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Plasma CD163 independently predicts all-cause mortality from HIV-1 infection

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ABSTRACT

Background: CD163, a monocyte- and macrophage-specific scavenger receptor, is shed as soluble CD163 (sCD163) during the proinflammatory response. Here, we assessed the association of plasma sCD163 levels in HIV-1 infection to AIDS and all-cause mortality.

Methods: Plasma sCD163 levels were measured in 933 HIV-1 infected individuals. Hazard ratios (HR) with 95% confidence intervals (95% CI) associated with mortality were computed by Cox proportional hazards regression.

Results: At baseline, 86% were on antiretroviral treatment, 73% had plasma HIV RNA < 50 copies/mL and the median CD4 T cell count was 503 cells/µl. During 10.5 years of follow up there were 167 (17.9%) deaths. Plasma sCD163 was higher in non-survivors than in survivors (4.92 mg/L (3.29-8.65) vs. 3.16 mg/L (2.16-4.64), P=0.0001). The cumulative incidence of death increased with increasing plasma sCD163 levels corresponding to a 6% or 35% increased risk of death for each mg/L or quartile increase in baseline plasma sCD163 (adjusted HR: 1.06 (95% CI: 1.03-1.09) and 1.35 (95% CI: 1.13-1.63), respectively).

Conclusion: Plasma sCD163 was an independent marker of all-cause mortality in a cohort of HIV-1 infected individuals suggesting that monocyte/macrophage activation may play a role in HIV pathogenesis and be a target of intervention.

INTRODUCTION

Immune activation and chronic inflammation is associated with disease progression in HIV infection. Although inflammation and immune activation is most profound during untreated HIV infection, virtually all components of innate and adaptive immunity remain dysfunctional despite antiretroviral treatment (ART). Consequently, many individuals experience persistent abnormalities of immune activation, inflammation and coagulation (1;2). T-cell activation rapidly declines following initiation of ART but changes in innate immune activation markers are more variable (3-5).. Selected markers of inflammation and coagulation have been correlated to HIV-associated outcomes (6-9).

CD163 is a haptoglobin-haemoglobin scavenger receptor expressed predominantly on monocytes and macrophages (10). CD163 is reported to be involved in erythroblast adhesion (11), immune sensing of bacteria (12), and binding of TWEAK (TNF-like weak inducer of apoptosis) (13). Upon proinflammatory stimuli such as Toll-like receptor (TLR) activation by lipopolysaccharide (LPS) or other microbial ligands, soluble CD163 (sCD163) is shed from monocytes by proteinase-mediated cleavage during the inflammatory response (14). The cleavage is mediated by ADAM-17, an inflammation-inducible enzyme that also leads to release of TNF- α, hence the alternative designation of ADAM17 as TNF-α-activating enzyme (TACE) (15;16).

The function of sCD163 is hitherto unknown but it is believed to be important in resolution of inflammation (17). Soluble CD163 has been associated with disease progression in viral hepatitis (18), and with increased mortality following sepsis and tuberculosis (19;20).

Recent studies have shown that levels of sCD163 are elevated in HIV infected individuals and that sCD163 plasma levels remain elevated despite ART suggesting residual monocyte/macrophage activation after HIV suppression (21-25). Co-infection with hepatitis C virus, ongoing HIV

replication and treatment with a protease inhibitor was associated with an attenuated decrease in plasma sCD163 in ART treated individuals (23). Further, elevated plasma sCD163 levels ahave been associated with coronary lesions and stenosis in HIV infected individuals receiving ART (21;24;26). Collectively, these studies indicate that plasma sCD163 levels are correlated with HIV-related morbidity. However, a role for sCD163 in disease progression and outcome has not been determined.

The objective of this study is to evaluate the influence of plasma sCD163 levels on progression to death and AIDS in a contemporary cohort of HIV infected individuals that were followed for more than 10 years.

METHODS

Hvidovre Hospital Clinic Cohort

Patients eligible for the current study were those alive and in care from August 2004 through February 2005 at the outpatient clinic of the Department of Infectious Diseases. Of 1083 consecutive patients, 933 with a plasma sample were included; 150 were excluded either due to lack of plasma for analysis (n=139), loss to follow up (n=7), infection with HIV-2 (n=2), or an invalid personal identifier (n=2). Blood was drawn at enrolment and plasma stored at -80^0 C until analysis in 2005. All patients had a clinical follow up every 3-6 months. AIDS events during follow up were captured through the prospective, ongoing nationwide Danish HIV Cohort Study (27). Antibody to Hepatitis C virus (HCV) and plasma HCV RNA was determined as previously described (28). Patients not receiving ART at inclusion were offered this during follow up according to national guidelines. ART is provided free of charge by the Danish healthcare system. The study was approved by the

regional ethics committee (record no. KF01272977(II)) and the Danish Data Protection Agency (record no. 2014-41-3492).

Data sources

Each resident of Denmark is assigned a unique personal identifier through the Civil Registration System (29). Changes in vital status, including date of emigration and date of death, are tracked daily by the Civil Registration System.

Date and cause of death was retrieved from the Danish Register of Causes of Death using the Civil Registration System identifier (30).

The Danish National Patient Register is updated monthly and contains information on all admissions to Danish hospitals and discharge diagnosis codes according to the International Classification of Disease (ICD)-10 from 1994 (31).

Comorbidity

The Charlson Comorbidity Index score was used to estimate comorbidity prior to determination of sCD163 (32;33). The score takes into account both the number and severity of comorbid disease. Using registrations 10 years prior to plasma sCD163 determination, we calculated a modified Charlson Comorbidity Index score for all cases. Each of 16 categories (HIV/AIDS was excluded) could only contribute once to the overall index. We defined three levels of comorbidity: low (score: 0), intermediate (score: 1-2) and high (score: >2).

Measurement of sCD163

Plasma levels of sCD163 were measured in duplicate using a previously described ELISA (34). In brief, control samples and standards traceable to purified CD163 were co-analyzed in each run. The total imprecision of the assay was <6 % with a detection limit of <0.006 mg/L. The reference range for healthy controls has previously been determined to 0.89-3.95 mg/L (35). Measurement and reading of sCD163 levels was carried out by laboratory technicians blinded to the outcome of study participants.

Statistics

All values are median and interquartile range. We calculated descriptive statistics and tested differences in medians with the Mann-Whitney or Kruskall-Wallis tests. Scatter plots and Spearman's rank correlation was used to examine the association between levels of plasma sCD163, plasma HIV RNA and CD4 T cell count.

Unadjusted and adjusted Cox regression analysis with 95% confidence interval (CI) was performed to determine the hazard ratio (HR) of death during follow up. Explanatory variables in the models included age, sex, race, transmission category, comorbidity level, ART, prior AIDS, plasma HIV RNA, blood CD4 T cell count, HCV antibody, plasma HCV RNA, smoking status and plasma sCD163. The models for each of the explanatory variables were adjusted for possible confounders and not intermediate variable; selection of confounders was made prior to model fit. All patients were followed from the date of study inclusion to event or cencoring. Patients were censored on the date of death, emigration or last follow up (up until May 22, 2015), whichever came first. Kaplan-Meier survival curves were constructed corresponding to quartiles of sCD163. Finally to verify whether the effect of sCD163 on time to death was modified by sex, prior AIDS, antiretroviral

treatment, plasma HIV RNA, injecting drug use, heterosexual transmission or smoking status, we extended the model for sCD163 with an interactions term between each of the possible mediators and sCD163. Analyses were performed using IBM SPSS Statistics version 22 (Armonk, New York, United States).

Results

Baseline characteristics

Clinical and demographic characteristics of the 933 individuals are shown in Table 1. The cohort was predominantly white (79%), male (72%) and treatment-experienced (85.6% on ART for a median of 6.0 years). By end of follow up, 104 of 134 treatment naïve individuals had started ART. Of the remaining 30 individuals, 12 died without starting ART. Eight-teen individuals had not started ART for different reasons as of May 2015.

The median plasma concentration of sCD163 was 3.39 mg /L (2.30-5.02); levels tended to be higher for women than for men (P=0.054). Asian race had lower sSC163 levels than other races (P=0.02). Individuals not receiving ART at baseline or who were not suppressed (HIV RNA ≥ 50 copies/mL) had higher sCD163 levels than individuals who were treated or who were suppressed (both P<0.0001). Individuals with a history of IDU or HCV antibody or HCV RNA positivity had higher sCD163 levels compared to individuals without (all P<0.0001). sCD163 increased with higher Charlson Comorbidity Index level (P=0.004) and was lower for never smokers compared to ever smokers or unknown smoking status (P=0.02). There was a positive correlation between plasma sCD163 and plasma HIV RNA for all patients (r=0.40, P=0.0001) and for the subgroup of patients with detectable plasma HIV RNA (> 50 copies/ml) (r=0.36, P=0.0001). There was an

inverse correlation between plasma sCD163 and blood CD4 T cell count (r=-0.25, P=0.0001) for all patients and for patients with detectable HIV RNA (r=-0.20, P=0.0001).

Death during follow up

There were 167 (17.9%) deaths during 10.5 years of follow up. The median time to death was 4.5 (2.2-7.2) years. Plasma sCD163 was higher in non-survivors than in survivors (4.92 mg/L (3.29-8.65) vs. 3.16 mg/L (2.16-4.64), P=0.0001).

The underlying cause of death had been determined for 144 (86.2%) cases. Infection was the most common cause of death (n=54), followed by cancer (n=25), respiratory or cardiovascular disease (n=17), and alimentary tract disease (n=7). Accident or suicide (n=17) , other or unknown causes (n=14) accounted for the remaining deaths.

Plasma soluble CD163 levels were associated with time to death

The cumulative incidence of death increased with increasing plasma sCD163 levels (Log rank test: P=0.0001) (Figure 1). By univariate Cox analysis, there was an increased risk of death for each mg/L increase in plasma sCD163 at baseline (HR: 1.11 (95% CI: 1.08-1.13) (Table 2). Further, age, race, comorbidity level, IDU, plasma HIV RNA level, blood CD4 T cell count and smoking status were associated with death during follow up. In adjusted analysis, the influence of plasma sCD163 levels on risk of death was attenuated (HR: 1.06 (95% CI: 1.03-1.09)). The adjusted HR of death per quartile increase of sCD163 was 1.35 (95% CI: 1.13-1.63). Similarly, a strong risk gradient was evident for adjusted HRs for the fourth, third, and second quartiles of sCD163 compared to the first quartile of 2.65 (95% CI: 1.47-4.80, P<0.001), 1.77 (95% CI: 0.98-3.17, P=0.06) and 1.15 (0.62-2.11, P=0.66), respectively. By adjustment for individually relevant confounders, age, sex, race,

transmission category, comorbidity, blood CD4 T cell counts and smoking status were each associated with death.

AIDS during follow up

There were 35 (3.8%) new cases of AIDS during 10.5 years of follow up. The median time to AIDS was 3.2 (0.7-6.8) years. Cases who developed AIDS during follow up had higher baseline plasma sCD163 than cases who did not develop AIDS (4.96 (3.80-7.48) vs. 3.36 (2.28-4.96) mg/L, P=0.0001). Levels of plasma sCD163, however, did not predict the development of AIDS (HR: 1.00 (95% CI: 0.92-1.09)) per mg increase in sCD163 after adjustment for covariates.

Subgroup and sensitivity analysis

Because our cohort was heterogeneous with regard to demographic composition and treatment history at baseline, we performed several subgroup analyses by including interaction terms to determine if there were differences in risk of death associated with plasma sCD163 levels (Table 3). Elevated plasma sCD163 levels conferred different increased risks of death per mg/L increment for individuals with undetectable (< 50 cp/ml) plasma HIV RNA at baseline compared to individuals with detectable HIV RNA; . with ART at baseline compared to not receiving ART; non-IDU transmission compared to IDU transmission; heterosexual transmission; females compared to males; no diagnosis of AIDS at baseline compared to AIDS at baseline; and never smokers compared to smokers and unknown. There was no statistically significant interaction between sCD163 and outcome and age, race, comorbidity, or CD4 cell count.

After excluding the 17 deaths attributed to accident or suicide, the risk of death associated with plasma sCD163 remained unchanged (HR: 1.07 (95% CI: 1.04-1.10)). Analysis of specific causes of

death showed that for every mg/L increment of sCD163 the risk of infectious disease death (HR: 1.06 (95% CI: 1.02-1.11)), non-infectious disease death (HR: 1.05 (95% CI: 1.01-1.09)) and cardiovascular death (1.08 (1.01-1.15)) was increased. The remaining categories were too small for individual analysis.

DISCUSSION

Here we show in a large contemporary cohort that high sCD163 levels were independently associated with an increased risk of all-cause mortality. The association was robust after controlling for factors traditionally associated with HIV outcomes, across different subgroups and was particularly high for HIV-infected individuals who acquired HIV heterosexually and for never smokers.

Subjects with the highest sCD163 levels had a 165% increased risk of death compared to those with the lowest levels of sCD163. The risk gradient was comparable across most groups. The increase in risk of death was not explained by untreated and uncontrolled HIV infection because sCD163 levels did not predict outcome in individuals who were not receiving ART. Untreated individuals were mostly healthy and did not receive ART at baseline because they had high CD4 T cell counts but initiated ART during follow up according to guidelines. Injecting drug users had a high risk of death and the highest sCD163 levels but sCD163 alone did not explain the increased risk of death associated with IDU. We speculate that this is likely a consequence of comorbidity, behavior and life style associated with IDU. The largest transmission category in our clinic (MSM) had an increased risk of death associated with sCD163 that was comparable to the overall cohort. Similarly, the large groups of individuals on ART or who had undetectable HIV RNA, had sCD163

associated risks that were comparable to the cohort in general. However, individuals who had acquired HIV through heterosexual transmission had a 40% higher increase in mortality for each 1 mg increase in plasma sCD163 than any other group. Heterosexual transmission is a heterogeneous group. However, heterosexual individuals who died during follow up were predominantly white and male but did not differ otherwise compared to other transmission categories (data not shown). Although they accounted for a minority of deaths, white heterosexual males had the highest risk of death during follow up. Our findings indicate that sCD163 levels in combination with patient characteristics may be used to identify those individuals at risk of disease and death.

Other inflammatory biomarkers have been linked to an increased risk of HIV-related all-cause mortality. Interestingly, the strongest associations with mortality were seen in untreated individuals for IL-6, D-dimer and sCD14 and to a lesser extent in treated individuals (6;7). Plasma sCD163 levels, in contrast, were predictive of mortality in treated but not in untreated individuals indicating that sCD163 could be useful to identify individuals with ongoing inflammation despite being successfully treated with ART. During untreated HIV, inflammation and activation is driven by HIV replication. In individuals receiving ART, low-level HIV replication, microbial translocation, viral coinfection (e.g. CMV or HCV), comorbidity and life style factors such as tobacco and alcohol use are believed to contribute to chronic inflammation (36). Beltran et al. showed that co-infection with HCV and ongoing HIV replication was associated with an attenuated decrease in plasma sCD163 after initiation of ART (23). In our study, we adjusted for both of these factors because they were associated with mortality in univariate analysis. Only HIV RNA level remained an independent predictor in adjusted analysis suggesting that HCV status is likely a marker of other unfavourable risks such as IDU. Comorbidity and smoking was high in our cohort and both

predictably associated with outcome. Importantly, however, the predictive value of sCD163 was unchanged after adjustment for these important drivers of inflammation. Emerging data suggest that chronic immune activation may accelerate the burden of several age-related comorbidities in the HIV population (37). Future studies should investigate a possible association between elevated sCD163 and diseases characterized by chronic inflammation such as cardiovascular disease, diabetes and cancer. The causes of death varied and included infection, cancer, cardiovascular, respiratory, hepatic and alimentary tract diseases. Our analysis did not indicate differences in risk of death caused by infectious disease, non-infectious disease or cardiovascular disease. The size of the other categories precluded analysis. Studies are warranted to investigate if the increased risk of mortality associated with sCD163 levels may be mediated through specific diseases.

We regard the large cohort with long-term and complete follow up as a particular strength of the present study. The cohort design permitted estimation of relative risks of outcome that cannot be estimated in case-control studies. The cohort consisted of a clinic population with diverse and heterogeneous characteristics that may be generalizable and relevant to many settings.

Limitations include a limited number of AIDS events during follow up precluding firm conclusions regarding smaller associations with sCD163 levels. We did not measure markers of microbial translocation that have been associated with chronic inflammation and disease progression (9). Obesity has recently been associated with high levels of sCD163 in HIV infection but information on body mass index was not available in our cohort (38). Causation cannot be inferred from non-randomized studies. In this respect it is of interest that sCD163 levels were lowered by 20% after two-weeks of treatment with an antiemetic, aprepitant (39). Future interventional studies using this drug or others that target pathways of sCD163 are required to determine if a strategy of monocyte/macrophage attenuation could reduce morbidity and mortality associated with HIV.

In conclusion, our study showed that sCD163 predicted all-cause mortality in antiretroviral treated individuals, suggesting the importance of monocyte/macrophage activation and a possible target for intervention. Further, our demonstration of a strong risk gradient in the highest quartile of patients suggests that elevated plasma sCD163 may help identifying a risk group requiring further work up and surveillance.

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Table 1. Baseline clinical and demographic characteristics of the Hvidovre Hospital Clinic Cohort

	n (%)	Plasma sCD163, mg/L Median (IQR)
All	, n=933	3.40 (2.31-5.04)
Age, years	43 (38-50)	-
Male	664 (72%)	3.31 (2.27-4.92)
Female	169 (28%)	3.62 (2.36-5.48)
Race		
White	739 (79%)	3.48 (2.36-5.20)
Black	121 (13%)	3.44 (2.21-4.64)
Asian	53 (6%)	2.39 (1.90-4.33)
Other	22 (2%)	3.24 (2.22-4.75)
Transmission group		
MSM	414 (44%)	3.03 (2.15-4.34)
HSX	327 (35%)	3.23 (2.14-4.71)
IDU	140 (15%)	5.96 (4.20-9.21)
Other	51 (6%)	3.06 (2.35-4.29)
Prior diagnosis of AIDS		
No	726 (78%)	3.43 (2.28-5.01)
Yes	207 (22%)	3.35 (2.33-5.08)
Modified Charlson Comorbidity Index		
Low	697 (74.6%)	3.30 (2.18-4.86)
Intermediate	203 (21.8%)	3.55 (2.70-5.50)
High	33 (3.5%)	3.78 (2.49-7.40)
Blood CD4 T cell count, cells/µL	503 (351-699)	-
Plasma HIV RNA, copies/mL	<20 (<20-92)	-
< 50 copies/mL	674 (74%)	2.98 (2.08-4.33)
> 50 copies/mL	239 (26%)	4.91 (3.45-7.54)
HCV antibody		
Negative	797 (85%)	3.12 (2.15-.49)
Positive	136 (15%)	6.24 (4.64-9.52)
Plasma HCV RNA		
Negative	844 (90%)	3.20 (2.18-4.62)
Positive	89 (10%)	6.91 (5.14-10.47)
Antiretroviral treatment		
No	134 (14%)	5.01 (3.62-7.54)
Yes	799 (86%)	3.16 (2.17-4.72)
Time on ART at inclusion, years	6.0 (3.5-7.6)	-
Smoking status, n=842		
Never	230 (24%)	3.29 (2.30-4.66)
Ever	612 66%)	3.37 (2.20-5.11)
Unknown	91 (10%)	3.82 (2.62-5.91)

IQR: interquartile range.

sCD163: soluble CD163; MSM: men who have sex with men; HSX: heterosexual; IDU: injecting drug use; HCV: Hepatitis C virus). Modified Charlson Comorbidity Index: low (score = 0), intermediate (score 1-2), and high (score > 2).

Table 2. Multiple analysis of factors associated with death in the Hvidovre Hospital Clinic Cohort during 10 years of follow up.

Variable	Crude HR (95% CI)	Adjusted HR (95% CI)	P value[l]
sCD163, per mg/L increment	1.11 (1.09-1.13)	1.06 (1.03-1.09)[a]	<0.0001
Age, per year increment	1.07 (1.05-1.08)	1.06 (1.05-1.08)[b]	<0.0001
Sex			
Male	1.0	1.0[c]	
Female	0.74 (0.52-1.07)	0.90 (0.60-1.35)	0.61
Race			
White	1.0	1.0[d]	
Black	0.07 (0.02-0.29)	0.14 (0.03-0.58)	0.007
Asian	0.16 (0.04-0.64)	0.33 (0.08-1.36)	0.13
Other	1.32 (0.58-2.99)	1.85 (0.81-4.23)	0.20
Transmission group			
MSM	1.0	1.0[e]	
HSX	0.71 (0.47-1.09)	1.45 (0.93-2.28)	0.10
IDU	3.86 (2.72-5.49)	7.22 (4.80-10.84)	<0.0001
Other	1.07 (0.51-2.24)	1.36 (0.64-2.88)	0.43
Prior AIDS			
No	1.0	1.0[f]	
Yes	1.15 (0.81-1.63)	1.33 (0.88-2.03)	0.18
Modified Charlson Comorbidity Index			
Low	1.0	1.0[g]	
Intermediate	2.91 (2.10-4.03)	1.90 (1.29-2.80)	0.001
High	7.41 (4.54-12.08)	4.75 (2.43-9.28)	<0.0001
Log HIV RNA, per log increment	1.08 (1.03-1.14)	1.02 (0.95-1.10)[h]	0.56
CD4 T cell count per doubling	0.65 (0.58-0.73)	0.78 (0.63-0.96)[i]	0.02
Antiretroviral treatment			
No	1.0	1.0[j]	
Yes	1.04 (0.67-1.62)	1.30 (0.76-2.22)	0.35
Plasma HCV RNA positive			
No	1.0	1.0[k]	
Yes	3.87 (2.72-5.50)	1.11 (0.68-1.81)	0.70
Smoking status			
Never	1.0	1.0[e]	
Ever	4.43 (2.32-8.46)	2.59 (1.28-5.22)	0.008
Unknown	20.02 (10.09-39.72)	9.84 (4.65-20.84)	<0.0001

a: adjusted for age, sex, race, transmission group, prior AIDS, comorbidity, HIV RNA, CD4 T cell count, antiretroviral treatment, HCV RNA and smoking status; b: adjusted for sex and race; c: adjusted for age, race and transmission group; d: adjusted for age, sex and transmission group; e: adjusted for age, sex and race; f: adjusted for age, sex, race, transmission group and smoking status; g: adjusted for age, sex, transmission group, prior AIDS and smoking status; h: adjusted for sCD163, age, sex, race, transmission group, prior AIDS, Charlson Comorbidity Index, CD4 T cell count, antiretroviral treatment, HCV RNA and smoking status; i: adjusted for sCD163, age, sex, race, transmission group, prior AIDS, Charlson Comorbidity Index, HIV RNA, antiretroviral treatment, HCV RNA and smoking status; j: adjusted for age, sex, transmission group, prior AIDS, HIV RNA, and CD4 T cell count; k: adjusted for sCD163, age, sex, race, transmission group, prior AIDS, Charlson Comorbidity Index, HIV RNA, CD4 T cell count, antiretroviral treatment and smoking status; l: Wald test

HR: hazard ratio; CI: confidence interval; sCD163: soluble CD163; MSM: men who have sex with men; HSX: heterosexual; IDU: injecting drug use; mCCI: modified Charlson Comorbidity Index; HCV: Hepatitis C virusModified Charlson Comorbidity Index: low (score = 0), intermediate (score 1-2), and high (score > 2).

Table 3. Multiple analysis of risk of death associated with plasma soluble CD163 levels for subgroups.

Patient group	**Adjusted HR (95% CI), per mg/L increment in plasma sCD163**	**P value[d]**	**P value for interaction[g]**
Antiretroviral treatment at baseline			0.005
No	1.05 (0.99-1.12)[a]	0.12	
Yes	1.12 (1.08-1.16)[a]	<0.0001	
Plasma HIV RNA < 50 cp/ml			0.008
No	1.05 (1.01-1.09)[b]	0.03	
Yes	1.13 (1.08-1.18)[b]	<0.0001	
Injecting drug use			0.04
No	1.14 (1.10-1.19)[c]	<0.0001	
Yes	1.07 (1.04-1.10)[c]	<0.0001	
Heterosexual transmission			<0.001
No	1.10 (1.08-1.13)[c]	<0.001	
Yes	1.39 (1.35-1.55)[c]	<0.001	
Sex			<0.01
Male	1.08 (1.06-1.11)[d]	<0.0001	
Female	1.10 (1.05-1.16)[d]	<0.0001	
Prior AIDS			<0.001
No	1.14 (1.10-1.18)[e]	<0.0001	
Yes	1.06 (1.02-1.11)[e]	0.005	
Smoking status			0.017
Never	1.41 (1.17-1.71)[f]	<0.0001	
Ever	1.13 (1.09-1.16)[f]	<0.0001	
Unknown	1.06 (1.04-1.09)[f]	<0.0001	

HR: Hazard ratio; CI: confidence interval; sCD163: soluble CD163

a: adjusted for age, sex, CD4, HIV RNA, transmission group, and prior AIDS.

b: adjusted for age, race, sex, modified Charlson Comorbidity Index, ART at baseline, CD4, transmission group, prior AIDS, HCV RNA, and smoking status

c: adjusted for age, race, and sex.

d: adjusted for age, race and transmission group

e: adjusted for age, sex, race, transmission group and smoking status

f: adjusted for age, sex and race

g: Wald test

Figure legend

Figure 1. Cumulative survival according to plasma soluble CD163 quartiles.