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Inflammation Related Morbidity and Mortality Among HIV-Positive Adults: How Extensive Is It?

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Abstract

Objective—To determine the rate of grade 4, potentially life-threatening, events not attributable to AIDS, cardiovascular disease (CVD) or non-AIDS cancer among participants on antiretroviral therapy (ART), and to describe associations of these events with interleukin-6 and D-dimer.

Design—Cohort study.

Methods—HIV-infected participants on ART (N=3,568) with an HIV RNA level ≤ 500 copies/mL were followed for grade 4, AIDS, CVD, non-AIDS cancer and all-cause mortality events. Grade 4 events were further classified blinded to biomarker levels as reflecting chronic-inflammation related disease (ChrIRD) or not (non-ChrIRD). Associations of baseline IL-6 and D-dimer with events were studied with Cox models.

Results—Over a median follow-up of 4.3 years, 339 participants developed a grade 4 event (22.9 per 1,000 person years); 165 participants developed a ChrIRD grade 4 event (10.7 per 1,000 person years). Grade 4 events were more common than AIDS (54 participants), CVD (132) and non-AIDS cancer (80) events, any of which developed in 252 participants (17.1 per 1,000 person years). Grade 4 and AIDS events were associated with similar risks of death. Higher IL-6 (hazard ratio=1.19 per doubling of biomarker; p=0.003) and D-dimer (HR=1.23; p<0.001) levels were

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associated with an increased risk of grade 4 events. IL-6 associations were stronger for ChrIRD (HR=1.38; p<0.001) than non-ChrIRD grade 4 events (HR=1.11; p=0.21).

Conclusions—Morbidity and mortality associated with activation of inflammatory and coagulation pathways include conditions other than AIDS, CVD and non-AIDS cancer events. Effective inflammation-dampening interventions could greatly impact the health of people with HIV.

Keywords

Grade 4 events; serious non-AIDS; AIDS; interleukin-6; D-dimer

Introduction

A shift from AIDS-related causes of morbidity and mortality to non-AIDS causes such as non-AIDS malignancy, liver cirrhosis, end stage renal disease and serious cardiovascular events occurred in HIV patients nearly one decade ago due to use of potent antiretroviral therapy [1]. A recent review examined the evidence suggesting a link between a persistent inflammatory state, even with suppressive antiretroviral therapy (ART), and morbidity and mortality attributed to these conditions termed serious non-AIDS events in HIV studies [2].

As in studies in the general population [3–5], higher levels of inflammatory and coagulation markers have been associated with an increased risk of all-cause mortality [6–8], cardiovascular disease (CVD) [9–12] and cancer [13] in people with HIV. Furthermore, markers of systemic inflammation, such as interleukin-6 (IL-6), and markers of coagulation, such as D-dimer, are elevated with HIV infection, despite effective antiretroviral treatment (ART) [14].

In two recent reports [15,16], IL-6 and D-dimer were strongly related to all-cause mortality among participants with HIV. Most of the deaths in these analyses were not attributable to AIDS or serious non-AIDS conditions such as CVD and cancer. This raises the question whether serious conditions other than AIDS, CVD and cancer that have heretofore not been studied, are a consequence of underlying increased inflammation and coagulation. In this paper we use data from two large international trials to describe rates of potentially life-threatening events not attributable to AIDS, CVD or non-AIDS cancer and assess whether these events have an inflammatory component by studying their association with IL-6 and D-dimer.

Methods

Study Population

This analysis includes participants from the control arms of two clinical trials conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT: the Strategies for Management of Antiretroviral Therapy (SMART) study and the Evaluation of Subcutaneous Proleukin® in a Randomized International Trial (ESPRIT) [17, 18]. In SMART, HIV-positive adults with a baseline $CD4^+$ cell count above 350 cells/mm^3 were randomized to receive either continuous antiretroviral treatment (ART) (control group) or

episodic ART based on the $CD4^+$ count. ESPRIT compared interleukin-2 plus ART versus ART alone (control) among HIV positive adults with $CD4^+$ counts ≥ 300 cells/mm^3. As in a previous report that examined morbidity and mortality rates by age [19], the analyses in this report are restricted to HIV-positive participants in the control groups of SMART and ESPRIT who were on ART with an HIV RNA level ≤ 500 copies/mL at their baseline visit in order to focus on serious outcomes that occur despite effective ART. Control arms in both studies were to receive continuous ART throughout follow-up aimed at viral suppression.

Baseline Measurements

Baseline measurements that were obtained prior to randomization in both SMART and ESPRIT included: age, sex, race, body mass index (BMI), baseline $CD4^+$ and nadir $CD4^+$ cell count, HIV-RNA level, duration of ART, history of an AIDS event, hepatitis B/C co-infection, diabetes, use of blood pressure and lipid lowering medication, and type of ART treatment. IL-6 and D-dimer were measured using stored plasma specimens collected at baseline for participants who provided written consent. Laboratory methods have been previously described [16]. All samples were analyzed blinded to treatment and event status.

Outcomes

Outcomes considered in this investigation were defined using the same criteria in SMART and ESPRIT. Using pre-established diagnostic criteria, an Endpoint Review Committee (ERC) reviewed documentation provided by clinical sites following events for AIDS events, and the following serious non-AIDS events (SNAs): CVD (myocardial infarction, stroke, coronary revascularization) events; cirrhosis; end-stage renal disease; and non-AIDS defining cancers (except for basal cell or squamous cell skin cancer). Events considered to be confirmed or probable by the ERC were counted as endpoints [20]. Causes of death were coded according to the CoDe system [21, 22].

Adverse experiences were graded on a four-point severity scale (1 to 4) by site clinicians using a National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS toxicity table (http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf). In ESPRIT and SMART only grade 4 events were reported; events of lesser severity were not. In general, grade 4 events were defined as symptoms, signs or diagnoses that were potentially life-threatening. For conditions which were not in the toxicity table clinician judgement was a key factor in determining each event's severity grade. In these cases, clinicians used the following generic definition of grade 4 events: extreme limitation in activity -- significant assistance required; significant medical intervention/therapy required; hospitalization possible. Grade 4 events were reported throughout each trial irrespective of the assumed relationship with ART or whether ART had been discontinued. Events that were limited to a laboratory abnormality were not reported. AIDS events were not reported as grade 4 events. Two trained nurses coded the grade 4 events using the *Medical Dictionary for Regulatory Activities* (MedDRA®), version 19.1. Each nurse participates in a NIAID quality control program that involves coding adverse events twice yearly. One nurse did the initial coding of grade 4 events for ESPRIT and SMART and the other nurse verified the coding. If there was a difference of opinion on

the coding, the final code was adjudicated by a discussion between the two nurses. MedDRA® System Organ Class (SOC) and Preferred Term (PT) codes are cited.

CVD, non-AIDS cancer events, liver cirrhosis, end stage renal disease which were reviewed by the ERC were also reported as grade 4 events if grade 4 criteria were met. CVD and cancer events that did not meet ERC criteria were frequently reported as grade 4 events.

Throughout the trial on-site visits were conducted to review charts for grade 4 events, AIDS events, and serious non-AIDS events which were not reported.

In order to define mutually exclusive event categories, we defined the following major outcomes for this investigation: 1) fatal or non-fatal AIDS according to the ERC; 2) fatal or non-fatal CVD meeting ERC criteria plus grade 4 events that did not meet ERC criteria considered to be CVD by one of us (DAD); 3) fatal or non-fatal non-AIDS defining cancer meeting ERC criteria; and 4) grade 4 events and deaths other than those in the three aforementioned categories. Liver cirrhosis and end stage renal disease events meeting ERC criteria are included in the 4th category because they occurred in too few participants to consider separately. The 4th category also includes some cancer events which did not meet ERC criteria (e.g. basal cell or squamous cell skin cancer).

Each participant was allowed to qualify for more than one event type during follow-up and then was counted in all relevant categories for event-specific analyses. All events were reviewed either by the ERC or trained nurses blinded to treatment assignment, event status, and baseline characteristics, including IL-6 and D-dimer levels.

Grade 4 events in the 4th category were also divided into two groups according to two recent reports from the Multi-Ethnic Study of Atherosclerosis (MESA) [23, 24]. In those investigations, International Classification of Diseases diagnostic codes for hospitalizations and deaths for diagnoses that that were not coded as CVD, cancer, injury, acute organ failure, psychoses, substance abuse, and metabolic disorders such as diabetes were reviewed and those medically considered to have a chronic inflammatory component or to require response to a massive infection were classified as chronic inflammation-related disease (ChrIRD) conditions. Diagnostic codes and records for the following chronic and severe pathologic conditions were reviewed: infectious diseases; endocrine; nutritional, and metabolic diseases; nervous, respiratory and digestive systems diseases; skin diseases; musculoskeletal and connective tissue disorders; genitourinary diseases; and blood disorders. Two physicians independently reviewed the diagnostic codes with no information about the study participants and identified conditions which they considered to have an important inflammatory component. In these investigations, lower levels of small-plus-medium high density lipoprotein (HDL) particles and higher levels of IL-6 and D-dimer were associated with an increased risk of ChrIRD events [23], and risks of death, CVD, ChrIRD, and cancer were associated with GlycA, IL-6, and D-dimer independently [24].

This finding motivated a similar classification of SMART and ESPRIT grade 4 events. In our investigation, one of us (DAD), who was also one of the two physicians in MESA who classified diagnostic codes, used the classification scheme developed for MESA to categorize MedDRA® PTs for grade 4 events and causes of death as ChrIRD or non-

ChrIRD. Supplemental Table S1 gives the PTs and frequencies corresponding to the ChrIRD and non-ChrIRD events.

Statistical Analyses

Event rates and 95% confidence intervals were estimated using Poisson regression. We then used Cox models to estimate the risk of death associated with AIDS, CVD, non-AIDS cancer, and grade 4 outcomes. For these analyses, events were considered as time-dependent covariates and all-cause mortality was the outcome. Unadjusted models are stratified by study (ESPRIT and SMART). Adjusted models are stratified by study and include the following baseline covariates: age, gender, race, BMI, $\log_{10}$-transformed baseline $CD4^+$ and nadir $CD4^+$ cell count, prior AIDS, hepatitis B or C co-infection, use of lipid lowering medication, use of blood pressure (BP) medication, $\log_2$-transformed IL-6, $\log_2$-transformed D-dimer, and type of ART treatment categorized as protease inhibitor (PI) without non-nucleoside reverse transcriptase inhibitor (NNRTI), NNRTI with or without a PI, and nucleoside reverse transcriptase inhibitors (NRTI) with neither a PI or NNRTI).

Cox regression, stratified by study, was also used to study predictors, including IL-6 and D-dimer, of the major outcomes previously defined. Log_2-transformed IL-6 and D-dimer were considered as predictors separately. With the $\log_2$ transformation, exponentiation of the parameter estimates from the Cox model gives the increased risk of the event associated with a doubling of the biomarker level. Other baseline covariates considered in the adjusted models with IL-6 and D-dimer were the same as those considered for the risk of death analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) are cited. The homogeneity of associations of IL-6 and D-dimer with the major outcomes was assessed using the method of Wei, Lin and Weissfeld (WLW) [25]. We also compared associations between biomarkers and ChrIRD and non-ChrIRD grade 4 events with this approach.

We examined the proportional hazards assumption for the biomarkers by introducing an interaction term between each $\log_2$ transformed biomarker and log follow-up time. We also calculated hazard ratios associated with a doubling of each biomarker after excluding events in the first two years. As a sensitivity analysis to consider whether an earlier event that might be considered a chronic inflammatory condition did not influence the rate of a subsequent event, when considering ChrIRD events, we censored follow-up if an AIDS, CVD or non-AIDS cancer event preceded it. Similarly, when considering non-ChrIRD events, we censored follow-up at the time of an AIDS, CVD, non-AIDS cancer or ChrIRD event.

All analyses were performed using SAS version 9.3 (Cary, NC). P-values < 0.05 were considered significant.

Results

In total, 4,792 participants were enrolled in the control arms of SMART and ESPRIT (2,752 and 2,040, respectively). After removing participants with $CD4^+$ levels < 300 cells/mm^3 (3 participants), participants on ART with HIV RNA > 500 copies/mL (756), and those not on ART (465), 3,568 participants remained. Women made up 22.8% of the 3,568 participants. Ages ranged from 19 to 77 with median (IQR) age being 42 (36, 49) years. The median

(IQR), baseline $CD4^+$ and nadir $CD4^+$ cell counts were 547 (421, 727) and 210 (108, 314) cells/mm^3, respectively. 25.6% percent reported an AIDS event prior to enrollment. The median (IQR) time on ART at baseline was 5 (3, 8) years. Median (IQR) follow-up time in years was 4.3 (2.1, 6.7); the total person-years of follow-up were 16,178.

The rate of grade 4 events (22.9 per 1000 person years) was higher than that of the composite of AIDS, CVD, non-AIDS cancer, and all-cause mortality (Table 1). 252 participants had at least one AIDS, CVD, or non-AIDS cancer event for a rate of 17.1 events per 1000 person years. Of those that experience a grade 4 event, most participants (252 of 339) experienced one grade 4 event; 54 experienced 2 events; and 33 experienced 3 or more events. ChrIRD grade 4 events accounted for 49% of the participants with a grade 4 event. The most common ChrIRD events were gastroenteritis (8 participants), hepatic cirrhosis (7), acute renal failure (6), and acute pancreatitis (6). The most common non-ChrIRD grade 4 events were depression (7), back pain (5), inguinal hernia (5), and suicide attempt (5) (Table S1). Grade 4 events were also summarized by SOC. Of the MedDRA® SOCs, the rates of infections and infestations and gastrointestinal disorders were highest (Table S2).

Severity as Measured by Risk of Death for Grade 4 and Other Events

In both the unadjusted and covariate adjusted models using time-dependent indicators for grade 4 events, the risk of death was significantly greater (p-value < 0.001) for those who experienced a grade 4 event as compared to those who did not (Table 2). For those who experienced two or three grade 4 events, risk of death was further increased compared to those who did not. Adjusted HRs associated with one, two and three or more events were 5.0 (95% CI: 2.8 – 9.0; p-value = <0.001), 7.8 (95% CI: 3.0 – 20.7; p-value = <0.001), and 27.9 (95% CI: 12.5 – 62.0; p-value = <0.001), respectively. The hazard ratio for grade 4 events was similar to that of AIDS events, but was smaller than those of CVD and non-AIDS cancer events. Risk of death was greatest for those with non-AIDS defining cancers (26.8; 95% CI: 15.7 – 45.7).

In separate models, adjusted HRs for death after ChrIRD and non-ChrIRD grade 4 events were 12.4 (95% CI: 7.4 – 20.8) and 5.2 (95% CI: 3.0 – 8.9), respectively. Additional models considered adjusted and unadjusted risk of death including time dependent covariates for both ChrIRD and non-ChrIRD grade 4 events in the same model. The estimated hazard ratios and 95% confidence intervals for the unadjusted and adjusted models, respectively, were 9.5 (6.1 – 14.9) and 10.5 (6.2 – 17.8) for ChrIRD events and 4.1 (2.6 – 6.6) and 3.8 (2.2 – 6.7) for non-ChrIRD events. Risk of death associated with ChrIRD events was significantly greater than the risk of death associated with non-ChrIRD grade 4 events in the unadjusted (p-value= 0.03) and adjusted (p-value = 0.02) models.

Associations with IL-6 and D-dimer

Higher baseline levels of IL-6 and D-dimer were associated with an increased risk with each of the major outcomes in unadjusted models (Table 3). In the covariate adjusted analysis, HRs were generally reduced but remained significant for most associations, including both biomarkers for ChrIRD events and D-dimer for non-ChrIRD events (Table 4). The association of D-dimer with CVD events that met ERC criteria was similar to the

associations with CVD events that met grade 4 but not ERC criteria, whereas IL-6 was more associated with CVD events that met ERC criteria than the grade 4 CVD events that did not meet ERC criteria (Table 4).

There was no evidence the proportional hazards assumption was violated for any of the biomarker-outcome associations. When events occurring in the first two years were excluded (128 of 339 events) from the analysis, HRs associated with a doubling of IL-6 for all grade 4, ChrIRD grade 4, and non-ChrIRD grade 4 events were 1.14 (95% CI: 0.96 – 1.36), 1.23 (95% CI: 0.97 – 1.56), and 1.15 (95% CI: 0.91 – 1.44) respectively. Excluding events in the first 2 years, HRs associated with a doubling of D-dimer for all grade 4, ChrIRD grade 4, and non-ChrIRD grade 4 events were1.28 (95% CI: 1.10 – 1.49), 1.39 (95% CI: 1.13 – 1.70), and 1.14 (95% CI: 0.94 – 1.40), respectively.

We also carried out a sensitivity analysis for the ChrIRD events in which follow-up was censored if an AIDS, CVD and non-AIDS cancer event occurred before the ChrIRD event. This had very little effect on the HRs for the two biomarkers (Table S3). Likewise, similar analyses for the non-ChrIRD events that censored follow-up for these events or a ChrIRD event also yielded similar HRs (Table S3).

We assessed the homogeneity of IL-6 and D-dimer associations with the major outcomes. The effect of D-dimer was homogenous across all major outcomes ($p=0.50$), whereas the effect of IL-6 varied across the major outcomes ($p<0.001$), largely reflecting the stronger associations with all-cause mortality as compared to other events.

We also assessed the homogeneity of IL-6 and D-dimer with ChrIRD grade 4 events and non-ChrIRD grade 4 events. The association with D-dimer was similar for ChrIRD and non-ChrIRD events ($p=0.66$). The association with IL-6 was stronger for ChrIRD events than non-ChrIRD events ($p=0.003$).

Given the positive association between the two markers and each event, we considered a model that included both biomarkers after log-transformation and other baseline covariates with the composite outcome of AIDS, CVD, non-AIDS cancer, grade 4 events, or death from any cause (n=564 participants with at least one event), to study the effect of each marker independent of the other. Based on this model, a doubling of IL-6 and D-dimer yielded HRs of 1.21 (95% CI: 1.10 – 1.33; $p<0.001$) and 1.23 (95% CI: 1.12 – 1.34; $p<0.001$), respectively.

Other Factors Associated with Grade 4 Events and with Those Classified as ChrIRD and non-ChrIRD Grade 4 Events

Grade 4 events were significantly associated with black race, use of BP lowering treatment, and co-infection with hepatitis in addition to IL-6 and D-dimer. (Table S4). Associations between baseline factors and ChrIRD and non-ChrIRD events were similar (Table S5 and S6). The associations with black race and co-infection with hepatitis were significant for both types of grade 4 events.

Discussion

Consistent with two other reports which included participants with lower CD4+ counts, we show that grade 4 events are a major source of morbidity among participants with HIV [26, 27]. Among the participants in our cohort, all of whom had CD4+ counts ≥ 300 cells/mm^3 at study entry, the rate of grade 4 events was 3 to 6 times higher than AIDS, CVD (expanded to include less serious events and CVD events that did not meet ERC criteria) or non-AIDS cancer considered separately and was higher than the rate for these three outcomes considered as a single composite outcome.

Everyone in our investigation was taking suppressive ART. Thus, we can only speculate whether the grade 4 events are due to underlying HIV disease or to ART. In the Strategic Timing of AntiRetroviral Trial (START) trial which compared immediate versus deferred ART in participants with much higher nadir CD4+ counts, rates of grade 4 events and unscheduled hospitalizations were small and not significantly different between the two ART strategies [28]. This suggests that among participants with higher nadir CD4+ counts, grade 4 events are more likely due to underlying HIV disease, other co-morbidities such as hepatitis co-infection, demographics (age and race), and lifestyle factors (e.g., hypertension) than ART.

We found that baseline measurements of IL-6 and D-dimer, often measured several years before the event, were strongly related to the risk of grade 4 events. The biomarker associations with grade 4 events were similar in strength to those for CVD and non-AIDS cancer, two non-AIDS conditions which have been widely studied in HIV [1]. This adds some support to our hypothesis that the consequences of underlying inflammation are broader than the end-organ diseases referred to as serious non-AIDS conditions.

Grade 4 events represent a variety of potentially life-threatening conditions. We used findings from a recent study in the general population to categorize grade 4 events as those likely to have an inflammatory component as a predominant pathology. ChrIRD events represented 49% of the participants with grade 4 events, and these events were more strongly associated with baseline IL-6 than non-ChrIRD events. However, the associations of baseline D-dimer with ChrIRD and non-ChrIRD events were similar -- both significant and of a magnitude similar to the association with CVD. Given the positive, but moderate, correlation between IL-6 and D-dimer [16, 29], in the setting of HIV, there may be larger number of grade 4 events due to HIV-induced activation of inflammatory and coagulation pathways than we classified as ChrIRD. While more research on the extent of morbidity and mortality due to inflammation is needed, it seems clear that there are a number of conditions associated with an increased risk of death other than AIDS and those that we and others have considered “serious non-AIDS conditions” that are influencing the health of patients with HIV and that could be targets of intervention trials that aim to reduce inflammation.

It is possible that the associations of IL-6 and D-dimer with grade 4 events may be different among patients with higher nadir CD4+ cell count. IL-6 levels are inversely related to nadir CD4+ count [30] but D-dimer levels are positively associated with nadir CD4+ cell counts [29]. In a recent review article [2] it was suggested that the drivers of inflammation may be

different in those who initiate ART early after infection compared to later as in this investigation. This result poses the question of whether the associations of IL-6 and D-dimer with grade 4 events depend on the nadir CD4+ count.

The findings from our investigation have implications for the design of trials of novel interventions that target inflammation in HIV. Such trials might be more efficiently carried out with composite primary or secondary outcomes that include not only AIDS, CVD, and non-AIDS cancer events, but also other inflammatory conditions such as all or a subset of grade 4 events.

Strengths of our study include the size of the cohort and the systematic collection of AIDS, CVD, non-AIDS cancer, and grade 4 events over a median follow-up of 4.3 years.

Weaknesses include the absence of data on the occurrence of grade 4 events prior to enrollment. Grade 4 events occurring during follow-up may not be incident events (e.g., they could be a worsening of a pre-existing condition). Also, while events reviewed by the ERC had extensive documentation, documentation of grade 4 events typically consisted of 2 or 3 terms that defined the medical event. Thus, classification of grade 4 events as CVD and as ChrIRD or non-ChrIRD is imperfect. Additionally, some grade 4 events may have been scheduled hospitalizations for procedures/conditions which were not life threatening. Finally, while the median baseline CD4+ count was 547 cells/mm^3 for our cohort, the median nadir CD4+ count was 210 cells/mm^3. As previously suggested, it will be important to understand the relative rate of grade 4, AIDS, CVD, and non-AIDS cancer and associations of these events with IL-6 and D-dimer among individuals with higher nadirs.

In conclusion, we found that IL-6 and D-dimer were strongly associated with grade 4 events. These events are associated with an increased risk of death, and among participants on suppressive ART with CD4+ counts ≥ 300 cells/mm^3, occur at a much higher rate than AIDS, CVD, and non-AIDS cancer events. Our findings showed that potentially life-threatening conditions associated with the activation of inflammatory and coagulation pathways due to HIV are more extensive than AIDS and serious non-AIDS events which heretofore have been considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Frequency and Rate of Outcomes at Low, Middle, and High Levels of Baseline CD4+ Cell Counts

Event	300 < CD4 < 450		450 < CD4 < 650		CD4 > 650		Total	
	N*	Rate and CI**	N*	Rate and CI**	N*	Rate and CI**	N*	Rate and CI**
AIDS event	23	3.2 (1.6 – 6.7)	20	3.7 (2.3 – 5.8)	11	2.2 (1.1 – 4.3)	54	3.4 (2.5 – 4.5)
CVD event	42	8.3 (5.6 – 12.2)	47	9.1 (6.8 – 12.1)	43	9.6 (7.1 – 13.1)	132	8.9 (7.4 – 10.5)
-CVD by ERC	25	4.6 (2.7 – 7.8)	30	5.8 (4.0 – 8.3)	31	6.7 (4.7 – 9.7)	86	5.8 (4.7 – 7.1)
-CVD by grade 4+	17	3.6 (2.1 – 6.3)	17	3.3 (2.0 – 5.3)	12	2.7 (1.6 – 4.8)	46	3.0 (2.2 – 4.1)
Non-AIDS cancer event	26	5.8 (3.7 – 8.9)	31	5.7 (4.0 – 8.3)	23	4.5 (2.8 – 7.2)	80	5.4 (4.3 – 6.7)
Grade 4 event	140	26.3 (20.9 – 33.2)	115	23.1 (19.2 – 27.7)	84	19.5 (15.7 – 24.1)	339	22.9 (20.5 – 25.6)
-ChrIRD grade 4 event#	68	12.7 (9.2 – 17.6)	54	10.5 (8.0 – 13.7)	43	9.8 (7.2 – 13.2)	165	10.7 (9.1 – 12.5)
-Non-ChrIRD grade 4 event#	89	15.6 (11.5 – 21.2)	76	15.0 (11.9 – 18.8)	49	10.8 (8.0 – 14.4)	214	14.2 (12.3 – 16.3)
Death	49	7.3 (4.6 – 11.6)	35	6.3 (4.5 – 9.0)	29	6.1 (4.2 – 9.0)	113	7.0 (5.8 – 8.6)
At Risk	1096		1240		1232		3568	

*N = number of participants with at least one of the designated event type

**Rate is per 1000 person years and CI is a 95% confidence interval

+CVD by grade 4 but not by ERC, i.e. CVD by ERC and CVD by grade 4 are mutually exclusive for each subject

#Some subjects have both a ChrIRD event and a non-ChrIRD event. These subjects would only be counted once for grade 4 events, so the ChrIRD and non-ChrIRD event counts do not sum to the grade 4 event count.

CVD = cardiovascular disease

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Table 2

Unadjusted and Adjusted Hazard Ratios for Death Associated with Different Types of Events (n=113)[^]

Event Type	Unadjusted HR	95% CI	Adjusted HR*	95% CI
AIDS event (n=54)	7.8	(3.8 – 16.1)	4.6	(1.8 – 12.0)
CVD event (n=132)	17.1	(11.1 – 26.1)	17.1	(10.0 – 29.3)
Non-AIDS cancer event (n=86)	34.6	(22.6 – 53.1)	26.8	(15.7 – 45.7)
Any grade 4 event (n=339)	8.9	(6.0 – 13.2)	6.9	(4.2 – 11.2)
-ChrIRD grade 4 event# (n=165)	13.0	(8.5 – 19.9)	12.4	(7.4 – 20.8)
-Non-ChrIRD grade 4 event# (n=214)	6.6	(4.3 – 10.3)	5.2	(3.0 – 8.9)

*Adjusted HRs for risk of death for those who did vs. those who did not experience an event use a time-dependent indicator for event type. Other covariates in the model include: age, race, gender, baseline $\log_2$ IL-6, baseline $\log_2$ D-dimer, baseline BMI, baseline $\log_{10}$ CD4, $\log_{10}$ nadir CD4, prior AIDS event, Hepatitis B or C co-infection, use of lipid-lowering medication, use of blood pressure medication, and type of ART treatment.

^All models were stratified by study (ESPRIT or SMART).

#Some subjects have both a ChrIRD event and a non-ChrIRD event. These subjects would only be counted once for grade 4 events.

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Table 3

Baseline IL-6 and D-dimer Levels of SMART and ESPRIT Participants with and without an Event

	SMART and ESPRIT Events				
	No Event	**Event**	**Unadjusted HR***	**95% CI***	**P-value***
AIDS events (n)	3514	54			
IL-6 [median (IQR)] (pg/ml)	1.72 (1.10 – 2.71)	2.05 (1.40 – 3.30)	1.36	(1.05 – 1.77)	0.019
D-dimer [median (IQR)] (μg/ml)	0.22 (0.15 – 0.35)	0.26 (0.18 – 0.38)	1.29	(1.01 – 1.64)	0.040
CVD events (n)	3436	132			
IL-6 [median (IQR)] (pg/ml)	1.70 (1.10 – 2.70)	2.50 (1.70 – 3.83)	1.51	(1.29 – 1.76)	<0.001
D-dimer [median (IQR)] (μg/ml)	0.22 (0.15 – 0.34)	0.29 (0.20 – 0.47)	1.36	(1.17 – 1.57)	<0.001
Non-AIDS cancer events (n)	3488	80			
IL-6 [median (IQR)] (pg/ml)	1.70 (1.10 – 2.70)	2.20 (1.70 – 3.32)	1.39	(1.13 – 1.70)	0.002
D-dimer [median (IQR)] (μg/ml)	0.22 (0.15 – 0.34)	0.27 (0.17 – 0.47)	1.27	(1.05 – 1.54)	0.014
Grade 4 events (n)	3229	339			
IL-6 [median (IQR)] (pg/ml)	1.70 (1.10 – 2.70)	2.19 (1.50 – 3.60)	1.36	(1.23 – 1.51)	<0.001
D-dimer [median (IQR)] (μg/ml)	0.22 (0.14 – 0.34)	0.28 (0.19 – 0.46)	1.31	(1.19 – 1.44)	<0.001
ChrIRD grade 4 events# (n)	3403	165			
IL-6 [median (IQR)] (pg/ml)	1.70 (1.10 – 2.70)	2.40 (1.67 – 4.15)	1.58	(1.37 – 1.81)	<0.001
D-dimer [median (IQR)] (μg/ml)	0.22 (0.15 – 0.34)	0.29 (0.19 – 0.46)	1.35	(1.17 – 1.55)	<0.001
Non-ChrIRD grade 4 events# (n)	3354	214			
IL-6 [median (IQR)] (pg/ml)	1.70 (1.10 – 2.70)	2.10 (1.40 – 3.50)	1.24	(1.09 – 1.42)	0.002
D-dimer [median (IQR)] (μg/ml)	0.22 (0.14 – 0.34)	0.28 (0.19 – 0.47)	1.29	(1.14 – 1.46)	<0.001
Deaths (n)	3455	113			
IL-6 [median (IQR)] (pg/ml)	1.70 (1.10 – 2.70)	2.94 (1.90 – 4.20)	1.83	(1.55 – 2.15)	<0.001
D-dimer [median (IQR)] (μg/ml)	0.22 (0.15 – 0.34)	0.33 (0.22 – 0.55)	1.52	(1.29 – 1.79)	<0.001

*From an unadjusted Cox regression model on the $\log_2$ transformed baseline IL-6 and D-dimer variables.

^All models were stratified by study (ESPRIT or SMART).

[#] Some subjects have both a ChrIRD event and a non-ChrIRD event. These subjects would only be counted once for grade 4 events, so the ChrIRD and non-ChrIRD event counts do not sum to the grade 4 event count.

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Table 4

Adjusted Hazard Ratios for Time to First Event[^]

	IL-6 (log_2 pg/ml)[*]			D-dimer (log_2 µg/ml)[*]		
Event	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
AIDS	1.36	(1.00 – 1.85)	0.048	1.23	(0.92 – 1.64)	0.17
CVD	1.29	(1.06 – 1.56)	0.010	1.19	(1.00 – 1.41)	0.054
-CVD by ERC	1.37	(1.09 – 1.72)	0.008	1.16	(0.94 – 1.43)	0.16
-CVD by grade 4[+]	1.15	(0.81 – 1.63)	0.44	1.24	(0.92 – 1.67)	0.17
Non-AIDS Cancer	1.22	(0.94 – 1.57)	0.13	1.04	(0.83 – 1.31)	0.75
Grade 4	1.19	(1.05 – 1.35)	0.006	1.23	(1.10 – 1.37)	<0.001
-ChrIRD[#]	1.38	(1.17 – 1.64)	<0.001	1.25	(1.06 – 1.46)	0.007
-Non-ChrIRD[#]	1.11	(0.94 – 1.30)	0.21	1.20	(1.05 – 1.39)	0.010
Death	1.65	(1.36 – 2.00)	<0.001	1.28	(1.05 – 1.56)	0.014

[*] Adjusted HRs use a time-dependent indicator for event type. Other baseline covariates in the model include: age, race, gender, BMI, log_{10} CD4, log_{10} nadir CD4, prior AIDS event, Hepatitis B or C co-infection, use of lipid-lowering medication, use of blood pressure medication, and type of ART treatment.

[^] All models were stratified by study (ESPRIT or SMART).

[+] CVD by grade 4 but not by ERC, i.e. CVD by ERC and CVD by grade 4 are mutually exclusive for each subject

[#] Some subjects have both a ChrIRD event and a non-ChrIRD event. These subjects would only be counted once for grade 4 events, so the ChrIRD and non-ChrIRD event counts do not sum to the grade 4 event count.

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