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Serum Albumin as a Long Term Predictor of Serious Non-AIDS Events among People Living with HIV

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BACKGROUND

- Serum albumin (sAlb) has been associated with AIDS progression and all-cause mortality in people living with HIV (PLWH)[1-3].
- sAlb was recently shown to be associated with development of serious non-AIDS events (SNAE) in PLWH in a randomized clinical trial[4].
- Using data from the D:A:D study we aimed to
  - i) confirm these findings in a large and heterogeneous cohort
  - ii) assess whether the association between sAlb and SNAE holds for the most common individual SNAEs including; cardiovascular disease (CVD) and non-AIDS defining malignancy (NADM)
  - iii) determine whether the association between sAlb and SNAEs wanes over time, and
  - iv) identify factors that may modify the effect of sAlb

METHODS

Study population: All individuals in the D:A:D cohorts with sufficient follow-up data on sAlb (**Figure 1**).

Endpoints: CVD (composite of myocardial infarction, stroke, invasive cardiovascular procedures or death from CVD); NADM (except for basal cell or squamous cell skin) cancer or death from NADM); and a composite endpoint of any SNAE (including CVD, NADM in addition to end stage renal disease (ESRD) or death from renal disease; end-stage liver disease (ESLD) or death from liver disease and any other non-AIDS death).

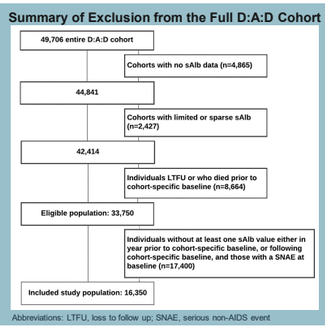
Follow up: Each cohort-specific baseline date was set to the later of the date of routine sAlb monitoring (arbitrarily defined for each cohort) or 1st February 2004. Participants were followed from the designated baseline date to the date of each endpoint; follow-up for each person was censored on the date of an AIDS death, six months after the person's last clinic visit or on 1st February 2016, whichever occurred earliest.

Statistics:

- Poisson regression was used to model the rate of any SNAE, CVD and NADM while adjusting for potential confounders (including demographics, HIV disease-related parameters and markers of organ system injury) defined on the baseline date.
- We compared the strength of the association between sAlb and the CVD endpoint with that of total cholesterol by standardizing each parameter to reflect a 1 standard deviation (SD) increase in the baseline value of the marker.
- We tested for interaction between sAlb and i) age-group, ii) follow-up time, iii) smoking status, iv) CD4 count, and v) HIV-RNA viral load (VL) (time-updated).

Figure 1

Summary of Exclusion from the Full D:A:D Cohort



Abbreviations: LTFU, loss to follow up; SNAE, serious non-AIDS event

Table 1

Baseline Characteristics

		N (%) /median (IQR)
Sex	Male	11737 (71.8)
Age (years)	Median (IQR)	44 (37,51)
Mode of transmission	MSM	6702 (41.0)
	IDU	2688 (16.4)
Race	White	8258 (50.5)
	Black African	1300 (8.0)
	Unknown	6433 (39.4)
Prior AIDS	No	12343 (75.5)
	Yes	4007 (24.5)
BMI (kg/m²)	<18	613 (3.8)
	≥18, <26	10926 (66.8)
	>26, ≤30	2832 (17.3)
	>30	1263 (7.7)
Smoking status	Current	6821 (41.7)
	Ex-smoker	3636 (22.2)
	Never	4536 (27.7)
Any prior ART	Yes	14726 (90.1)
CD4 count (cells/mm³)	≤200	1242 (7.6)
	>200, ≤350	2553 (15.7)
	>350, ≤500	3703 (22.7)
	>500	8814 (54.0)
CD4 nadir count (cells/mm3)	Median (IQR)	208 (99-310)
HIV RNA (log_{10} copies/ml)	≤50 copies/ml	11129 (68.5)
HCV+ve[2]	Yes	4288 (26.2)
eGFR (ml/min)	≤60	436 (2.7)
	>60, ≤90	2504 (15.3)
	>90, ≤120	4160 (25.4)
	>120	3442 (21.1)
	Not known	5808 (35.5)

Abbreviations: BMI, body mass index; ART, Anti-retroviral Therapy, HCV+ve, hepatitis C virus (HCV)-antibody positive and/or HCV-RNA positive, eGFR, estimated Glomerular Filtration Rate

Table 2

Event Rates Stratified by Baseline Serum Albumin Measurements

	PYRS	Any SNAE		CVD		NADM	
		N events	Rate (95% CI)/100 PYRS	N events	Rate (95% CI)/100 PYRS	N events	Rate (95% CI)/100 PYRS
Overall	80264	1463	1.82 (1.73, 1.92)	371	0.46 (0.42, 0.51)	553	0.69 (0.63, 0.75)
Albumin (g/L)							
<30	1574	116	7.37 (6.03, 8.71)	8	0.51 (0.22, 1.00)	26	1.65 (1.02, 2.29)
≥30, <35	2975	121	4.07 (3.34, 4.79)	24	0.81 (0.48, 1.13)	33	1.11 (0.73, 1.49)
≥35, <40	13702	331	2.42 (2.16, 2.68)	83	0.61 (0.48, 0.74)	104	0.76 (0.61, 0.91)
≥40, <45	35642	575	1.61 (1.48, 1.75)	161	0.45 (0.38, 0.52)	241	0.68 (0.59, 0.76)
≥45, <50	23032	286	1.24 (1.10, 1.39)	86	0.37 (0.29, 0.45)	131	0.57 (0.47, 0.67)
≥50	3339	34	1.02 (0.68, 1.36)	9	0.27 (0.12, 0.51)	18	0.54 (0.32, 0.85)

Abbreviations: CVD, cardiovascular disease; NADM, non-AIDS defining malignancy; PYRS, person years of follow up

RESULTS

- Of 16,350 individuals, 1463 developed a SNAE (371 CVD, 200 ESLD, 40 ESRD, 553 NADM, 299 deaths from other non-AIDS causes)
- Baseline characteristics and event rates for each endpoint stratified by baseline sAlb measurement are depicted in **Table 1 and 2**.
- Lower sAlb was associated with any SNAE, CVDs, NADMs and rate ratios (RRs) were only modified slightly after adjustment (**Table 3**).
- Adjustment for the latest CD4 cell count, had only a minimal effect on the association (aRR 0.81 [95%CI: 0.78, 0.83], p<0.001). Excluding either ESRD or ESLD from the combined SNAE endpoint did not change the estimates.
- A 1 SD higher sAlb was associated with a 15% lower CVD rate (aRR 0.85 [0.76, 0.94], p<0.01), whereas a 1 SD lower total cholesterol was associated with a 12% lower CVD rate (aRR 0.88 [0.83, 0.94], p<0.001).
- Interaction-analyses are depicted in **Figure 2**. The association between sAlb and SNAEs were similar across age and CD4 categories (p-interaction<0.001 for both). The association between sAlb and all SNAE endpoints was still evident six years after baseline sAlb measurement and there was no evidence of interaction between sAlb and follow-up time for any SNAE, CVDs and NADMs (all p-interaction>0.3).
- We found evidence for an interaction between smoking and sAlb with a stronger association between sAlb and SNAEs for current smokers vs. never smokers (p-interaction=0.01).
- There was some evidence of effect modification with the latest VL with associations being slightly stronger in those with a non-suppressed VL (p-interaction<0.01).

LIMITATIONS

- sAlb was measured irregularly in the participating cohorts. Thus, to avoid the effects of increased monitoring in sick individuals we only considered fixed timepoint analysis.
- Not all individuals in the D:A:D cohort had sAlb measurements available

CONCLUSIONS

- sAlb is independently and linearly associated with development of SNAEs
- The association between sAlb and SNAEs did not wane over time (>6 years of follow up) and the association seemed to be strongest for current smokers
- SAlb may be considered to be included in future HIV-prognostic indices for SNAEs and studies exploring mechanistic associations between sAlb and SNAEs are warranted.

References: 1. Sabin CA et al. Lancet 2002; 360: 1546-51.; **2**. Scherzer R et al. AIDS 207; 31:71-79; **3.** Sudfeld CR et al. J Infect Dis 2013; 207:1370-78; **4.** Ronit A et al. J Infect Dis 2017, In press.

Table 3

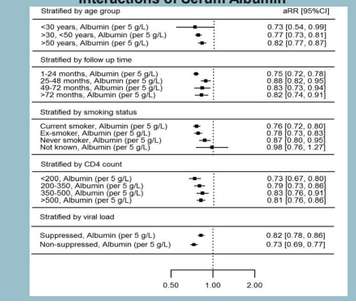
Associations between Baseline Serum Albumin Values and any SNAE, CVD and NADM Events

	Unadjusted		Adjusted	
	RR (95% CI)	p-value	aRR (95% CI)	P-value
a) Any SNAE				
Albumin (g/L)				
<30	4.57 (3.74, 5.58)	<0.0001	3.57 (2.89, 4.40)	<0.0001
≥30, <35	2.52 (2.07, 3.07)	<0.0001	2.30 (1.88, 2.82)	<0.0001
≥35, <40	1.50 (1.31, 1.71)	<0.0001	1.33 (1.16, 1.52)	<0.0001
≥40, <45	Ref.	-	Ref.	-
≥45, <50	0.77 (0.67, 0.89)	<0.001	0.82 (0.71, 0.95)	<0.01
≥50	0.63 (0.45, 0.89)	<0.01	0.73 (0.51, 1.03)	0.07
Albumin (continuous, per 5g/L)	0.75 (0.73, 0.78)	<0.0001	0.79 (0.76, 0.82)	<0.0001
a) Any CVD event				
Albumin (g/L)				
<30	1.12 (0.55, 2.29)	0.75	1.23 (0.60, 2.51)	0.58
≥30, <35	1.79 (1.16, 2.74)	<0.01	2.33 (1.50, 3.62)	<0.001
≥35, <40	1.34 (1.03, 1.75)	0.03	1.31 (1.00, 1.71)	0.05
≥40, <45	Ref.	-	Ref.	-
≥45, <50	0.83 (0.64, 1.07)	0.15	0.81 (0.62, 1.07)	0.13
≥50	0.60 (0.30, 1.17)	0.13	0.63 (0.32, 1.24)	0.18
Albumin (continuous, per 5g/L)	0.87 (0.80, 0.94)	<0.001	0.87 (0.80, 0.94)	<0.001
a) Any NADM event				
Albumin (g/L)				
<30	2.44 (1.63, 3.66)	<0.0001	1.98 (1.28, 3.04)	<0.01
≥30, <35	1.64 (1.14, 2.36)	<0.01	1.54 (1.05, 2.24)	0.03
≥35, <40	1.12 (0.89, 1.41)	0.32	1.00 (0.79, 1.26)	0.98
≥40, <45	Ref.	-	Ref.	-
≥45, <50	0.84 (0.68, 1.04)	0.11	0.92 (0.74, 1.14)	0.44
≥50	0.80 (0.49, 1.29)	0.35	0.94 (0.58, 1.53)	0.81
Albumin (continuous, per 5g/L)	0.84 (0.79, 0.89)	<0.0001	0.88 (0.82, 0.95)	<0.001

*Adjusted for cohort, gender, risk group, race, and following covariates defined at baseline: Age, BMI, smoking status, dyslipidemia, total cholesterol, ALT, eGFR, HCV, HBV, CD4, VL<50 copies/ml, current exposure to NRTIs, PIs, NNRTIs and INSTIs.

Figure 2

Interactions of Serum Albumin



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