

Serum albumin as a prognostic marker for serious non-AIDS endpoints in the Strategic Timing of AntiRetroviral Treatment (START) study

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Summary: Serum albumin is associated with serious non-AIDS occurrence in HIV-positive persons with high CD4 counts: results from the Strategic Timing of AntiRetroviral Treatment (START) study

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Background: Serum albumin may be used to stratify HIV-positive persons with high CD4 count according to their risk of serious non-AIDS endpoints.

Methods: Cox proportional hazard models were used to analyze the risk of serious-non AIDS events in the Strategic Timing of AntiRetroviral Treatment (START) study (NCT00867048) with serum albumin as fixed and time-updated predictor. Models with exclusion of events during initial follow-up years were built to assess the ability of serum albumin to predict beyond shorter periods of time. Secondly, we considered hospitalizations and AIDS events.

Results: Among 4576 participants, 71 developed a serious non-AIDS event, 788 were hospitalized, and 63 experienced an AIDS event. After adjusting for a range of variables associated with hypoalbuminemia, higher baseline serum albumin (per 1 g/dL) was associated with a decreased risk of serious non-AIDS events (hazard ratio (95%CI): 0.37 (0.20-0.71), $p=0.002$). Similar results were obtained in a time-updated model, after controlling for interleukin-6, and after excluding initial follow-up years. Serum albumin was independently associated with hospitalization but not with risk of AIDS.

Conclusions: A low serum albumin is a predictor for short and long-term serious non-AIDS events, and may be a useful marker of risk of non-communicable diseases, particularly in resource-limited settings.

Keywords: albumin, biomarker, HIV, non-communicable disease, non-AIDS comorbidity

INTRODUCTION

With the advent of modern antiretroviral therapy (ART), HIV-positive persons are living longer and non-communicable diseases are becoming a global health issue in this population [1]. Identification of clinically available prognostic markers may help inform non-communicable disease pathogenesis in HIV-positive persons as well as provide added value for a personalized approach to these conditions.

One disease marker that is regularly obtained in most settings, and has been well studied in acute and chronic conditions in the general population, is serum albumin. Serum albumin is involved in a number of biological processes including oncotic pressure maintenance [2], storage and transport properties [3], and antioxidant activity [4]. Low serum albumin levels may be associated with multiple conditions that are related to HIV, e.g. poor nutritional status, inflammation, liver disease, and nephropathy [5]. Thus, an association between serum albumin and health may be expected in this population.

A number of observational studies have examined the association between serum albumin and mortality in HIV-positive persons. As in the general population [6], these studies have shown a consistent and strong inverse association between serum albumin and incident health related outcomes, including overall mortality [7-16], and AIDS related morbidity [13-16]. Serum albumin was also found to be associated with non-AIDS morbidity in a US veteran study assessing cardiovascular disease (CVD) specifically [8].

In people with HIV who have a high CD4 count, the role of serum albumin amongst predictors of serious non-AIDS events has not been extensively described. The Strategic Timing of AntiRetroviral Treatment (START) study enrolled ART naïve HIV+ individuals with CD4 counts above 500 cells/mm³ and randomized them to either immediate ART initiation or deferred initiation when the CD4 count dropped below 350 cells/mm³ or when an AIDS defining illness occurred. We assessed the ability of serum albumin to predict serious non-AIDS over varying follow-up intervals in the context of other prognostic and/or potentially causal factors.

MATERIALS AND METHODS

Study population and design

The multicontinental randomized START trial has been described elsewhere [17, 18]. The study was approved by the institutional review board or ethics committee at each participating site, and written informed consent was obtained from all participants. A total of 4684 people were enrolled in the trial between 2009 and 2013. After an average of 3.0 years of follow-up, the trial was unblinded on 26 May, 2015. This report presents data accrued through the unblinding date. Locally measured baseline serum albumin was available from 4576 (98%) participants. Participants were followed up 1 month and 4 months after randomization and every 4 months thereafter for data collection and routine follow-up clinical evaluation.

Study endpoints

The primary endpoint for this analysis was serious non-AIDS events consisting of the following conditions: CVD (myocardial infarction, stroke, or coronary revascularization) or death from CVD, end-stage renal disease (initiation of dialysis or renal transplantation) or death from renal disease, liver disease (decompensated liver disease) or death from liver disease, non-AIDS-defining cancer (except for basal-cell or squamous-cell skin cancer) or death from cancer, and any death not attributable to AIDS, accident or violence. Secondary endpoints included: (i) unscheduled hospitalizations that were not related to AIDS, (ii) AIDS events, i.e. death from AIDS or any AIDS-defining event, (iii) CVD events, and (iv) non-AIDS cancer. All primary endpoints in START (serious-non-AIDS, AIDS, and death) were reviewed by a committee, using pre-established INSIGHT criteria

[19]. The primary predictor serum albumin was measured at baseline and annually. Serum albumin was modelled as a continuous variable (fixed and time up-dated), and categorized in tertiles (defined by cut-offs of 4.2 and 4.5 g/dL) for Kaplan-Meier survival curves. Baseline categorical covariates investigated included a joint gender/risk group variable (heterosexual women, heterosexual men, men who have sex with men; intravenous drug use [any gender], other [any gender]), race/ethnicity (Asian, black, white, Latino or Hispanic, other), region (Africa, Asia, Europe/Israel, North America, Oceania, South America), smoking status (current vs. ex/never), hepatitis B or C, and randomization arm. Baseline numeric covariates investigated were age, randomization date, body mass index (BMI), systolic blood pressure (SBP), hemoglobin, platelet count, neutrophil count, lymphocyte count, CD4 and CD8 counts, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), alanine aminotransferase (ALT), estimated glomerular filtration (eGFR, by EPI formula), urine dipstick protein (negative, trace, 1+, 2+, 3+, 4+, 5+), HIV-1 RNA (\log_{10}), interleukin (IL)-6.

Statistical methods

Summary statistics were calculated for the entire cohort and persons with hypoalbuminemia (<3.5g/dL). Uni-and multivariate linear regression analyses were used to assess the association between baseline albumin levels and covariates. A longitudinal mixed model was fit using PROC MIXED in SAS to assess the difference in the mean change in laboratory markers from study entry, between the treatment groups. Kaplan-Meier survival curves and log rank tests were used to depict and compare cumulative incidence for SNA events stratified by baseline serum albumin tertiles.

Multivariable Cox proportional hazard models were used to model the time to serious non-AIDS events. Uni- and multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) were

computed. Serum albumin was also fitted as a time updated covariate. Follow-up was until the time of a serious non-AIDS event. For those not experiencing the event follow-up was censored on the last day of study contact, or at study unblinding, whichever occurred earliest. To assess the ability of serum albumin to predict beyond shorter periods of time, and to address the possibility of bias by reverse causality, we considered the effect of left truncation of the survival time. Selection of potential confounders to be adjusted for in multivariable Cox models was based on clinical knowledge about the relation between serum albumin and the primary endpoint, with the thinking made explicit via the use of directed acyclic graphs. Besides unadjusted analyses (model 1), we considered a Cox model controlled for all covariates considered as potentially related to the outcome and listed above (model 2), as well as a Cox model controlling only for variables that were significantly ($p < 0.05$) associated with the outcome (model 3). The proportional hazards assumption was tested by fitting the interaction between baseline albumin and log (follow-up time). An interaction term for serum albumin and randomization arm was included, as well as gender and region, to test if the effect of serum albumin was different according to treatment status, gender, or region. Finally, receiver operating characteristics (ROC) analysis and area under the curve (AUC) was used as another means to assess the diagnostic ability of baseline serum albumin.

Missing covariates were infrequent and analyses were based on a complete case scenario. All P-values reported were two-sided. Analyses were conducted in SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA) and graphs in R (V.3.3.0).

RESULTS

A total of 4576 HIV+ START participants with non-missing baseline albumin levels were included. 108 individuals did not have a serum albumin level at baseline. This included two of the 63 participants experiencing a serious non-AIDS event and 18 of the 788 experiencing hospitalization. Over a total of 14,312 person-years of follow-up (PYFU) 71 participants experienced an serious non-AIDS event (immediate-initiation group= 24, deferred initiation group= 47). The first such event was a non-AIDS defining cancer in 27 people, a CVD event in 26, in 4 a liver or renal event; 20 people the event was fatal. For the secondary outcomes, there were 788 participants with unscheduled hospitalizations and 63 with AIDS events.

Demographic and baseline clinical characteristics of the study population and persons with hypoalbuminemia (<3.5 g/dL; n=77) are depicted in Table 1. Overall, the centiles for albumin were 1%: 3.3, 5%: 3.7, 10%: 3.9, 25%: 4.1, 50%: 4.4, 75%: 4.6, 90%: 4.8, 95%: 5.0, 99%: 5.2 g/dL. Mean (SD) albumin were 4.4 (0.4) in Europe/US/Australian, 4.2 (0.4) in Africa, 4.5 (0.3) in Latin America, and 4.4 (0.4) in Asia (p<0.001). Most participants in START were non-smokers, and the geographic regions with the most participants enrolled were Europe and Israel (N=1476), South America (N=1173), and Africa (N=957). Among persons with hypoalbuminemia at baseline, four (6%, 95% CI: 2-13%) experienced a serious non-AIDs event. Cross-sectional multivariate comparisons at baseline showed that lower serum albumin levels were associated with several factors including older age, being heterosexual male, black race, living in Australia, current smoking, higher BMI, hepatitis B and C infection, lower hemoglobin, higher HDL and LDL, higher eGFR, higher urinary protein, and higher HIV RNA (Table 2).

Immediate initiation of ART was significantly associated with higher average serum albumin concentrations over follow-up (0.086 g/dL, 95% CI: 0.070-0.102, $p < 0.0001$) compared to deferral.

We then performed prospective analyses for the risk of the primary composite endpoint (serious non-AIDS event) by baseline serum albumin. In crude analysis (model 1), higher serum albumin was associated with a decreased risk of serious non-AIDS events (HR 0.26, 95% CI: 0.15-0.46 per 1 g/dL higher level, $p < 0.0001$ (Table 3). We also utilized serial measurements of serum albumin and considered serum albumin as a time-updated variable which moved the effect estimate slightly towards one: HR 0.34, 95% CI: 0.22-0.54, $p < 0.0001$. In analyses adjusted for all factors potentially related with the outcome (model 2), serum albumin persisted to be a predictor for serious non-AIDS events (HR 0.39, 95% CI: 0.20-0.79, $p = 0.009$) (Table 3). The interaction term between serum albumin and randomization arm was non-significant ($p = 0.391$). While all models were stratified by region we did fit one un-stratified model in which we divided regions into Europe/US/Australia, Africa, Latin America, and Asia and assessed whether there was an interaction between this and the effect of albumin on SNA, but we found no evidence for this ($p > 0.1$). There was also no evidence for an interaction between gender and the effect of albumin ($p > 0.1$). In model 3, factors that were univariately associated with the outcome (i.e. age, total cholesterol, eGFR, hemoglobin, randomization arm, and systolic blood pressure), higher serum albumin was also associated with a decreased risk of serious non-AIDS events (HR 0.37, 95% CI: 0.20-0.71, $p = 0.002$) (Table 3). IL-6 (\log_{10}) was added to model 3, which had little effect on the estimate (HR 0.47, 95% CI: 0.25-0.91, $p = 0.024$). Left truncating events and follow-up occurring in the first, second, and third year of follow-up, had little effect on the hazard ratios, although the CIs widened due to reduced numbers of events (Table

4). Kaplan-Meier survival curves for serious non-AIDS events stratified by baseline serum albumin tertiles are depicted in Figure 1 (log-rank $p < 0.01$).

We also assessed the ability of baseline serum albumin to discriminate according to the future occurrence of a serious non-AIDS event. AUC was 0.64. A ROC curve for baseline serum albumin is depicted in online supplementary material 1.

Secondary analysis

Serum albumin was not associated with AIDS but was found to be independently associated with hospitalization in all models, including when IL-6 was added (Table 3). Kaplan-Meier survival curves for hospitalization stratified by baseline serum albumin tertiles are depicted in Figure 2 (log-rank $p < 0.001$). As with the primary outcome, restriction of follow-up time to after years 1, 2 and 3 did not change the effect estimates on hospitalization, although the CIs widened (Table 3). Finally, components of the serious non-AIDS endpoints were assessed separately. In crude analysis, serum albumin was associated with the rate of non-AIDS cancers (HR 0.29, 95% CI: 0.12-0.72, $p < 0.01$), but this association did not persist after controlling for additional factors (Table 3). Serum albumin was not found to be associated with CVD in crude analysis (HR 0.58, 95% CI: 0.21-1.57, $p < 0.284$). Interaction between treatment status and serum albumin was not significant for any of the above outcomes.

DISCUSSION

We found that lower serum albumin was a strong predictor of serious non-AIDS events and hospitalization in seemingly healthy HIV-positive persons entering the START study with high CD4 counts (median 652 /mm³). These associations were independent of traditional risk factors and various laboratory measures. Serum albumin had an ability to predict serious non-AIDs events over both short and potentially long-term. Although early initiation of ART increased the serum albumin level, baseline albumin level remained a predictor of serious non-AIDs and hospitalization despite controlling for randomization arm.

The association between serum albumin and non-communicable diseases was first reported in the British Regional Heart Study in 1989, where serum albumin was shown to be associated with all-cause mortality and CVD mortality [6]. Since then a number of studies have found a consistent and strong association between serum albumin and various disease endpoints in the general population [20-22]. To our knowledge, only one HIV cohort study has investigated serum albumin and a non-AIDS endpoint [8]. This study found a 12-fold and 3-fold increased hazard for heart failure and atherosclerotic events among HIV-infected US veterans, respectively, for persons in the lowest albumin quartile (2.5-2.9 g/dL). As these results were comparable across pre and post-ART eras, the authors suggested that albumin is a strong predictor irrespective of ART status. Although the change in serum albumin since study entry was higher in the immediate-initiation group compared to the deferred-initiation arm in the START study, we confirm these data, and show that adjustment of early ART initiation did not change the predictive ability of serum albumin.

We also found evidence that albumin might provide information about the outlook for serious non-AIDS events over longer term. The hazard ratio remained similar after excluding the initial years of follow-up for both serious non-AIDs and hospitalization, although the CIs widened. These results indicate that prediction for later years may be as strong as prediction in the initial years of follow-up. Although these results may contradict a previous analysis of overall mortality in HIV-positive persons, which showed that serum albumin primarily predicted all-cause mortality occurring within one year [8], early studies from the general population have also shown that serum albumin may predict cardiac and cancer related deaths when the initial years of follow-up were excluded [6]. Finally, we also utilized serial serum albumin measurements and fitted albumin as a time-updated model for the primary outcome. The HR for this model moved slightly towards one, and although serum albumin remained a strong predictor in this model, these findings suggest that serial measurements of albumin may not improve its predictive ability.

As the prognostic ability of HIV RNA and CD4 may be diminished in the ART era [23], and these markers may not always be available in resource-limited setting [24], serum albumin has also been investigated in the context of HIV progression. In an earlier study of 111 hemophilia patients co-infected with hepatitis C, serum albumin was associated with risk of developing AIDS (of which half of the population did) [15]. Low serum albumin was also independently associated with all-cause mortality, pulmonary tuberculosis, severe anemia, wasting, and weight loss in a study examining the effect of multivitamins in 2145 Tanzanian adults initiating ART, most of who were in World Health Organization HIV stage III [16]. It has consequently been suggested that serum albumin may be used as a low-cost predictor of HIV disease progression. We were, however, not able to confirm

these findings and found no association between serum albumin and AIDS. Individuals were screened for good health before entering the START study and had well preserved CD4 counts, and serum albumin may therefore only be capable of predicting HIV-progression in a population with a poorer disease stage. Albumin appeared to be lowest in Africa and may, thus be associated with other environmental (or host) factors that may affect its prognostic capacity in resource limited settings. However, we did not find a significant interaction between albumin and region. We also found no interaction of albumin and gender.

It is not clear how hypoalbuminemia should alter clinical management of HIV-positive individuals, and the association found in this study does not necessarily mean that serum albumin is valuable for risk stratification at an individual level. Serum albumin has been associated with various diseases and is consequently non-specific. However, serum albumin may help triage individuals and hypoalbuminemia should probably prompt further clinical investigations to pinpoint the cause. Clarifying the cause of hypoalbuminemia is also important since manipulations to increase albumin production, such as nutritional support, would be indicated for reduced synthesis, but not increased albumin catabolism in which the underlying pathology would have to be treated.

To our knowledge, only one prognostic index has actually utilized serum albumin. The Child-Pugh score uses serum albumin tertiles to predict mortality and need for liver transplantation in patients with cirrhosis [25]. Other HIV specific risk stratification indices, such as the Veterans Aging Cohort Study Index, have not utilized serum albumin [26]. We only assessed serum albumin as a stand-alone biomarker and included covariates in our models based on clinical assumptions. Serum

albumin is also more easily obtained than other markers that have previously been associated with non-AIDS disease i.e. markers of chronic inflammation, hypercoagulation, microbial translocation, and immune activation [27-30], of which none have been accepted into routine clinical practice. Thus, based on our data, and previous reports, serum albumin may be considered to be included in future HIV-prognostic indices for non-AIDS morbidity.

Even though strong associations between serum albumin and disease outcomes have been found, such observations preclude us from drawing conclusions about causality. To our knowledge there is no evidence from Mendelian randomization studies in the general population to support a causal relation between serum albumin and non-communicable diseases. Thus, hypoalbuminemia could well be an epiphenomena to other disease condition, e.g. poor nutritional status, liver disease, renal disease, which may confound the association explored in this study. However, serum albumin remained an independent predictor in multivariate analyses, and the association even persisted after controlling for IL-6, which may affect hepatic production of albumin [31]. Thus, it is likely that serum albumin may capture something broader than an inflammatory state in HIV-positive individuals. Low serum albumin could also be associated with structural abnormalities of the gut (leakage) that are also hallmarks of HIV [32], and which we were not able to control for. A direct protective effect of the molecule may include its ability to scavenge free radicals [33], its binding capacity of endogenous and exogenous compounds (e.g. fatty acids and carcinogens) [3], or its potential anti-aggregatory effect on platelets [34], that could all be associated with serious non-AIDs pathogenesis.

Our study has limitations. First, although these results may suggest that low serum albumin levels may be present pre-disease, we cannot rule out that the long natural pre-clinical course of most serious non-AIDS events *per se* may have caused diminished levels of the molecule. In any case, serum albumin concentrations seemed to be low before disease manifestation, which is an interesting observation. Second, we were not powered to study different serious non-AIDS events separately, and it is possible that serum albumin may only be proxy for some events and not others. Third, we considered serious non-AIDS and AIDS separately and there may be an issue of competing risk, as these two endpoints may be related. However, when studying each outcome we did not censor at the other and only two patients had both events. Fourth, we studied serum albumin alone and combining other biomarkers may have provided additional information. The study also has strengths. The controlled nature of the START study with serial measurements of albumin at pre-specified time points enabled us to study serum albumin as a time updated variable. It also enabled us to rule out the confounding effect of blood sampling that registry based studies are exposed to. Moreover, as opposed to previous studies, we were able to control for the effect of early ART initiation, and a review committee validated all endpoints.

In conclusion, serum albumin was found to be a predictor for short- and potentially long term serious non-AIDS events. This effect was found to be independent of other measures of poor health, early ART initiation, and measures of systemic inflammation. Further studies are needed to ascertain whether 1) serum albumin can be combined with other biomarkers in prognostic or frailty indexes, 2) to determine if serum albumin is associated with development of specific non-AIDS pathologies, 3) it is possible to identify interventions, other than ART, that lower or raise serum albumin.

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Author contributions

All authors contributed to the formulation of the hypotheses and research questions and the analysis plan, and provided critical input into the draft manuscript. Data collection: all authors (except for AR, ANP); statistical analyses: AR (in part), ANP; interpretation of results: all authors; drafted the manuscript: AR, ANP; revised the work for important intellectual content: all authors. A complete list of members in the Strategic Timing of AntiRetroviral Treatment (START) Study Group is available in a supplement to reference [17].

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Potential conflicts of interest

AR: Travelling grants from Gilead; ANP: speaker fees for Gilead Sciences. All other authors declare no competing interests.

Table 1. Baseline characteristics of START study participants (n=4576)

Characteristics	Hypoalbuminemia (<3.5g/dL) (n=77)	All participants (n= 4576)
Age (years), mean (SD)	41.0 (10.1)	36.8 (10.2)
Female sex, n (%)	39 (50.6)	1218 (26.6)
Ethnicity, n (%)		
- Black	54 (70.1)	1361 (29.8)
- White	19 (24.7)	2031 (44.4)
- Asian, Latino, and other	4 (5.2)	1184 (25.9)
Route of infection with HIV, n (%)		
- Same sex	15 (19.5)	2544 (55.6)
- Opposite sex	51 (66.2)	1748 (38.2)
- Intravenous drug use	5 (6.5)	60 (1.3)
- Other	6 (7.8)	224 (4.9)
Geographic region of residence		
- Africa	41 (53.3)	957 (20.9)
- Asia	3 (3.9)	356 (7.8)
- Europe/Israel	15 (19.5)	1476 (32.3)
- North America	14 (18.2)	505 (11.0)
- Oceania	1 (1.3)	109 (2.4)
- South America	3 (3.9)	1173 (25.6)
Hepatitis B-positive, n (%)	4 (5.4)	128 (2.9)
Hepatitis C-positive, n (%)	9 (12.0)	167 (3.7)
Ever smoker, n (%)	20 (26.0)	1466 (32.0)
BMI (kg/m ²), mean (SD)	28.0 (7.8)	25.7 (5.4)
SBP (mmHg), mean (SD)	123.9 (20.4)	121.6 (14.8)
CD4 count (cells/mm ³), mean (SD)	695 (156)	700 (170)
HDL (mg/dL), mean (SD)	36.6 (13.0)	43.3 (12.8)
LDL (mg/dL), mean (SD)	95.5 (29.9)	104.7 (31.8)
HIV RNA (log ₁₀ copies per mL), mean (SD)	4.2 (0.9)	4.0 (0.9)
Hemoglobin (g/dL), mean (SD)	12.7 (1.9)	14.3 (1.5)
ALT (IU/L), mean (SD)	29.2 (19.2)	30.1 (29.5)
eGFR (ml/min/1.73m ²), mean (SD)	117 (20.1)	110 (18.6)

Abbreviations: ALT, alanine transaminase; BMI, body mass index; eGFR, estimated GFR by creatinine using chronic kidney disease (CKD)-EPI formula; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IQR, interquartile range; LDL, low-density lipoprotein; RNA, ribonucleic

acid; SBP, systolic blood pressure; SD, standard deviation; START, Strategic Timing of AntiRetroviral Treatment study.

Table 2. Cross-sectional multivariate risk factor analyses for baseline serum albumin concentration (n=4576)

Characteristics	Univariate analysis Coefficient (β) (95% CI)‡	Multivariate analysis Coefficient (β) (95% CI)‡	P-value*
Age per decade	-0.08 (-0.09-(-0.01))	-0.08 (-0.09-(-0.07))	<.0001
Ethnicity			
- White	Ref	Ref	
- Black	-0.20 (-0.23-(-0.18))	-0.06 (-0.10-(-0.02))	0.002
- Latino	0.04 (0.01-0.07)	0.04 (0.01-0.08)	0.027
- Asian	-0.05 (-0.09-(-0.01))	0.01 (-0.11-0.12)	0.935
- Other	0.01 (-0.05-0.07)	0.01 (-0.11-0.12)	0.938
Geographic region of residence			
- North America	Ref	Ref	
- Africa	-0.07 (-0.11-(-0.02))	0.03 (-0.02-0.07)	0.160
- South America	0.17 (0.13-0.21)	0.07 (0.03-0.11)	0.001
- Europe/Israel	0.16 (0.12-0.20)	0.08 (0.04-0.12)	0.001
- Oceania	-0.01 (-0.09-0.07)	-0.09 (-0.16-(-0.02))	0.016
- Asia	0.09 (0.04-0.14)	0.02 (-0.10-0.14)	0.706
Joint risk group/gender			
- Heterosexual female	Ref	Ref	
- Heterosexual male	-0.18 (-0.22-(-0.14))	-0.05 (-0.09-(-0.01))	0.010
- MSM	0.08 (0.04-0.11)	-0.01 (-0.05-0.02)	0.462
- Intravenous drug use (any gender)	-0.20 (-0.30-(-0.10))	-0.09 (-0.19-0.01)	0.078
- Other (any gender)	-0.08 (-0.14-(-0.03))	-0.07 (-0.12-(-0.01))	0.015
Hepatitis B-positive	-0.11 (-0.17-(-0.04))	-0.09 (-0.15-(-0.03))	0.002
Hepatitis C-positive	-0.12 (-0.19-(-0.06))	-0.04 (-0.10-0.02)	0.175
Current smoker	0.02 (-0.01-0.04)	-0.06 (-0.08-(-0.04))	<0.0001
BMI (kg/m ²)	-0.01 (-0.01-(-0.01))	-0.01 (-0.01-(-0.00))	<0.0001
CD4 count per 100 cells/mm ³	-0.00 (-0.01-0.00)	0.00 (-0.01-0.01)	0.712
HIV RNA (log ₁₀ copies per mL)	-0.02 (-0.03-(-0.00))	-0.03 (-0.04-(-0.02))	<0.0001
SBP per 10 mmHg	0.00 (-0.01-0.01)	0.01 (0.01-0.02)	0.001
Hemoglobin (g/dL)	0.10 (0.10-0.11)	0.08 (0.07-0.09)	<0.0001
ALT per 10 IU/L	0.00 (0.00-0.00)	0.00 (-0.00-0.00)	0.918
eGFR per 10 ml/min/1.73m ²	-0.01 (-0.02-(-0.01))	-0.01 (-0.02-0.01)	0.001
HDL per 10 mg/dL	0.04 (0.03-0.05)	0.04 (0.03-0.05)	<0.0001
LDL per 10 mg/dL	0.01 (0.01-0.02)	0.01 (0.01-0.02)	<0.0001
Urinary (per 1 category higher)	-0.08 (-0.09-(-0.06))	-0.05 (-0.7-(-0.3))	<0.0001
D-dimer μg/mL (log ₁₀)	-0.22(-0.23-(-0.20))	-0.06(-0.07-(-0.03))	<0.0001
IL-6 pg/ml (log ₁₀)	-0.14 (-0.16-(-0.12))	-0.07 (-0.03-(-0.01))	<0.0001

‡ β -coefficient expresses the expected increase/decrease in serum albumin (mg/dL) for specified change in a predictor from regression models. *P-value for the multivariate model only. Abbreviations: ALT, alanine transaminase; BMI, body mass index; CI, confidence interval; eGFR, estimated GFR by creatinine using chronic kidney disease (CKD)-EPI formula; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IL, interleukin; LDL, low-density lipoprotein; SD, standard deviation; START, Strategic Timing of AntiRetroviral Treatment study.

Table 3. Hazard Ratios for the risk of serious non-AIDS events, hospitalization, and AIDS per 1 g/dL higher baseline serum albumin

Outcome (No. of participants with event)	Crude HR (95% CI)	Adjusted HR		Adjusted HR		Adjusted HR	
		Model 2 ‡ (95% CI, P value)		Model 3 # (95% CI, P value)		Model 3 + IL-6 (95% CI, P value)	
Serious non-AIDS (71)	0.26 (0.15-0.46)	0.39 (0.20-0.79)	0.009	0.37 (0.20-0.71)	0.002	0.47 (0.25-0.91)	0.024
Hospitalization (788)	0.61 (0.51-0.73)	0.77 (0.62- 0.96)	0.019	0.78 (0.64-0.96)	0.018	0.77 (0.62-0.95)	0.013
AIDS (63)	1.07 (0.57-2.03)	--	--	--	--	--	--
CVD (26)	0.58 (0.21- 1.57)	--	--	--	--	--	--
Non-AIDS cancer (27)	0.29 (0.12-0.72)	0.40 (0.12- 1.31)	0.131	--	--	--	--

‡ In model 2 all covariates were included, i.e. age, joint gender/risk group, ethnicity/race, randomization arm, smoking, hepatitis C virus, hepatitis B virus, body mass index, systolic blood pressure, hemoglobin, lymphocyte count, neutrophil count, platelets, CD4 and CD8 cell count, HIV RNA (\log_{10}), cholesterol, low-density lipoprotein, high-density-lipoprotein, estimated glomerular filtration, alanine transaminase, and urinary protein. # In model 3 covariates were included if they were univariately associated with the outcome ($P < 0.05$). For the primary outcome (SNA events) this included age, randomization arm, hemoglobin, eGFR, and systolic blood pressure, and for hospitalization this included joint gender/risk group, current smoking, BMI, hemoglobin, CD4/CD8 ratio, HIV RNA, low density lipoprotein, and urinary protein. # Finally, IL-6 (\log_{10}) was added to model 3. Only crude analyses for AIDS and CVD are reported as serum albumin was not univariately associated with these endpoints. Abbreviations: CVD, cardiovascular disease.

Table 4. Hazard Ratios for the risk of serious non-AIDS events, hospitalization, and AIDS per 1 g/dL higher baseline serum albumin by year of follow-up

Outcome (No. of participants with event)	Adjusted HR (95% CI)‡
Serious non-AIDS	
- Restricted to follow-up beyond 1 year from baseline (50)	0.46 (0.23-0.93)
- Restricted to follow-up beyond 2 years from baseline (34)	0.35 (0.15-0.82)
- Restricted to follow-up beyond 3 years from baseline (20)	0.47 (0.16-1.37)
Hospitalization	
- Restricted to follow-up beyond 1 year from baseline (587)	0.61 (0.49-0.76)
- Restricted to follow-up beyond 2 years from baseline (321)	0.59 (0.44-0.79)
- Restricted to follow-up beyond 3 years from baseline (138)	0.61 (0.39-0.95)

‡ All models were age-adjusted. Abbreviations: AIDS; acquired immune deficiency syndrome; CI, confidence interval; HR, hazard ratio.

Figure 1. Kaplan Meier survival curves for serious non-AIDS events according to baseline serum albumin levels

Kaplan-Meier survival curves with risk-table for serious non-AIDS events (n=71) stratified by serum albumin tertiles at baseline. Log-rank test of equality of strata (p=0.001).

Figure 2. Kaplan Meier survival curves for hospitalization according to baseline serum albumin levels

Kaplan-Meier survival curves with risk-table for hospitalizations events (n=788) stratified by serum albumin tertiles at baseline. Log-rank test of equality of strata (p<0.0001).

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