuously maintained on ART.

Statistical Analyses:

- HRs (95% CIs) stratified by study of each endpoint for $\log_2$-transformed hsCRP, IL-6 and D-dimer levels considered singly were calculated using the following Cox models: (1) unadjusted; (2) adjusted for the following covariates assessed at baseline: demographics, ART use, nadir and baseline CD4, HIV RNA, prior AIDS and CVD, diabetes and HBV/HCV. HRs were also estimated from a model (3) that included the aforementioned baseline covariates, D-dimer and each inflammatory marker considered singly.
- Because biomarkers were measured at different central laboratories in SMART and ESPRIT, we also calculated HRs (95% CIs) of each endpoint for quartiles of biomarkers defined differently by study. The same afore mentioned Cox models were used.
- The Wei-Lin-Weissfeld test[8] was used to model multiple unordered events and to test for equal effects of biomarkers on different clinical endpoints.

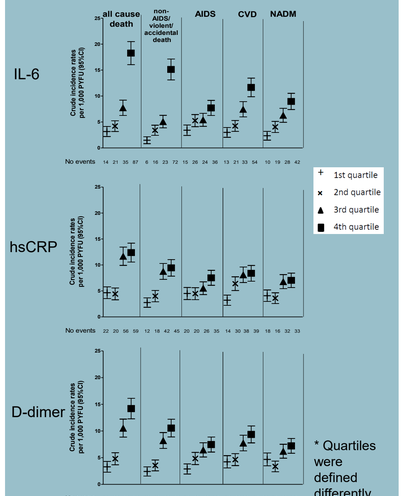
Table 1

Baseline characteristics SMART and ESPRIT control arm participants

Baseline Characteristics N (%) or Median [IQR]	All participants N= 4,304	All-cause deaths N=157	non-AIDS and non-violent/ accidental deaths N=117	AIDS N=101	CVD N=121	NADM N=99
Age (years)	42 [36 , 49]	48 [40 , 54]	48 [41 , 55]	44 [38 , 50]	49 [43 , 56]	50 [44 , 57]
Female sex	1,002 (23.3)	28 (17.8)	17 (14.5)	22 (21.8)	14 (11.6)	14 (14.1)
Black Race	907 (21.1)	29 (18.5)	25 (21.4)	18 (17.8)	26 (21.5)	26 (26.3)
BMI (kg/m²)	24.4 [22.1 , 27.1]	23.5 [21.4 , 27.3]	23.3 [21.3 , 27.1]	25.2 [22.6 , 29.0]	24.0 [22.1 , 27.4]	23.9 [21.7 , 25.8]
Prior AIDS	1,093 (25.4)	46 (29.3)	32 (27.4)	42 (41.6)	47 (38.8)	21 (21.2)
Hepatitis B/C	761 (17.7)	54 (34.4)	41 (35.0)	16 (15.8)	18 (14.9)	27 (27.3)
Prior CVD	112 (2.6)	14 (9.0)	12 (10.3)	1 (1.0)	16 (13.3)	5 (5.1)
Diabetes	217 (5.1)	14 (9.0)	10 (8.6)	7 (6.9)	14 (11.7)	9 (9.1)
PI based cART	1,478 (34.3)	53 (33.8)	45 (38.5)	31 (30.7)	52 (43.0)	41 (41.4)
NNRTI based	1,643 (38.2)	52 (33.1)	39 (33.3)	34 (33.7)	30 (24.8)	30 (30.3)
CD4 (cells/mm³)	526 [415 , 701]	451 [370 , 594]	470 [384 , 639]	466 [376 , 599]	515 [401 , 673]	526 [404 , 679]
CD4 Nadir (cells/mm³)	230 [120 , 337]	194 [93 , 297]	194 [85 , 282]	190 [90 , 298]	187 [74 , 301]	219 [97 , 311]
HIV RNA ≤500 copies/mL)	3,263 (75.8)	97 (61.8)	77 (65.8)	51 (50.5)	88 (72.7)	75 (75.8)
IL-6 (pg/mL)	1.80 [1.18 , 2.90]	3.09 [2.10 , 4.40]	3.17 [2.10 , 4.49]	2.42 [1.40 , 3.33]	2.60 [1.78 , 4.30]	2.50 [1.81 , 3.58]
hsCRP (pg/mL)	1.60 [0.69 , 3.67]	2.83 [1.53 , 6.27]	2.70 [1.57 , 6.18]	2.03 [0.83 , 4.50]	2.33 [1.02 , 5.05]	2.54 [1.13 , 4.93]
D-dimer (pg/mL)	0.24 [0.15 , 0.38]	0.33 [0.23 , 0.55]	0.35 [0.23 , 0.55]	0.31 [0.22 , 0.53]	0.31 [0.20 , 0.51]	0.28 [0.18 , 0.52]

Figure 1

Crude incidence rates of clinical outcomes across biomarker quartiles*



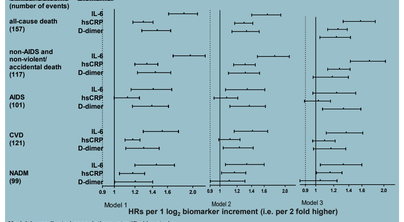
* Quartiles were defined differently by study

RESULTS

- There were 19,000 person-years of follow-up among 4,304 participants (median age 42y, median CD4 526, 77% men), including 157 all-cause deaths, 117 non-AIDS and non-violent/accidental deaths, 101 progressions to AIDS, 121 CVD and 99 NADM.
- Baseline characteristics of study participants who developed the different clinical outcomes are shown in Table 1.
- Crude incidence rates of clinical outcomes increased across higher quartiles of all biomarkers (Figure 1).
- In multivariable analyses with $\log_2$-transformed biomarker levels (model 3), independent associations between IL-6 and clinical endpoints were strongest for non-AIDS and non-violent/accidental death (1.71; 1.43-2.04) and similar for all-cause death (1.56; 1.33-1.84), CVD (1.35; 1.12-1.62) and NADM (1.30; 1.06-1.61) (Figure 2).
- When compared to hsCRP, IL-6 was more strongly associated with all outcomes investigated both in univariable and multivariable models that considered $\log_2$ transformed biomarkers. Likewise, IL-6 was a stronger predictor for most outcomes than D-dimer, except for progression to AIDS (Figure 2).
- In multivariable analyses using biomarker quartiles, the strength of association between higher quartiles of IL-6 and D-dimer with all-cause death was similar. However, higher quartiles of IL-6 were independently associated with steeper risk gradients for non-AIDS and non-violent/accidental death, CVD and NADM (Figure 3).
- The Wei-Lin-Weissfeld test found evidence of heterogeneity in the association of IL-6 with different endpoints (p<0.001), but not of hsCRP (p=0.15) or D-dimer (p=0.20).

Figure 2

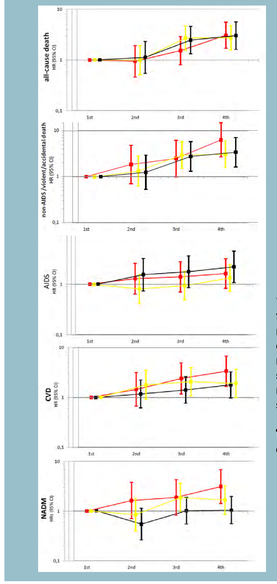
HRs (95%CI) for clinical outcomes associated with baseline biomarkers (per 1 $\log_2$ increment)



Model 1: unadjusted associations, stratified by study
Model 2: adjusted for the following covariates assessed at baseline :demographics, ART use, nadir and baseline CD4, HIV RNA, prior AIDS and CVD, diabetes and HBV/HCV.
Model 3: adjusted for the aforementioned baseline covariates, D-dimer and each inflammatory marker considered singly

Figure 3

Adjusted HRs* (95%CI) for clinical outcomes associated with biomarker quartiles¶



*HRs adjusted for factors included in model 2. HRs calculated as in models (1) and (3) showed consistent results (data not shown)

¶ quartiles defined differently by study

CONCLUSIONS

- The upstream inflammatory marker IL-6 has a higher risk gradient for a variety of non-AIDS clinical events than the downstream inflammatory marker hsCRP or the coagulation marker D-dimer.
- IL-6 is more strongly associated with non-AIDS and non-violent/accidental death than with fatal/non-fatal CVD and fatal/non-fatal NADM, which suggests that IL-6 is a stronger predictor of fatal events than non-fatal CVD and NADM events.
- Evaluation of the clinical benefits from interventions able to reduce levels of inflammatory and coagulation biomarkers is warranted in treated HIV disease.

REFERENCES: 1) Borges AIDS 2014; 2) Béténé JAIDS 2014; 3) Rodger JID 2009; 4) Duprez Plos One 2012; 5) Nordell JAHA 2014; 6) Borges AIDS 2013; 7) Kuller Plos Med 2008; 8) Wei-Lin-Weissfeld J Am Stat Assoc 1989

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