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 anaemia1, diabetes2, progression to AIDS3, cardiovascular disease4,5,6,7, cancer8 and death4 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 log2-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 the aforementioned baseline covariates, D-dimer and each inflammatory marker.

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 log2-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 log2-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).

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: