Association of Serum Albumin Concentration With Mortality, Morbidity, CD4 T-cell Reconstitution Among Tanzanians Initiating Antiretroviral Therapy

Christopher R. Sudfeld,1 Sheila Isanaka,2 Said Aboud,5 Ferdinand M. Mugusi,6 Molin Wang,3 Guerino E. Chalamilla,4,7 and Wafaie W. Fawzi1,2,4

1Department of Epidemiology, 2Department of Nutrition, 3Department of Biostatistics, and 4Department of Global Health and Population, Harvard School of Public Health, Boston, Massachusetts; and 5Department of Microbiology and Immunology and 6Department of Internal Medicine, Muhimbili University of Health and Allied Sciences, and 7Management and Development for Health, Dar es Salaam, Tanzania

Background. Prospective studies of serum albumin concentration measurement as a low-cost predictor of human immunodeficiency virus (HIV) disease progression are needed for individuals initiating antiretroviral therapy (ART) in resource-limited settings.

Methods. Serum albumin concentration was measured at ART initiation for 2145 adults in Tanzania who were enrolled in a trial examining the effect of multivitamins on HIV disease progression. Participants were prospectively followed for mortality, morbidity, and anthropometric outcomes at monthly visits (median follow-up duration, 21.2 months). Proportional hazard models were used to analyze mortality, morbidity, and nutritional outcomes, while generalized estimating equations were used to analyze CD4+ T-cell counts.

Results. Individuals with hypoalbuminemia (defined as a serum albumin concentration of <35 g/L) at ART initiation had a hazard of death that was 4.52 times (95% confidence interval, 3.37–6.07; P < .001) that of individuals with serum albumin concentrations of ≥35 g/L, after multivariate adjustment. Hypoalbuminemia was also independently associated with the incidence of pulmonary tuberculosis (P < .001), severe anemia (P < .001), wasting (P = .002), and >10% weight loss (P = .012). Secondary analyses suggested that serum albumin concentrations of <38 g/L were associated with increased mortality and incident pulmonary tuberculosis. There was no association between serum albumin concentration and changes in CD4+ T-cell counts (P = .121).

Conclusions. Serum albumin concentrations can identify adults initiating ART who are at high risk for mortality and selected morbidities. Future research is needed to identify and manage conditions that reduce the serum albumin concentration.

Keywords. albumin; HIV; tuberculosis; nutrition; mortality.

Clinical management of patients with human immunodeficiency virus (HIV) infection often relies on markers of disease progression, primarily CD4+ T-cell count and HIV load, to guide treatment plans [1]. Both CD4+ T-cell count and HIV load are routinely monitored in developed countries. However, in many resource-limited settings, routine viral load assessment is not in the national guidelines because of the high cost of testing and other logistical difficulties [2]. Accordingly, low-cost markers of HIV disease severity may improve HIV treatment in resource-limited settings.

Serum albumin is a plasma protein produced by the liver that has a role in many physiologic processes, including vasodilation, endothelial cell apoptosis, and antioxidant reactions [3, 4]. Individuals with conditions such as malnutrition, chronic inflammation, enteropathy, or liver disease can have reduced serum
albumin concentrations [4]. As a result, the serum albumin concentration can be considered an indicator of overall health, and studies have shown that a low serum albumin concentration is a strong predictor of mortality for various acute and chronic illnesses [5–8].

Several studies of HIV-infected individuals have determined that hypoalbuminemia (defined as a serum albumin concentration of <35 g/L) is associated with more rapid progression to AIDS and all-cause mortality in developed countries [9–12]. Similar results were found in the few studies conducted in resource-limited settings, where monitoring the serum albumin concentrations may have a greater impact on clinical management and treatment of HIV infection. However, there is some indication that the association between serum albumin concentration and HIV progression may be modified by CD4+ T-cell counts [12–16]. A study of Kenyan HIV-infected women determined that hypoalbuminemia was significantly associated with mortality among those with CD4+ T-cell counts of ≥50 cells/µL (hazard ratio [HR], 5.7; 95% confidence interval [CI], 1.4–9.8) but not among women with CD4+ T-cell counts of <50 cells/µL (HR, 1.0; 95% CI, 4–2.5) [13]. No studies have investigated the association of serum albumin concentration with morbidity outcomes.

Here, we present the largest prospective study of serum albumin concentration and HIV disease progression to date to assess the association of serum albumin concentration with mortality and to detect effect modification by CD4+ T-cell count and other commonly assessed markers of disease severity. We also present the first prospective study examining the relationship between the serum albumin concentration and incident diagnosis of comorbidities. In secondary analyses, we examine whether the generally used 35 g/L cutoff to define hypoalbuminemia captures the relationship of serum albumin concentration with mortality and morbidity outcomes among HIV-infected individuals.

METHODS

Study Population

This prospective cohort study consists of HIV-infected adult men and women initiating ART enrolled in a trial of vitamins B-complex, C, and E at high levels versus standard levels of the recommended dietary allowance conducted in the HIV care and treatment clinics (CTC) in Dar es Salaam, Tanzania during 2006–2009 (Clinicaltrials.gov NCT00383669) [17]. Individuals were eligible for the study if they were aged ≥18 years, infected with HIV, initiated ART at enrollment, and intended to stay in Dar es Salaam city for at least 2 years. The primary outcome of the trial was HIV disease progression or death, and there was no difference between treatment arms [17]. At the time of the study, the Tanzanian national treatment guidelines recommended that HIV-infected patients with World Health Organization (WHO) HIV disease stage IV, a CD4+ T-cell count of <200 cells/µL, or WHO HIV stage III disease and a CD4+ T-cell count of <350 cells/µL initiate highly active ART [18]. Women who were pregnant or lactating were excluded from the study. First-line drug combinations included stavudine (d4T), lamivudine (3TC), nevirapine (NVP), zidovudine (AZT), and efavirenz (EFV). AZT was substituted for d4T for individuals who had peripheral neuropathy or could not tolerate d4T. EFV was substituted for NVP in patients who could not tolerate NVP. Cotrimoxazole prophylaxis was provided when CD4+ T-cell counts were <200 cells/µL, and treatment for all opportunistic infection was provided according to the national and WHO guidelines.

Serum Albumin and Baseline Covariate Assessment

A total of 3418 individuals consented and were enrolled into the parent trial. At enrollment, a structured interview was completed to collect information on demographic characteristics. Study physicians also performed a complete medical examination and assessed HIV disease stage in accordance with WHO guidelines [18]. Blood specimens were collected at baseline, and serum albumin concentrations were quantified using the Cobas Integra 400 Plus analyzer (Roche Diagnostics, Basel, Switzerland). Samples from 2145 individuals were available within 2 weeks of ART initiation. Absolute CD4+ T-cell count (FACS Calibur system, Becton Dickinson, San Jose, CA) and complete blood count (AcT5 Diff AL analyzer, Beckman Coulter, Miami, FL) were also determined at baseline. Height and weight measurements were obtained by trained research nurses, using standardized procedures.

Outcome Assessment and Definitions

Study participants were followed at monthly clinic visits, and individuals who missed a clinic visit were followed up by means of telephone calls and/or home visits, during which relatives or neighbors were questioned about the vital status of the participant. Physicians performed a clinical examination, assessed the WHO HIV disease stage, and diagnosed and treated any emerging illness [18]. Pneumonia, Kaposi sarcoma, and oral thrush were diagnosed on the basis of symptoms reported by patients and signs assessed by study physicians. Chronic diarrhea was defined as report of diarrheal symptoms for ≥14 days. Pulmonary tuberculosis was diagnosed according to Tanzanian National Tuberculosis and Leprosy Programme guidelines. Participants with symptoms of pulmonary tuberculosis provided 3 sputum samples: a spot sputum specimen at the first clinic visit during which symptoms were noted; an early morning specimen on the next day, before a second clinic visit; and a third sputum specimen at the second clinic visit. Participants received a diagnosis of pulmonary tuberculosis if at least 1 of the 3 sputum smears had acid-fast bacilli detected by Ziehl-Neelsen staining techniques.
or if chest radiography showed radiological features consistent with tuberculosis in the absence of a positive sputum smear result [19]. Presumptive diagnosis of extrapulmonary (EP) tuberculosis was based on known specific or constitutional features (eg, fever, weight loss, and night sweats) and organ-specific signs assessed by the study physician (eg, stony dullness on percussion and pleural effusion on aspiration for pleural tuberculosis). Height and weight were determined by clinic study nurses at each clinic visit. Wasting was defined as a body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared) of \(<18.5\) [20]. Weight loss of \:>10\% from baseline was also selected as an outcome, on the basis of the definition of HIV-related wasting [21]. Absolute CD4\(^+\) T-cell count and a complete blood count were determined at clinic visits every 4 months. Anemia was defined as a hemoglobin concentration of \(<130\) g/L for men and \(<120\) g/L for women, whereas severe anemia was defined as a hemoglobin concentration of \(<85\) g/L for both sexes [22].

**Statistical Methods**

Baseline hypoalbuminemia was defined as a serum albumin concentration of \(<35\) g/L, which is the generally used clinical definition that was also used in previous studies of HIV-infected individuals [23]. We examined risk factors for baseline hypoalbuminemia with log-binomial regression models to obtain risk ratio estimates [24, 25]. In a few instances, the models did not converge, and log-Poisson models, which provide consistent but not fully efficient estimates of the relative risk and its confidence intervals (CIs), were used [26]. Variables included in this analysis were sex and baseline age (30, 30–39, 40–49, and \(\geq50\) years), BMI (\(<16.0\) [severely underweight], 16.0–18.4 [underweight], 18.5–25.0 [normal], and \(\geq25.0\) [overweight]), WHO HIV disease stage (I/II, III, and IV), CD4\(^+\) T-cell count (\(<50\), 50–99, 100–199, and \(\geq200\) cells/\(\mu\)L), alanine transaminase (ALT) concentration (\(\leq40\) and \(>40\) IU/L), and hemoglobin concentration (\(8.5, 8.5–11, \) and \(\geq11\) g/dL). Effect modification was assessed with the likelihood ratio test, using variables included in the risk factor analyses listed above.

Proportional hazard models were used to investigate the relationship between hypoalbuminemia at baseline and death, the incidence of WHO HIV stage IV disease or death, and the first occurrence of morbidity and nutritional outcomes, including pneumonia, oral thrush, pulmonary tuberculosis, chronic diarrhea, Kaposi sarcoma, EP tuberculosis, severe anemia, anemia, wasting, and \(>10\%\) weight loss [27]. We excluded individuals who received a diagnosis of the event of interest at baseline. Individuals without events were censored at the date of last follow-up. The results of these analyses are reported as adjusted hazard ratios (HRs) and 95% CIs. In secondary analyses, we conducted continuous analyses of baseline serum albumin concentration to examine whether the generally used definition of hypoalbuminemia captured mortality and morbidity relationships for HIV-infected individuals, since the cutoff may differ by disease. The possible nonlinear relationship between serum albumin concentration and death and morbidity outcomes was examined nonparametrically with restricted cubic splines [28, 29]. Tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. We also present categorical analyses, using cutoffs suggested by continuous analyses.

Associations between serum albumin concentration at ART initiation and CD4\(^+\) T-cell counts were analyzed with generalized estimating equations (GEEs). Change in CD4\(^+\) T-cell count between consecutive visits was treated as a longitudinal continuous outcome, and baseline serum albumin concentration time since ART initiation, and baseline covariates (excluding baseline CD4\(^+\) T-cell count) were treated as explanatory variables. We used an m-dependent working correlation matrix (\(m=1\)), which assumes the correlation coefficients of adjacent observations are nonzero and equal. Robust estimators of the variances, which are consistent estimators even if the working correlation matrix is misspecified, were used to construct CIs. The potential nonlinear relationship of the change in T-cell counts between consecutive visits over time was examined nonparametrically with restricted cubic splines for time since ART initiation [28, 29]. If a nonlinear relationship was found, we added the selected cubic spline terms to the model as covariates. To assess the association of baseline serum albumin concentration and change in CD4\(^+\) T-cell count between consecutive visits over time, we included the interactions between serum albumin concentration and time since ART initiation and its splines. The robust score test was used to determine whether the categorical serum albumin concentration groups differed in CD4\(^+\) T-cell count trajectory.

Confounders included in proportional hazard and GEE models were selected on the basis of our risk factor analysis and a review of the literature and consisted of sex and baseline age, BMI, WHO HIV disease stage (except for incidence of WHO stage IV disease or death), CD4\(^+\) T-cell count, hemoglobin concentration, and ALT concentration. Baseline CD4\(^+\) T cell count was not adjusted for in CD4\(^+\) T-cell analyses because this would have yielded biased estimates. Effect modification by all covariates listed above, randomized multivitamin regimen, and ART regimen were considered for all analyses. To assess whether effect modification was significant, we used the likelihood ratio test, for proportional hazard models, and the robust score test, for GEE analyses. Missing data for covariates were retained in the analysis, using the missing indicator method for variables [30]. All \(P\) values were 2 sided, and a \(P\) value of \(<.05\) was considered statistically significant. Statistical analyses were performed using SAS v 9.2 (SAS Institute, Cary, NC, USA).
RESULTS

A total of 2172 individuals enrolled in the parent trial had their serum albumin concentration measured at ART initiation. There were no significant differences between individuals with serum albumin measurements at baseline and the trial population (n = 3418) in age, sex, or baseline CD4+ T-cell count.
count, WHO HIV disease stage, hemoglobin concentration, and ALT concentration. Baseline characteristics of the study cohort are presented in Table 1, by serum albumin concentration. A total of 858 individuals (39.5%) had hypoalbuminemia at baseline. A multivariate cross-sectional analysis determined that baseline hypoalbuminemia was significantly associated with older age ($P = .033$), decreasing BMI ($P < .001$), more severe WHO HIV disease stage ($P < .001$), decreasing hemoglobin level ($P < .001$), and an ALT level of $>40$ IU/L ($P = .003$) at the baseline study visit (Table 1).

We then performed a prospective analysis of mortality, morbidity, and change in CD4$^+$ T-cell count, by baseline serum albumin concentration. The median follow-up time of the cohort was 21.2 months, during which 238 deaths (mortality rate, 11.2%) were recorded. The cumulative incidence of mortality was 19.3% for individuals with hypoalbuminemia and 5.0% for those with a serum albumin concentration of $\geq 35$ g/L. Individuals with hypoalbuminemia had a hazard of death that was 3.35 (95% CI, 2.42–4.63; $P < .001$) times that for individuals with a serum albumin concentration of $\geq 35$ g/L, after adjustment for sex and baseline age, BMI, WHO HIV disease stage, CD4$^+$ T-cell count, hemoglobin level, and ALT level. There was no detection of effect modification of the mortality association by baseline CD4$^+$ T-cell count ($P = .808$). Hypoalbuminemia was significantly associated with increased mortality for individuals with baseline CD4$^+$ T-cell counts of $<50$ cells/μL (HR, 3.39; 95% CI, 1.61–7.13; $P = .001$) and $\geq 50$ cells/μL (HR, 3.21; 95% CI, 2.24–4.61; $P < .001$). Furthermore, no statistically significant effect modification by sex or baseline age, WHO disease stage, hemoglobin level, ALT level, randomized multivitamin regimen, and ART regimen was detected. Second, we analyzed serum albumin concentration continuously and found a significant nonlinear relationship with increasing risk of mortality for serum albumin concentrations $<38$ g/L ($P = .002$ for nonlinear relation; Figure 1). In a post hoc categorical analysis, individuals with a baseline serum albumin concentration of 35–38 g/L had a hazard of death that was 1.95 (95% CI, 1.17–3.24; $P = .01$) times that for individuals with a serum albumin concentration of $\geq 38$ g/L, after multivariate adjustment.

Study clinicians performed a clinical examination and diagnosed opportunistic infections and other comorbidities at monthly clinic visits. We present analyses of the composite incident WHO stage IV disease or death end point and co-morbidities, by baseline presence of hypoalbuminemia, in Table 2. Hypoalbuminemia was significantly associated with incident WHO stage IV disease or death in univariate analysis (HR, 1.24; 95% CI, 1.08–1.43; $P = .003$), but there was no statistically significant association after multivariate adjustment (HR, 1.14; 95% CI, .97–1.33; $P = .107$). After multivariate adjustment, individuals with hypoalbuminemia had a significantly increased risk of incident pulmonary tuberculosis as compared to individuals with a serum albumin concentration of $\geq 35$ g/L (HR, 1.80; 95% CI, 1.17–2.76; $P = .007$). When analyzing the relationship continuously, we found a significantly nonlinear relationship with an increasing hazard of pulmonary tuberculosis for serum albumin concentrations of $<38$ g/L ($P = .03$ for nonlinear relation; Figure 2). In a post hoc analysis, we found a significant nonlinear relationship with an increasing hazard of pulmonary tuberculosis for serum albumin concentrations of $<38$ g/L ($P = .03$ for nonlinear relation; Figure 2).
serum albumin concentration of <35 g/L. Individuals with outcome events at baseline were excluded from analyses.

Abbreviations: CI, confidence interval; EP tuberculosis, extrapulmonary tuberculosis; HIV, human immunodeficiency virus; WHO, World Health Organization.

a Adjusted for sex and baseline age (30, 30–50, and ≥50 years), body mass index (calculated as the weight in kilograms divided by the height in meters squared; <16.0, 16.0–18.4, 18.5–25.0, and >25.0), WHO HIV disease stage (I/I, II, and IV, except for the outcome of WHO stage IV or death), CD4+ T-cell count (<50, 50–199, 200–39, 40–99, 100–199, and ≥200 cells/μL), hemoglobin level (<8.5, 8.5–11, and ≥11 g/dL), and alanine transaminase level (<25.0, and >25.0), World Health Organization human immunodeficiency virus disease stage (I/I, III, and IV), CD4+ T-cell count (<50, 50–99, 100–199, and ≥200 cells/μL), hemoglobin level (<8.5, 8.5–11, and ≥11 g/dL), and alanine transaminase level (<40 and >40 IU/L).

b WHO stage IV HIV disease.

categorical analysis, individuals with a baseline serum albumin concentration 35–38 g/L had an increased but not statistically significant hazard of incident pulmonary tuberculosis as compared to individuals with a serum albumin concentration ≥38 g/L, after multivariate adjustment (HR, 1.51; 95% CI, 0.72–3.10; P = .213). Serum albumin concentrations were not associated with the incidence of pneumonia, oral thrush, chronic diarrhea, and Kaposi sarcoma or with EP tuberculosis, after multivariate adjustment. There was also no indication of effect modification detected for any morbidity association by sex or baseline age, CD4+ T-cell count, WHO HIV disease stage, hemoglobin level, ALT level, randomized multivitamin regimen, and ART regimen.

Hemoglobin levels were assessed every 4 months after the baseline ART initiation visit. During follow-up, 179 individuals (11.0%) experienced incident severe anemia. For individuals with baseline hypoalbuminemia, the hazard of incident severe anemia was 2.28 (95% CI, 1.67–3.10; P < .001) times that for individuals with a serum albumin concentration of ≥35 g/L, after multivariate adjustment (Table 3). Individuals with hypoalbuminemia also had an elevated but not statistically significant hazard of incident anemia (HR, 1.42; 95% CI, .96–2.12; P = .081). There was no indication of effect modification of anemia associations by sex, ART regimen, randomized multivitamin regimen, or any other variable.

A total of 175 individuals (11.0%) experienced incident wasting during follow-up (Table 3). After multivariate adjustment, individuals with baseline hypoalbuminemia had an increased hazard of wasting as compared to individuals with a

Table 2. Hazard Ratios (HRs) for All-Cause Mortality and Incident Morbidities Among Individuals With Versus Those Without Hypoalbuminemia at Baseline

<table>
<thead>
<tr>
<th>Outcome (No. of Events)</th>
<th>Crude HR (95% CI)</th>
<th>P</th>
<th>Adjusted HRa (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (242)</td>
<td>4.52 (3.37–6.07)</td>
<td>&lt;.001</td>
<td>3.35 (2.42–4.63)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WHO stage IV or death (785)</td>
<td>1.24 (1.08–1.43)</td>
<td>.003</td>
<td>1.14 (0.97–1.33)</td>
<td>.107</td>
</tr>
<tr>
<td>Pneumonia (812)</td>
<td>1.15 (1.00–1.32)</td>
<td>.051</td>
<td>0.96 (0.83–1.12)</td>
<td>.633</td>
</tr>
<tr>
<td>Oral thrush (238)</td>
<td>1.07 (0.83–1.39)</td>
<td>.602</td>
<td>0.83 (0.62–1.11)</td>
<td>.209</td>
</tr>
<tr>
<td>Pulmonary tuberculosis (107)</td>
<td>2.35 (1.59–3.47)</td>
<td>&lt;.001</td>
<td>1.80 (1.17–2.76)</td>
<td>.007</td>
</tr>
<tr>
<td>Chronic diarrhea (87)</td>
<td>1.15 (.75–1.76)</td>
<td>.526</td>
<td>1.06 (.66–1.71)</td>
<td>.810</td>
</tr>
<tr>
<td>Kaposi sarcoma (49)</td>
<td>1.21 (.68–2.13)</td>
<td>.520</td>
<td>1.07 (.57–2.03)</td>
<td>.828</td>
</tr>
<tr>
<td>EP tuberculosis (35)</td>
<td>2.11 (1.15–3.89)</td>
<td>.017</td>
<td>1.77 (.89–3.52)</td>
<td>.102</td>
</tr>
</tbody>
</table>

Hypoalbuminemia was defined as a serum albumin concentration of <35 g/L. Individuals with outcome events at baseline were excluded from analyses.

Figure 2. Restricted cubic spline analysis illustrating the shape of the adjusted relationship between continuous serum albumin concentration at antiretroviral therapy initiation and incident pulmonary tuberculosis. The solid line shows the estimated hazard ratio for serum albumin concentrations relative to the reference concentration of 38 g/L, with the horizontal dotted line designating a hazard ratio of 1.0. The 95% confidence intervals of the hazard ratio are represented by the dashed lines. Adjusted analyses controlled for sex and baseline age (30, 30–39, 40–49, and ≥50 years), body mass index (calculated as the weight in kilograms divided by the height in meters squared; <16.0, 16.0–18.4, 18.5–25.0, and >25.0), WHO HIV disease stage (I/I, II, and IV, except for the outcome of WHO stage IV or death), CD4+ T-cell count (<50, 50–99, 100–199, and ≥200 cells/μL), hemoglobin level (<8.5, 8.5–11, and ≥11 g/dL), and alanine transaminase level (<40 and >40 IU/L). P = .030 for nonlinear relation.
In secondary continuous analyses, the hazard of mortality and tuberculosis events appeared to be increased for serum albumin concentrations of <38 g/L.

This study confirms the findings from previous cohort studies that showed that hypoalbuminemia was associated with increased mortality among HIV-infected individuals [9–12]. Previous studies have suggested that hypoalbuminemia may not predict mortality at low CD4⁺ T-cell counts, because of a plateau effect in individuals with advanced HIV disease [10, 13]. In our study, which is the largest conducted to date, we found no statistical evidence of effect modification of the mortality association by CD4⁺ T-cell count. Hypoalbuminemia was significantly associated with increased mortality among individuals with a baseline CD4⁺ T-cell count of <50 cells/μL and appeared to be of the same magnitude as that among individuals with a baseline CD4⁺ T-cell count of ≥50 cells/μL. Furthermore, some of these previous studies did not adjust for BMI, which is likely to capture malnutrition and increase statistical power [11, 12, 14]. We felt it necessary to adjust for BMI, since BMI is routinely and easily measured in resource-limited settings and, consequently, because the serum albumin measurement would have limited clinical usefulness if its predictability was not independent of BMI.

We found that baseline hypoalbuminemia was significantly associated with increased risk of incident pulmonary tuberculosis and also had a borderline significant relationship with EP tuberculosis, which may be a result of low power or nondifferential misclassification. Individuals infected with Mycobacterium tuberculosis are characterized immunologically by acute phase responses, which are systemic inflammatory reactions that can lead to reductions in serum albumin concentrations [31, 32]. Worodria et al found that C-reactive protein (CRP), an acute phase response protein, which was not measured in our study, was significantly associated with incident tuberculosis-associated immune reconstitution inflammatory syndrome [33]. Accordingly, a possible explanation for our findings is that latent M. tuberculosis infection or M. tuberculosis infections that become clinically active after initiating ART will reduce serum albumin concentration.

In secondary analyses, we examined the relationship of serum albumin concentration with mortality and morbidity outcomes continuously. The results of these analyses suggest that individuals initiating ART with a serum albumin concentration of <38 g/L have an increased risk of mortality and pulmonary tuberculosis. A serum albumin concentration of <38 g/L has also been used as a diagnostic criterion by the International Society of Renal Nutrition and Metabolism for protein energy wasting in acute and chronic kidney disease [34]. Consequently, individuals with serum albumin concentrations of 35–38 g/L at ART initiation should also be identified as having an increased risk of adverse HIV treatment outcomes and managed appropriately.
Baseline hypoalbuminemia was also associated with incident severe anemia. These findings may be due to malnutrition and chronic inflammation, which decrease the serum albumin concentration and also suppress erythropoiesis [35, 36]. Studies among individuals undergoing hemodialysis and patients with acute coronary syndrome have also documented that the serum albumin concentration is a strong predictor of anemia cross-sectionally, as well as prospectively [37, 38]. Additionally, hypoalbuminemia was associated with incident wasting and weight loss. Serum albumin concentration is commonly considered a laboratory indicator for malnutrition; however, the association is not clear for HIV-infected individuals, particularly those with higher CD4+ T-cell counts [38, 39].

In this study, we found that serum albumin concentration was strongly associated with death and weight loss but not with the composite end point of WHO stage IV disease or death and change in CD4+ T-cell count. A plausible explanation linking these findings is that the serum albumin concentration is not associated with the incidence of morbidities that arise due to impaired CD4+ T-cell immune reconstitution, which would dilute the mortality association when WHO stage IV disease end points were included. There may also be increased nondifferential misclassification of morbidity outcomes as compared to the firm mortality end point, which will bias morbidity results to the null. Furthermore, the strong association of serum albumin concentration with weight loss may indicate that the serum albumin concentration is acting as an independent marker of increased severity of opportunistic infections. A limitation of this study is that we did not have data on the severity of opportunistic infections, and as a result future studies are needed to investigate this potential mechanism.

This study has several other important limitations. First, we were unable to adjust for HIV load, which may result in residual confounding. Nevertheless, HIV load is often not available in resource-limited settings. Second, we only had a single measurement of the serum albumin concentration, at ART initiation, and it is unclear from this study whether long-term concentrations or changes in serum albumin concentration after ART initiation are superior morbidity and mortality predictors.

Serum albumin concentration is a strong independent predictor of mortality, pulmonary tuberculosis, severe anemia, wasting, and weight loss among HIV-infected individuals initiating ART. Serum albumin concentration may be a useful and low-cost marker of disease severity in resource-limited settings with access to clinical chemistry equipment. Future research should focus on identification and management of conditions that reduce serum albumin concentration level, to improve the treatment and clinical management of individuals initiating ART.

Notes

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