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MAJOR ARTICLE

Plasma Soluble CD163 Level Independently Predicts All-Cause Mortality in HIV-1–Infected Individuals

Troels Bygum Knudsen,[1] Gideon Ertner,[1] Janne Petersen,[2,4] Holger Jon Møller,[6] Søren K. Moestrup,[7,8] Jesper Eugen-Olsen,[3] Gitte Kronborg,[1,5] and Thomas Benfield[1,3,5]

[1]Department of Infectious Diseases, [2]Optimed, Clinical Research Center, [3]Clinical Research Center, Hvidovre Hospital, [4]Section of Biostatistics, Department of Public Health, [5]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, [6]Department of Clinical Biochemistry, Aarhus University Hospital, [7]Department of Biomedicine, Aarhus University, and [8]Institute of Molecular Medicine, University of Southern Denmark, Odense

Background. CD163, a monocyte- and macrophage-specific scavenger receptor, is shed as soluble CD163 (sCD163) during the proinflammatory response. Here, we assessed the association between plasma sCD163 levels and progression to AIDS and all-cause mortality among individuals infected with human immunodeficiency virus type 1 (HIV).

Methods. Plasma sCD163 levels were measured in 933 HIV–infected individuals. Hazard ratios (HRs) with 95% confidence intervals (CIs) associated with mortality were computed by Cox proportional hazards regression.

Results. At baseline, 86% were receiving antiretroviral treatment, 73% had plasma a HIV RNA level of <50 copies/mL, and the median $CD4^+$ T-cell count was 503 cells/μL. During 10.5 years of follow-up, 167 (17.9%) died. Plasma sCD163 levels were higher in nonsurvivors than in survivors (4.92 mg/L [interquartile range {IQR}, 3.29–8.65 mg/L] vs 3.16 mg/L [IQR, 2.16–4.64 mg/L]; $P = .0001$). The cumulative incidence of death increased with increasing plasma sCD163 levels, corresponding to a 6% or 35% increased risk of death for each milligram per liter or quartile increase, respectively, in baseline plasma sCD163 level (adjusted HR, 1.06 [95% CI, 1.03–1.09] and 1.35 [95% CI, 1.13–1.63], respectively).

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

Keywords. HIV; soluble CD163; inflammation; outcome; mortality.

Immune activation and chronic inflammation is associated with disease progression in human immunodeficiency virus (HIV) infection. Although inflammation and immune activation are 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 involving immune activation, inflammation, and coagulation [1, 2]. T-cell activation rapidly declines following initiation of antiretroviral therapy (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-hemoglobin 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 the cytokine TWEAK [13]. Upon exposure to proinflammatory stimuli such as Toll-like receptor activation by lipopolysaccharide 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 tumor necrosis factor α (TNF-α); hence the alternative designation of ADAM17 as TNF-α–activating enzyme [15, 16].

The function of sCD163 is hitherto unknown, but it is believed to be important in resolution of inflammation [17]. sCD163 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]. Coinfection with hepatitis C virus (HCV), ongoing HIV replication, and treatment with a protease inhibitor were associated with an attenuated decrease in plasma sCD163 level in ART recipients [23]. Further, elevated plasma sCD163 levels have 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

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Correspondence: T. Benfield, Department of Infectious Diseases, Hvidovre Hospital, Kettegaard Alle 30, 2650 Hvidovre, Denmark (tlb@dadlnet.dk).

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contemporary cohort of HIV-infected individuals who were followed for >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 because of a 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 specimens were collected at enrollment, and plasma was stored at −80°C until analysis in 2005. All patients underwent clinical follow-up every 3–6 months. AIDS-defining events during follow-up were captured through the prospective, ongoing nationwide Danish HIV Cohort Study [27]. Antibody to HCV and plasma HCV RNA level was determined as previously described [28]. Patients who were not receiving ART at study inclusion were offered ART 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, Tenth Revision*, from 1994 [31].

Comorbidity

The Charlson comorbidity index was used to estimate comorbidity prior to determination of sCD163 levels [32, 33]. The score takes into account both the number and severity of comorbid disease. Using registrations 10 years prior to determination of plasma sCD163 levels, we calculated a modified Charlson comorbidity index for all cases. Each of 16 categories (HIV/AIDS was excluded) could only contribute once to the overall index. We defined 3 levels of comorbidity: low (score, 0), intermediate (score, 1–2), and high (score, >2).

Measurement of sCD163 Levels

Plasma levels of sCD163 were measured in duplicate, using a previously described enzyme-linked immunosorbent assay [34]. In brief, control samples and standards traceable to purified CD163 were coanalyzed 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.

Statistical Analysis

All values are medians and interquartile ranges (IQRs). We calculated descriptive statistics and tested differences in medians with the Mann–Whitney or Kruskal–Wallis tests. Scatterplots and Spearman rank correlation were used to examine the association between levels of plasma sCD163, plasma HIV RNA load, and $CD4^+$ T-cell count.

Unadjusted and adjusted Cox regression analyses were performed to determine the hazard ratio (HR; with 95% confidence intervals [CIs]) of death during follow-up. Explanatory variables in the models included age, sex, race, transmission category, comorbidity level, ART receipt, prior AIDS diagnosis, plasma HIV RNA load, blood $CD4^+$ T-cell count, HCV antibody positivity, plasma HCV RNA positivity, smoking status, and plasma sCD163 level. The models for each of the explanatory variables were adjusted for possible confounders but not intermediate variables; selection of confounders was made prior to model fit. All patients were followed from the date of study inclusion to event or censoring. Patients were censored on the date of death, emigration, or last follow-up visit (until 22 May 2015), whichever came first. Kaplan–Meier survival curves were constructed corresponding to quartiles of sCD163 level. Finally, to verify whether the effect of sCD163 levels on time to death was modified by sex, prior AIDS, ART receipt, plasma HIV RNA load, injection drug use, heterosexual transmission, or smoking status, we extended the model for sCD163 with an interaction term between each of the possible mediators and sCD163. Analyses were performed using IBM SPSS Statistics, version 22 (Armonk, New York).

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% were receiving ART, with a median ART duration of 6.0 years). By the end of follow-up, 104 of 134 treatment-naive individuals had started ART. Of the remaining 30 individuals, 12 died without starting ART. Eighteen individuals had not started ART, for different reasons, as of May 2015.

The median plasma concentration of sCD163 was 3.39 mg/L (IQR, 2.30–5.02 mg/L); levels tended to be higher for women than for men ($P = .054$). Asian race was associated with lower sSC163 levels than other races ($P = .02$). Individuals not receiving ART at baseline or whose HIV loads were not suppressed (HIV RNA load, ≥50 copies/mL) had higher sCD163 levels than individuals who were receiving ART or who had

Table 1. Baseline Clinical and Demographic Characteristics of the Hvidovre Hospital Clinic Cohort

Characteristic	Value	Plasma sCD163 Level, mg/L
Overall	. . .	3.40 (2.31–5.04)
Age, y	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)
Heterosexual	327 (35)	3.23 (2.14–4.71)
Injection drug user	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[a]		
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 load, copies/mL	<20 (<20–92)	. . .
<50	674 (74)	2.98 (2.08–4.33)
>50	239 (26)	4.91 (3.45–7.54)
HCV antibody test result		
Negative	797 (85)	3.12 (2.15–0.49)
Positive	136 (15)	6.24 (4.64–9.52)
Plasma HCV RNA test result		
Negative	844 (90)	3.20 (2.18–4.62)
Positive	89 (10)	6.91 (5.14–10.47)
ART receipt		
No	134 (14)	5.01 (3.62–7.54)
Yes	799 (86)	3.16 (2.17–4.72)
ART duration at inclusion, y	6.0 (3.5–7.6)	. . .
Smoking status[b]		
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)

Data are no. (%) of patients or median value (interquartile range) and are for 933 patients, unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MSM, men who have sex with men; sCD163, soluble CD163.

[a] Low denotes a score of 0; intermediate, a score of 1–2; and high, a score of >2.

[b] Data are for 842 individuals.

suppressed HIV loads (both $P < .0001$). Individuals with a history of injection drug use or HCV antibody or HCV RNA positivity had higher sCD163 levels than individuals without these characteristics (all $P < .0001$). sCD163 level increased with higher Charlson comorbidity index ($P = .004$) and was lower for never smokers as compared to ever smokers or those with an unknown smoking status ($P = .02$). There was a positive correlation between plasma sCD163 levels and plasma HIV RNA loads for all patients ($r = 0.40$, $P = .0001$) and for the subgroup of patients with detectable plasma HIV RNA loads (>50 copies/mL; $r = 0.36$, $P = .0001$). There was an inverse correlation between plasma sCD163 levels and blood $CD4^+$ T-cell counts ($r = -0.25$, $P = .0001$) for all patients and for patients with detectable HIV RNA loads ($r = -0.20$, $P = .0001$).

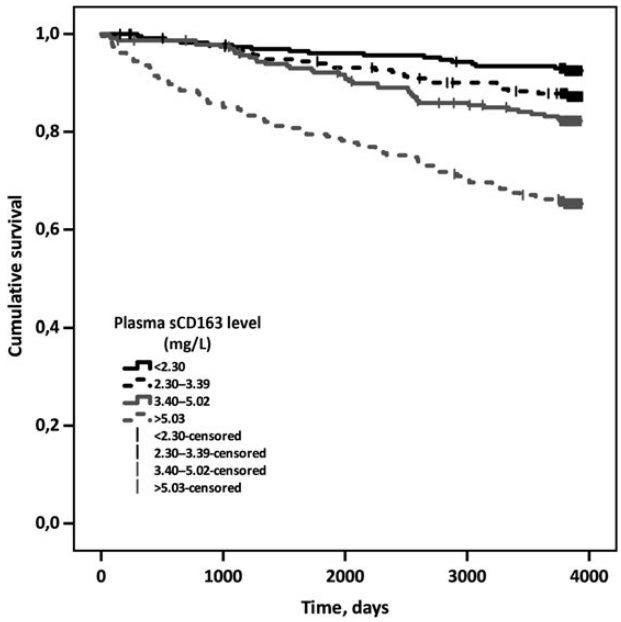

Figure 1. Cumulative survival, according to plasma soluble CD163 (sCD163) level quartiles.

Death During Follow-up

A total of 167 patients (17.9%) died during 10.5 years of follow-up. The median time to death was 4.5 years (IQR, 2.2–7.2 years). Plasma sCD163 levels were higher in nonsurvivors than in survivors (4.92 mg/L [IQR, 3.29–8.65 mg/L] vs 3.16 mg/L [IQR, 2.16–4.64 mg/L]; $P = .0001$).

The underlying cause of death had been determined for 144 cases (86.2%). 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). Unintentional injury or suicide (n = 17) and other or unknown causes (n = 14) accounted for the remaining deaths.

Plasma sCD163 Levels Were Associated With Time to Death

The cumulative incidence of death increased with increasing plasma sCD163 levels ($P = .0001$, by the log-rank test; Figure 1). By univariate Cox analysis, there was an increased risk of death for each milligram per liter increase in plasma sCD163 level at baseline (HR, 1.11; 95% CI, 1.08–1.13; Table 2). Further, age, race, comorbidity index, injection drug use, 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 the risk of death was

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[a]
sCD163 level, per mg/L increment	1.11 (1.09–1.13)	1.06 (1.03–1.09)[b]	<.0001
Age, per y increment	1.07 (1.05–1.08)	1.06 (1.05–1.08)[c]	<.0001
Sex			
Male	1.0	1.0[d]	
Female	0.74 (.52–1.07)	0.90 (.60–1.35)	.61
Race			
White	1.0	1.0[e]	
Black	0.07 (.02–.29)	0.14 (.03–.58)	.007
Asian	0.16 (.04–.64)	0.33 (.08–1.36)	.13
Other	1.32 (.58–2.99)	1.85 (.81–4.23)	.20
Transmission group			
MSM	1.0	1.0[f]	
Heterosexual	0.71 (.47–1.09)	1.45 (.93–2.28)	.10
Injection drug user	3.86 (2.72–5.49)	7.22 (4.80–10.84)	<.0001
Other	1.07 (.51–2.24)	1.36 (.64–2.88)	.43
Prior AIDS			
No	1.0	1.0[g]	
Yes	1.15 (.81–1.63)	1.33 (.88–2.03)	.18
Modified Charlson comorbidity index[h]			
Low	1.0	1.0[i]	
Intermediate	2.91 (2.10–4.03)	1.90 (1.29–2.80)	.001
High	7.41 (4.54–12.08)	4.75 (2.43–9.28)	<.0001
Log HIV RNA load, per log increment	1.08 (1.03–1.14)	1.02 (.95–1.10)[j]	.56
$CD4^+$ T-cell count, per doubling	0.65 (.58–.73)	0.78 (.63–.96)[k]	.02
ART receipt			
No	1.0	1.0[l]	
Yes	1.04 (.67–1.62)	1.30 (.76–2.22)	.35
Plasma HCV RNA positive			
No	1.0	1.0[m]	
Yes	3.87 (2.72–5.50)	1.11 (.68–1.81)	.70
Smoking status			
Never	1.0	1.0[f]	
Ever	4.43 (2.32–8.46)	2.59 (1.28–5.22)	.008
Unknown	20.02 (10.09–39.72)	9.84 (4.65–20.84)	<.0001

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; MSM, men who have sex with men; sCD163, soluble CD163.

[a] By the Wald test.

[b] Adjusted for age, sex, race, transmission group, prior AIDS, Charlson comorbidity index, HIV RNA load, $CD4^+$ T-cell count, ART receipt, HCV RNA positivity, and smoking status.

[c] Adjusted for sex and race.

[d] Adjusted for age, race, and transmission group.

[e] Adjusted for age, sex, and transmission group.

[f] Adjusted for age, sex, and race.

[g] Adjusted for age, sex, race, transmission group, and smoking status.

[h] Low denotes a score of 0; intermediate, a score of 1–2; and high, a score of >2.

[i] Adjusted for age, sex, transmission group, prior AIDS, and smoking status.

[j] Adjusted for sCD163 level, age, sex, race, transmission group, prior AIDS, Charlson comorbidity index, $CD4^+$ T-cell count, ART receipt, HCV RNA positivity, and smoking status.

[k] Adjusted for sCD163 level, age, sex, race, transmission group, prior AIDS, Charlson comorbidity index, HIV RNA load, ART receipt, HCV RNA positivity, and smoking status.

[l] Adjusted for age, sex, transmission group, prior AIDS, HIV RNA load, and $CD4^+$ T-cell count.

[m] Adjusted for sCD163 level, age, sex, race, transmission group, prior AIDS, Charlson comorbidity index, HIV RNA load, $CD4^+$ T-cell count, ART receipt, and smoking status.

Table 3. Multiple Analysis of Risk of Death Associated With Plasma Soluble CD163 (sCD163) Levels for Subgroups

Patient Group	Adjusted HR[a] (95% CI)	*P* Value[b]	*P* for Interaction[b]
ART at baseline			.005
No	1.05 (.99–1.12)[c]	.12	
Yes	1.12 (1.08–1.16)[c]	<.0001	
Plasma HIV RNA level <50 copies/mL			.008
No	1.05 (1.01–1.09)[d]	.03	
Yes	1.13 (1.08–1.18)[d]	<.0001	
Injection drug use			.04
No	1.14 (1.10–1.19)[e]	<.0001	
Yes	1.07 (1.04–1.10)[e]	<.0001	
Heterosexual transmission			<.001
No	1.10 (1.08–1.13)[e]	<.001	
Yes	1.39 (1.35–1.55)[e]	<.001	
Sex			<.01
Male	1.08 (1.06–1.11)[f]	<.0001	
Female	1.10 (1.05–1.16)[f]	<.0001	
Prior AIDS			<.001
No	1.14 (1.10–1.18)[g]	<.0001	
Yes	1.06 (1.02–1.11)[g]	.005	
Smoking status			.017
Never	1.41 (1.17–1.71)[e]	<.0001	
Ever	1.13 (1.09–1.16)[e]	<.0001	
Unknown	1.06 (1.04–1.09)[e]	<.0001	

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio.

[a] Per mg/L increment in plasma sCD163 level.

[b] By the Wald test.

[c] Adjusted for age, sex, $CD4^+$ T-cell count, HIV RNA load, transmission group, and prior AIDS.

[d] Adjusted for age, race, sex, modified Charlson comorbidity index, ART at baseline, $CD4^+$ T-cell count, transmission group, prior AIDS, hepatitis C virus RNA positivity, and smoking status.

[e] Adjusted for age, race, and sex.

[f] Adjusted for age, race, and transmission group.

[g] Adjusted for age, sex, race, transmission group, and smoking status.

attenuated (HR, 1.06; 95% CI, 1.03–1.09). The adjusted HR of death per quartile increase in sCD163 level 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 level, compared with the first quartile, of 2.65 (95% CI, 1.47–4.80; $P < .001$), 1.77 (95% CI, .98–3.17; $P = .06$), and 1.15 (95% CI, .62–2.11; $P = .66$), respectively. By adjustment for individually relevant confounders, age, sex, race, transmission category, comorbidity index, blood $CD4^+$ T-cell counts, and smoking status were each associated with death.

AIDS During Follow-up

Thirty-five patients (3.8%) had a new case of AIDS during 10.5 years of follow-up. The median time to AIDS was 3.2 years (IQR, 0.7–6.8 years). Cases who developed AIDS during follow-up had higher baseline plasma sCD163 levels than cases who did not develop AIDS (median, 4.96 mg/L [IQR, 3.80–7.48 mg/L] vs 3.36 mg/L [IQR, 2.28–4.96 mg/L]; $P = .0001$).

Levels of plasma sCD163, however, did not predict the development of AIDS (HR, 1.00 per mg increase in sCD163 level [95% CI, .92–1.09]), 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 whether 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 milligram per liter increment for individuals who had undetectable plasma HIV RNA (<50 copies/mL) at baseline as compared to individuals with detectable HIV RNA; who were receiving ART at baseline as compared to those who were not receiving ART; those with non–injection drug use transmission as compared to those with injection drug use transmission; those with heterosexual transmission; females as compared to males; those with no diagnosis of AIDS at baseline as compared to those with a diagnosis of AIDS at baseline; and never smokers as compared to smokers and those with an unknown smoking history. There was no statistically significant interaction between sCD163 levels and outcome and age, race, comorbidity index, or $CD4^+$ T-cell count.

After excluding the 17 deaths attributed to unintentional injury or suicide, the risk of death associated with plasma sCD163 levels remained unchanged (HR, 1.07; 95% CI, 1.04–1.10). Analysis of specific causes of death showed that for every milligram per liter increment in sCD163 level, the risk of death due to infectious disease (HR, 1.06; 95% CI, 1.02–1.11), death due to causes other than infectious disease (HR, 1.05; 95% CI, 1.01–1.09), and death due to cardiovascular disease (HR, 1.08; 95% CI, 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 and across different subgroups and was particularly high for HIV-infected individuals who acquired HIV heterosexually and those who were never smokers.

Subjects with the highest sCD163 levels had a 165% increased risk of death as 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. Injection 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 injection drug use. We speculate that this is likely a consequence of comorbidity, behavior, and lifestyle associated with injection drug use. The largest transmission category in our clinic (men who have sex with men) had an increased risk of death associated with sCD163 levels that was comparable to that of the overall cohort. Similarly, the large groups of individuals receiving ART or who had undetectable HIV RNA loads had sCD163-associated risks that were comparable to that of 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 level than any other group. Heterosexual transmission is a heterogeneous HIV-transmission group. However, heterosexual individuals who died during follow-up were predominantly white and male but did not differ otherwise as 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 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 interleukin 6, D-dimer, and sCD14 levels and to a lesser extent in treated individuals [6, 7]. Plasma sCD163 levels, in contrast, were predictive of mortality in treated but not untreated individuals, indicating that sCD163 levels could be useful to identify individuals with ongoing inflammation despite successful ART. During untreated HIV infection, inflammation and activation is driven by HIV replication. In individuals receiving ART, low-level HIV replication, microbial translocation, viral coinfections (eg, cytomegalovirus or HCV infection), comorbidities, and lifestyle factors, such as tobacco and alcohol use, are believed to contribute to chronic inflammation [36]. Beltran et al showed that coinfection with HCV and ongoing HIV replication was associated with an attenuated decrease in plasma sCD163 levels 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 unfavorable risks, such as injection drug use. Comorbidity and smoking prevalence were high in our cohort, and both were predictably associated with outcome. Importantly, however, the predictive value of sCD163 level 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-infected population [37]. Future studies should investigate a

possible association between elevated sCD163 levels 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, noninfectious disease, or cardiovascular disease. The size of the other categories precluded analysis. Studies are warranted to investigate whether 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 diagnoses 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 nonrandomized studies. In this respect, it is of interest that sCD163 levels were lowered by 20% after 2 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 whether a strategy of monocyte/macrophage attenuation could reduce morbidity and mortality associated with HIV infection.

In conclusion, our study showed that sCD163 predicted all-cause mortality in ART recipients, 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 levels may help identifying a risk group requiring further work-up and surveillance.

Note

Potential conflicts of interest. T. B. reports receiving travel grants, research grants, honoraria, and consultancy fees from Abbvie, Bristol-Myers-Squibb, GlaxoSmithKline, and Gilead. H. J. M. reports receiving royalties from IQ-products. S. K. M. is minority shareholder of the biotech company Affinicon ApS. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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