Supplementary Table. Multivariate analyses showing associations between pre-HAART immune-activation biomarker levels grouped by quartile and incident WHO Stage 3 or 4 disease or death after stratifying for country and treatment group and adjusting for age, gender, BMI, baseline CD4+ T-cell count, hemoglobin, and baseline TB.[a]

Biomarker	Model 2 (with TB)[b]		
	HR	95% CI	p-value
CRP (mg/L); n=413			
Q1 (< 1.43)	1	-	-
Q2 (1.43 to < 3.67)	0.91	0.36 – 2.31	0.84
Q3 (3.67 to < 10.50)	1.59	0.70 – 3.62	0.27
Q4 (≥ 10.50)	2.43	0.98 – 6.04	0.06
sCD14 (pg/mL); n=400			
Q1 (< $0.58x10^6$)	1	-	-
Q2 ($0.58x10^6$ to < $2.20x10^6$)	2.22	0.94 – 5.25	0.07
Q3 ($2.20x10^6$ to < $2.80x10^6$)	0.98	0.39 – 2.50	0.97
Q4 (≥ $2.80x10^6$)	1.98	0.85 – 4.60	0.11
†LPS[c]; n=367	-	-	-
Undetectable	1.26	0.64 – 2.46	0.50
Detectable			
EndoCAb IgM (MMU/mL); n=417			
Q1 (< 29.33)	1	-	-
Q2 (29.33 to < 46.62)	1.05	0.49 – 2.26	0.91
Q3 (46.62 to < 69.85)	1.07	0.51 – 2.23	0.87
Q4 (≥ 69.85)	1.35	0.65 – 2.79	0.42
IL-6 (pg/mL); n=356			
Q1 (< 8.90)	1	-	-
Q2 (8.90 to < 23.77)	0.79	0.36 – 1.81	0.57
Q3 (23.77 to < 49.98)	1.19	0.53 – 2.65	0.67
Q4 (≥ 49.98)	0.58	0.25 – 1.35	0.21
TNFα (pg/mL); n=372			
Q1 (< 13.42)	1	-	-
Q2 (13.42 to < 19.11)	0.99	0.40 – 2.47	0.99
Q3 (19.11 to < 26.68)	0.44	0.17 – 1.11	0.08
Q4 (≥ 26.68)	1.21	0.53 – 2.75	0.65
IP-10 (pg/mL); n=378			
Q1 (< 585.07)	1	-	-
Q2 (585.07 to < 1297.57)	1.23	0.54 – 2.78	0.62
Q3 (1297.57 to < 2842.54)	1.22	0.49 – 3.01	0.67
Q4 (≥ 2842.54)	2.02	0.78 – 5.24	0.15
IFNγ (pg/mL); n=351			
Q1 (< 5.53)	1	-	-
Q2 (5.53 to < 15.85)	1.16	0.45 – 2.99	0.77
Q3 (15.85 to < 38.43)	1.04	0.43 – 5.56	0.93
Q4 (≥ 38.43)	2.03	0.77 – 5.34	0.15
CD4+/DR+/CD38+(% CD4); n=155			
Q1 (< 14.93)	1	-	-
Q2 (14.93 to < 22.22)	0.44	0.08 – 2.40	0.34
Q3 (22.22 to < 33.15)	1.11	0.23 – 5.40	0.89

Q4 (≥ 33.15)	5.56	1.04 – 29.76	0.045
CD8+/DR+/CD38+(% CD8); n=157			
Q1 (< 34.75)	1	-	-
Q2 (34.75 to < 44.94)	1.34	0.29 – 6.20	0.71
Q3 (44.94 to < 55.29)	1.15	0.21 – 6.32	0.87
Q4 (≥ 55.29)	4.55	0.88 – 23.53	0.07

Abbreviations: HR, hazard ratio; 95%CI, 95% confidence interval; CRP, C-reactive protein; LPS, Gram-negative bacterial lipopolysaccharide; n, number of samples tested.

[a]Data presented as hazard ratio and 95% confidence interval, comparing each quartile with the first quartile for the specified marker.

*Multivariate models, stratified for country and treatment group and adjusted for gender, age, BMI, CD4+ T cell count, hemoglobin, and baseline TB are shown for each marker. The hazard ratios of quartiles 2, 3, and 4 are shown in comparison to quartile 1, which was used as reference. The quartile breakpoints for each marker are listed below the marker.

[c]Since LPS was treated as a binary variable (detectable vs. undetectable), quartiles are not indicated.

Supplemental Figure.

SFig. 1. Classification of incident WHO stage 3 or 4 events and death among cases.

The frequency of individual, incident WHO stage 3 or 4 events and death among the 236 cases meeting the primary outcome definition is shown, as a proportion of the total number of cases.

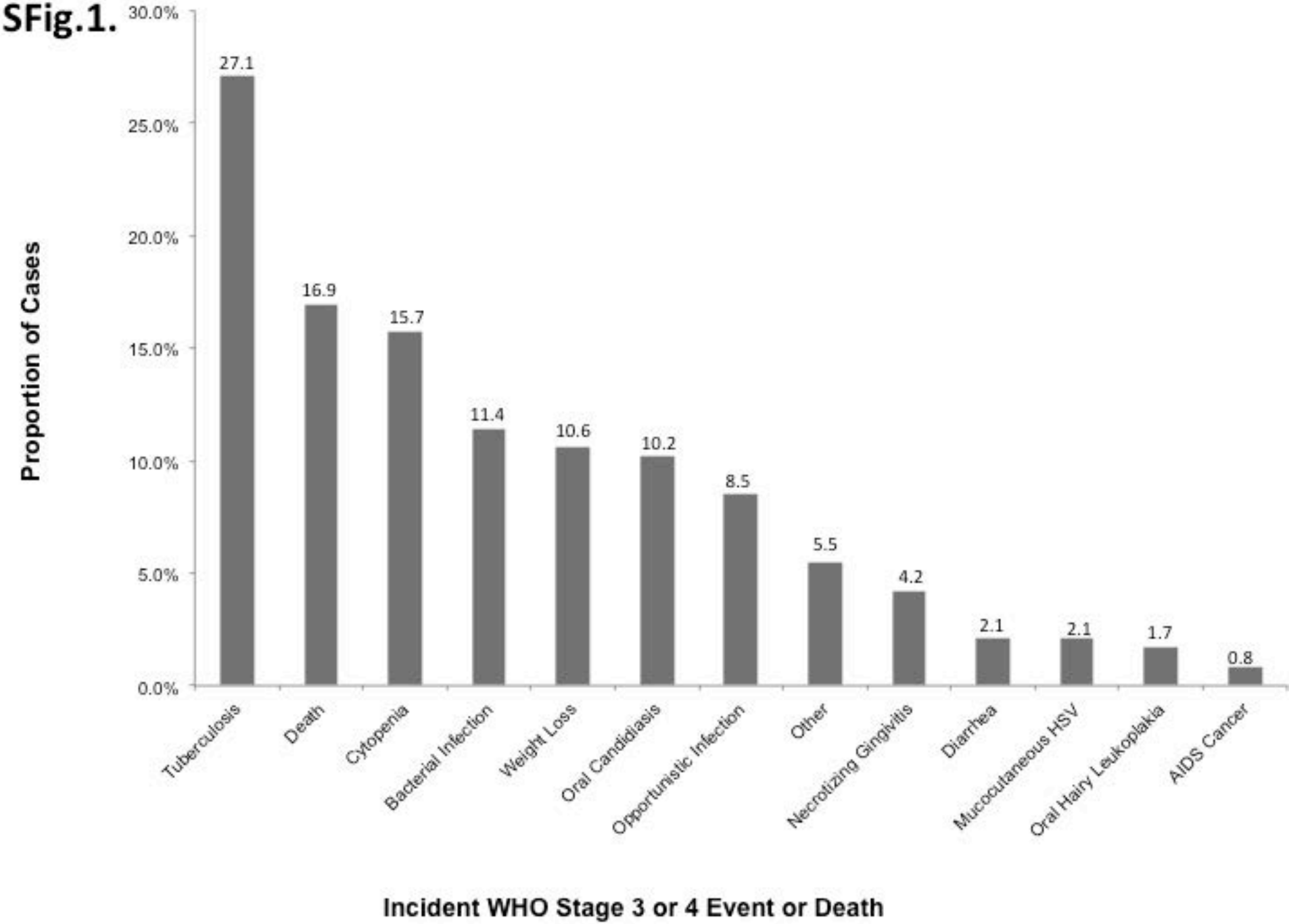
SFig. 2. Immune activation biomarkers by country.

Pre-cART levels of **(A)** CRP, **(B)** IL-6, **(C)** sCD14, and **(D)** CD4+/HLA-DR+/CD38+ are shown by country. P values were calculated for each marker using the Kruskal-Wallis method and are included below each plot.

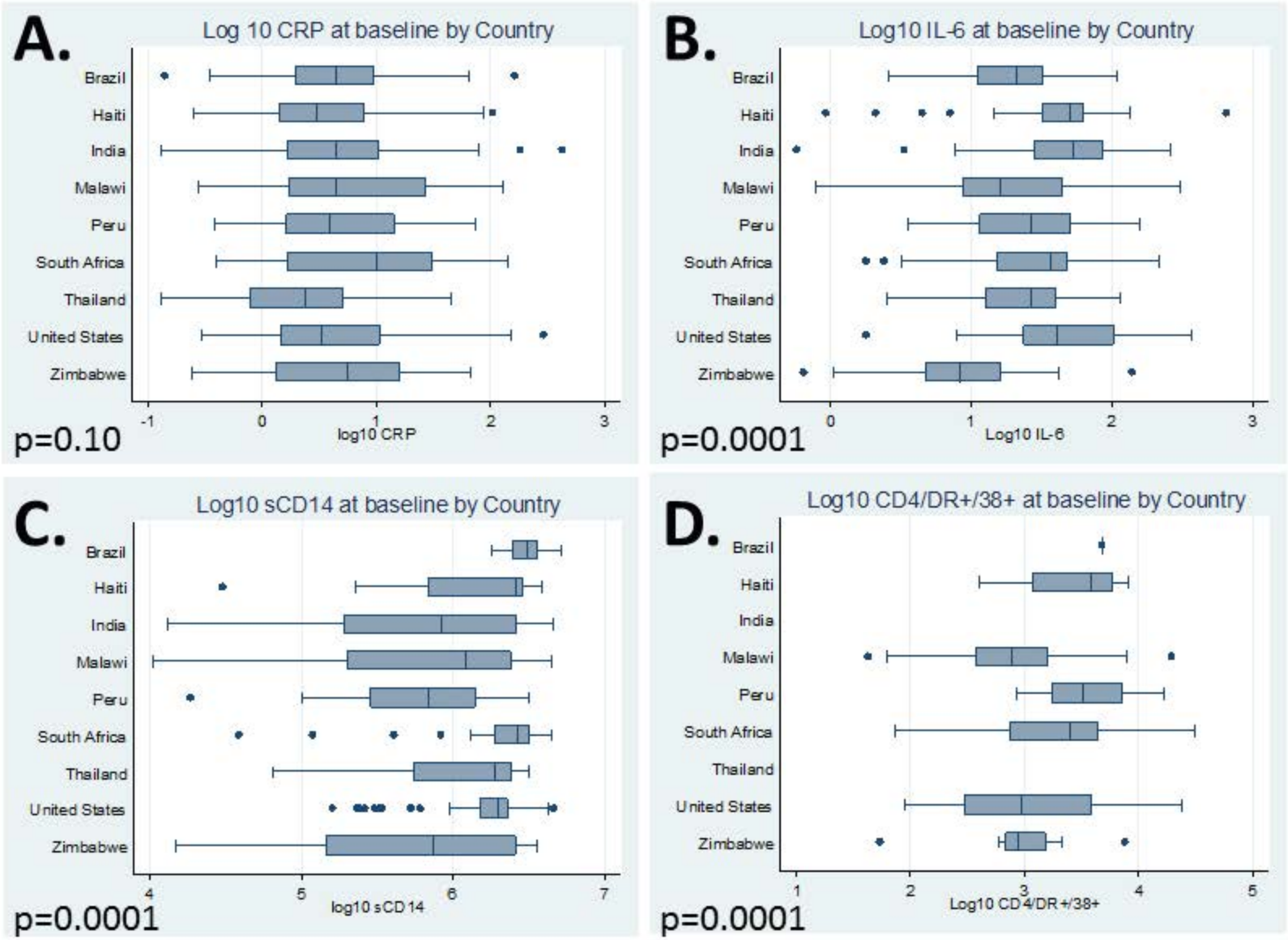
SFig. 3. Adjusted hazards ratios and 95% confidence intervals of incident WHO Stage 3 or 4 or death by 96 weeks for each immune activation biomarker

The results of multivariate Cox proportional hazards models stratified by country and treatment group and adjusted for baseline age, sex, body mass index, CD4+ T-cell count, and hemoglobin are shown for each immune-activation biomarker. Except for LPS, which was treated as a binary variable (detectable vs. undetectable), pre-HAART biomarker values were grouped by quartile (Q) as indicated below each biomarker name. The indicated quartile comprises the interval from the next lowest quartile to labeled quartile. Adjusted hazards ratios (aHR) are shown for each quartile using Q1 as referent and for detectable LPS using undetectable as referent. Dots and lines indicate adjusted hazards ratios and 95% CI, respectively. Only Q4 pre-HAART C-Reactive protein (CRP) concentration and CD4+ T-cell activation are significantly associated with increased hazards of incident WHO Stage 3 or 4 event or death within 96 weeks post HAART initiation, when compared to Q1.

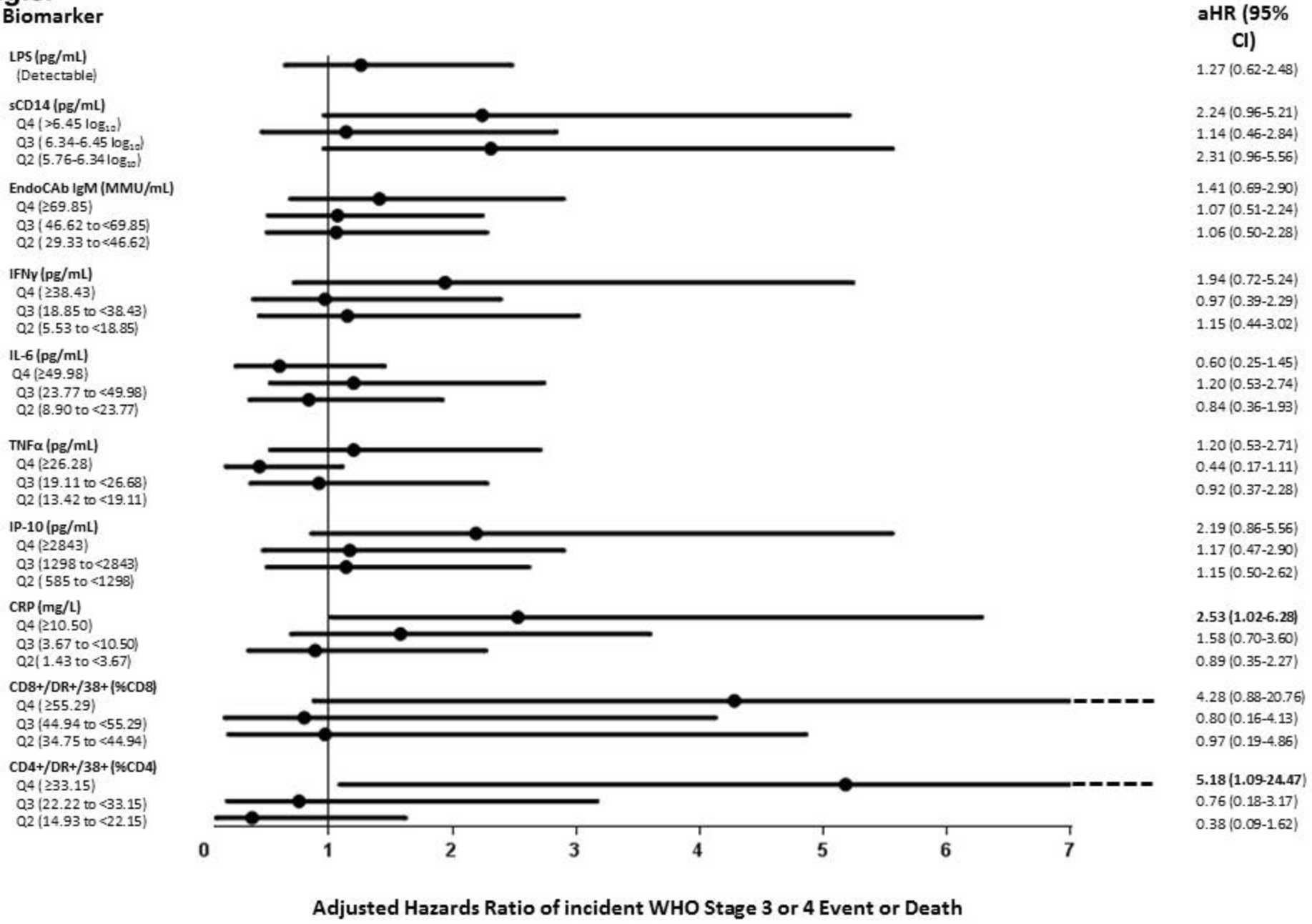
SFig.1.


30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
Proportion of Cases
27.1
16.9
15.7
11.4
10.6
10.2
8.5
5.5
4.2
2.1
2.1
1.7
0.8
Tuberculosis
Death
Cytopenia
Bacterial Infection
Weight Loss
Oral Candidiasis
Opportunistic Infection
Other
Necrotizing Gingivitis
Diarrhea
Mucocutaneous HSV
Oral Hairy Leukoplakia
AIDS Cancer
Incident WHO Stage 3 or 4 Event or Death

SFig. 2.


A.
Log 10 CRP at baseline by Country
Brazil
Haiti
India
Malawi
Peru
South Africa
Thailand
United States
Zimbabwe
-1
0
1
2
3
log10 CRP
p=0.10
B.
Log10 IL-6 at baseline by Country
Brazil
Haiti
India
Malawi
Peru
South Africa
Thailand
United States
Zimbabwe
0
1
2
3
Log10 IL-6
p=0.0001
C.
Log10 sCD14 at baseline by Country
Brazil
Haiti
India
Malawi
Peru
South Africa
Thailand
United States
Zimbabwe
4
5
6
7
log10 sCD14
p=0.0001
D.
Log10 CD4/DR+/38+ at baseline by Country
Brazil
Haiti
India
Malawi
Peru
South Africa
Thailand
United States
Zimbabwe
1
2
3
4
5
Log10 CD4/DR+/38+
p=0.0001

SFig.3.


Biomarker
aHR (95% CI)
LPS (pg/mL)
(Detectable)
1.27 (0.62-2.48)
sCD14 (pg/mL)
Q4 (>6.45 log10)
Q3 (6.34-6.45 log10)
Q2 (5.76-6.34 log10)
2.24 (0.96-5.21)
1.14 (0.46-2.84)
2.31 (0.96-5.56)
EndoCAb IgM (MMU/mL)
Q4 (≥69.85)
Q3 (46.62 to <69.85)
Q2 (29.33 to <46.62)
1.41 (0.69-2.90)
1.07 (0.51-2.24)
1.06 (0.50-2.28)
IFNγ (pg/mL)
Q4 (≥38.43)
Q3 (18.85 to <38.43)
Q2 (5.53 to <18.85)
1.94 (0.72-5.24)
0.97 (0.39-2.29)
1.15 (0.44-3.02)
IL-6 (pg/mL)
Q4 (≥49.98)
Q3 (23.77 to <49.98)
Q2 (8.90 to <23.77)
0.60 (0.25-1.45)
1.20 (0.53-2.74)
0.84 (0.36-1.93)
TNFα (pg/mL)
Q4 (≥26.28)
Q3 (19.11 to <26.68)
Q2 (13.42 to <19.11)
1.20 (0.53-2.71)
0.44 (0.17-1.11)
0.92 (0.37-2.28)
IP-10 (pg/mL)
Q4 (≥2843)
Q3 (1298 to <2843)
Q2 (585 to <1298)
2.19 (0.86-5.56)
1.17 (0.47-2.90)
1.15 (0.50-2.62)
CRP (mg/L)
Q4 (≥10.50)
Q3 (3.67 to <10.50)
Q2(1.43 to <3.67)
2.53 (1.02-6.28)
1.58 (0.70-3.60)
0.89 (0.35-2.27)
CD8+/DR+/38+ (%CD8)
Q4 (≥55.29)
Q3 (44.94 to <55.29)
Q2 (34.75 to <44.94)
4.28 (0.88-20.76)
0.80 (0.16-4.13)
0.97 (0.19-4.86)
CD4+/DR+/38+ (%CD4)
Q4 (≥33.15)
Q3 (22.22 to <33.15)
Q2 (14.93 to <22.15)
5.18 (1.09-24.47)
0.76 (0.18-3.17)
0.38 (0.09-1.62)
0
1
2
3
4
5
6
7
Adjusted Hazards Ratio of incident WHO Stage 3 or 4 Event or Death