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Point-of-care C-reactive protein and risk of early mortality among adults initiating antiretroviral therapy

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Abstract

Objectives: In resource-limited settings, mortality in the initial months following antiretroviral therapy (ART) initiation remains unacceptably high. Novel tools to identify patients at highest risk of poor outcomes are needed. We evaluated whether elevated C-reactive protein (CRP) concentrations predict poor outcomes among people living with HIV (PLWH) initiating ART.

Methods: We enrolled and followed for three-months consecutive PLWH with pre-ART CD4+ T-cell count ≤350 cells/uL initiating ART from two HIV clinics in Uganda. Pre-ART CRP concentrations were measured from capillary blood using a point-of-care (POC) assay. After excluding patients with prevalent TB—the leading cause of HIV death—we measured three-month mortality rates using Kaplan-Meier curves, used Cox regression to compare differences in survival, and used logistic regression to compare differences in the odds of opportunistic infections, between patients with and without elevated POC CRP (≥8 mg/L).

Results: Of 1,293 patients included (median CD4+ T-cell count 181 [IQR 82–278]), 23 (1.8%) died within three months, including 19/355 (5.4%) with elevated POC CRP and 4/938 (0.4%) with non-elevated POC CRP. Eighty-six (6.7%) patients were diagnosed with opportunistic infections, including 39/355 (11.0%) with elevated POC CRP and 47/938 (5.0%) with non-elevated POC CRP. Elevated POC CRP was associated with mortality (adjusted HR 10.87, 95% CI: 3.64–32.47) and opportunistic infection (adjusted OR 1.95, 95% CI: 1.23–3.07).

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

Conclusions: Among PLWH with advanced HIV, elevated pre-ART POC CRP concentrations are associated with early mortality and opportunistic infections. Pre-ART POC CRP testing may reduce mortality by identifying patients at high risk for poor outcomes.

Keywords

HIV; C-reactive protein; mortality; opportunistic infections; screening

BACKGROUND

In 2017, 25.7 million people living with HIV (PLWH) lived in sub-Saharan Africa and 670,000 died, representing 71% of HIV-related deaths worldwide [1]. Despite expanded access to antiretroviral therapy (ART) and increasing uptake of World Health Organization (WHO) guidelines recommending immediate ART initiation for all PLWH [2], mortality in sub-Saharan Africa remains substantially higher than in resource-rich countries, even after accounting for lower average pre-ART CD4+ T-cell counts of patients presenting to care [3]. Mortality has been shown to be highest in the initial months following ART initiation [3] and post-mortem studies confirm that undiagnosed opportunistic infections are leading causes of death [3,4]; these results suggest that early mortality is most likely caused by underlying infections that were present at the time of ART initiation or infections that developed in the context of persistent immunologic instability. Identifying baseline factors that are strong predictors of early death and opportunistic infection that can also be measured using low-cost and simple point-of-care assays would help clinicians identify those patients requiring closer monitoring and/or more intensive clinical investigations, thereby improving patient outcomes.

Several markers have been associated with increased early mortality and opportunistic infections [5–9]. Of these, C-reactive protein (CRP), which can be performed at the point-of-care using a low-cost assay, has been most consistently associated with poor outcomes, in both resource-rich [5–7,9,10] and resource-limited [8,9,11,12] settings and regardless of CD4+ T-cell count and ART status. However, studies demonstrating these associations have been mostly case-control and measured CRP using lab-based assay from stored specimens [5–9]. Furthermore, most prior studies included patients with prevalent tuberculosis (TB), the leading cause of death among PLWH, which is known to cause elevated CRP concentrations [13–15]. As such, TB may have driven the associations observed between pre-ART CRP concentrations and overall mortality, and it remains unclear whether the strong association of CRP and morbidity and mortality is independent of TB status. Therefore, we conducted a prospective cohort study in Uganda to evaluate whether pre-ART CRP measured at the point-of-care is associated with early mortality and opportunistic infection among PLWH without prevalent TB.

METHODS

Study population

Between July 2013 and December 2016, we prospectively enrolled consecutive HIV-infected adults initiating ART from two urban HIV clinics in Kampala, Uganda in a study evaluating

novel TB screening and confirmatory testing algorithms. Patient recruitment, study procedures, and laboratory methods have been previously described and the diagnostic accuracy of point-of-care (POC) CRP and active TB prevalence among PLWH in this cohort have been previously reported [13]. We enrolled ART-naïve adults (age ≥18 years) with a pre-ART CD4+ T-cell count ≤350 cells/uL within three months of study enrollment. We excluded patients taking medication with anti-mycobacterial activity (anti-TB therapy, isoniazid preventive therapy, fluoroquinolones) within three days of enrollment. All patients provided written informed consent and the study was approved by the Institutional Review Boards of the University of California, San Francisco, Makerere University School of Medicine Research Ethics Committee, and Uganda National Council for Science and Technology.

Study procedures

Patient evaluation and follow-up.—We collected demographic and clinical data at enrollment and three-month follow-up using a standardized form. We assessed three-month vital status for all patients in person or by telephone and determined dates of death by reviewing medical records and interviewing patients' household members. We extracted interim diagnosis of opportunistic infections, based on routine clinical assessment, from chart review of clinic records. We considered patients to be lost to follow-up if they did not return or could not be contacted up to six months following study enrollment.

POC CRP testing.—For all study participants, we measured baseline CRP levels from capillary blood using a standard POC assay (iCHROMA POC CRP Reader, BodiTech Med Inc., South Korea) in accordance with the manufacturer's guidelines. We considered patients with POC CRP ≥8 mg/L to have elevated CRP levels, based on receiver operating characteristics analysis described in the parent study [13] and results from epidemiological studies demonstrating that CRP ≥8 mg/L strongly differentiates healthy individuals from those with ongoing pyogenic infection and/or systemic inflammatory process [16].

Pre-ART TB testing.—We collected two spot sputum samples at enrollment and performed 1) acid-fast bacilli smear microscopy on both specimens, 2) Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) testing on decontaminated sediment from the first sputum specimen, and 3) mycobacterial culture (BACTEC 960 Mycobacterial Growth Indicator Tube [MGIT]) on the remaining sediment from the first specimen and on decontaminated sediment from the second specimen. From April 2014 to December 2016, we collected spontaneously voided urine specimens and performed urine lipoarabinomannan (LAM) testing (Determine LAM, Alere, USA), as previously described [17]. We considered patients to have prevalent TB if active TB was diagnosed based on any positive microbiologic test result or if treatment was initiated within two weeks of enrollment based on clinical suspicion. All laboratory staff were blinded to clinical and demographic information, including symptom screen status and POC CRP levels.

Predictors of mortality.—POC CRP was studied as a categorical variable (<8 mg/L vs. ≥8 mg/L). Patient characteristics included age and body mass index (BMI) at study entry,

and sex. Candidate predictors related to HIV infection included being new to HIV care and baseline CD4+ T-cell count, which was studied as a categorical variable.

Statistical analysis

After excluding patients with prevalent TB, we compared demographic and clinical characteristics of non-TB patients with and without elevated baseline POC CRP using Chi-squared tests or Wilcoxon rank-sum tests. We measured three-month mortality rates using Kaplan-Meier curves, with duration of time in the study defined as the time from enrollment to death, loss to follow-up, or administrative censoring at 110 days after enrollment, whichever occurred first. We used log-rank tests to compare incidence of death between patients with and without elevated baseline POC CRP. In addition, we performed analyses stratified by baseline CD4+ T-cell count (<200 cells/uL vs. ≥200 cells/uL).

We used unadjusted Cox regressions to compare differences in three-month survival between patients with and without elevated POC CRP. In addition, we used unadjusted Cox regressions to compare differences in survival for baseline demographic and clinical characteristics. We fit a final adjusted Cox regression model including baseline POC CRP, age, sex, pre-ART CD4+ T-cell count *a priori*, and variables identified through backward stepwise selection methods. We assessed proportionality of hazards using Schoenfeld residuals and proportional hazards plots. In addition, we compared clinical characteristics of patients who did and did not develop an opportunistic infection during follow-up using Chi-squared tests or Fisher's exact tests, and fit a multivariable logistic regression model to estimate the odds of developing an opportunistic infection during follow-up for patients with elevated baseline POC CRP compared to those without elevated baseline POC CRP. In addition, we performed a sensitivity analysis of the association between elevated baseline POC CRP and developing a non-TB opportunistic infection, excluding all patients diagnosed with pulmonary or extrapulmonary TB during follow-up. We performed all statistical analyses using Stata 13 (College Station, TX).

RESULTS

Study participants

We enrolled 1,836 patients during the study period. Of these, 7 were receiving ART at enrollment, 10 had an unknown ART status, 3 were receiving anti-TB medications at enrollment, 174 had unknown baseline TB status (due to incomplete or contaminated cultures), 1 had a missing POC CRP result, and 28 had missing follow-up data (Figure 1). Of the remaining 1,613 patients, we excluded 320 (19.8%) prevalent TB cases who initiated anti-TB therapy based on microbiologic test results (287, 17.8%) or clinical suspicion despite negative test results (33, 2%); of these, 256/320 (80.0%) had elevated POC CRP levels, including 29/256 (11.3%) who died within three months of study enrollment.

Of 1,293 patients included in the study, 573 (44.3%) were male, median age was 33 years (IQR 27–40), median CD4+ T-cell count was 181 (IQR 82–278), 902 (69.8%) were new to HIV care, and 954 (73.8%) started ART on the day of enrollment (Table 1). Overall, 355 (27.5%) had elevated (≥8 mg/L) POC CRP levels. Patients with elevated POC CRP were

more often male (55.2% vs. 40.2%, p<0.001), more often new to HIV care (77.2% vs. 67.0%, p<0.001), had lower median CD4+ T-cell counts (146 vs. 195 cells/uL, p<0.001), and lower median BMI (20.7 vs. 22.1 kg/m^2, p<0.001) than patients with non-elevated baseline POC CRP levels.

Three-month mortality

Overall, there were 23 (1.8%) deaths among 1,293 patients, including 19/355 (5.4%) deaths among patients with elevated baseline POC CRP levels and 4/938 (0.4%) deaths among patients with non-elevated POC CRP levels. Median time-to-death was 30 days (IQR 18–59) and 56 days (IQR 32–79) among patients with elevated and non-elevated baseline POC CRP levels, respectively (p=0.19). A total of 31 (2.4%) patients were lost to follow-up; the proportion of patients lost to follow-up was similar between patients with and without elevated baseline POC CRP levels (3.1% vs. 2.1%, p=0.31).

The overall three-month mortality rate was 0.019 per 100 person-days and was over 10-times higher for patients with elevated POC CRP as compared with patients with non-elevated POC CRP (0.060 vs. 0.005 deaths per 100 person-days, log-rank p<0.001; Figure 2a). The rate of death differed by POC CRP stratum; for POC CRP levels 8–29 mg/L, 30–99 mg/L and ≥100 mg/L, the three-month mortality rate was 0.057, 0.055, and 0.090 deaths per 100 person-days, respectively (log-rank p<0.001, Supplementary Figure 1a). The three-month mortality rate was more than twice as high for patients with CD4+ T-cell counts <200 cells/uL as compared with patients with CD4+ T-cell counts ≥200 cells/uL (0.024 vs. 0.013 deaths per 100 person-days, log-rank p=0.15; Figure 2b). The rate of death increased with decreasing CD4+ T cell count, with the highest mortality rate among patients with CD4+ T-cell counts <50 cells/uL (0.050 deaths per 100 person-days, Supplementary Figure 1b). The rate of death was 0.065 deaths per 100 person-days among patients with both elevated POC CRP and CD4+ T-cell counts <200 cells/uL (Figure 2c).

The unadjusted hazard of death for patients with elevated POC CRP was 13.06 (95% CI 4.44–38.39, p<0.001) times that of patients with non-elevated POC CRP (Table 2). Patients with baseline CD4+ T-cell counts <200 cells/uL had a hazard of death 1.91 (95% CI 0.79–4.65) times that of patients with CD4+ T-cell counts ≥200 cells/uL (p=0.15). In a multivariable model, patients with elevated baseline POC CRP levels had a hazard of death 10.87 (95% CI 3.64–32.47, p<0.001) times greater than patients with non-elevated POC CRP, after adjusting for age, sex, CD4+ T-cell count, and BMI (Table 2).

Opportunistic infections

A total of 86 (6.7%) patients were diagnosed with 103 opportunistic infections following study enrollment, including 39/355 (11.0%) with elevated baseline POC CRP and 47/938 (5.0%) with non-elevated CRP (p<0.001, Supplementary Table 1). The leading opportunistic infections diagnosed during follow-up included pulmonary TB (24), extrapulmonary TB (13), Kaposi Sarcoma (12), typhoid (11), herpes simplex virus (8) and cryptococcal meningitis (6). Of the 86 patients diagnosed with an opportunistic infection during the 3-month follow-up period, 39/86 (11.0%) had elevated baseline POC CRP and 47/86 (5.0%) had non-elevated baseline POC CRP levels (p<0.001). Overall, 8/86 (8.1%) patients

diagnosed with an opportunistic infection died, compared with 15/1,207 (1.2%) patients not diagnosed with an opportunistic infection (p<0.001). POC CRP was elevated in 7/8 (87.5%) patients diagnosed with an opportunistic infection who died, and 12/15 (80.0%) patients not diagnosed with an opportunistic infection who died (p=0.99).

After adjusting for age, sex, CD4+ T-cell count, and BMI, the odds of being diagnosed with an opportunistic infection over follow-up for patients with elevated POC CRP was 1.95 (95% CI 1.23–3.07, p=0.004, Table 3) times that of patients with non-elevated POC CRP. The adjusted odds of being diagnosed with an opportunistic infection for patients with a baseline CD4+ T-cell count <200 cells/uL was 2.45 (95% CI 1.45–4.15, p=0.001) times that of patients with a baseline CD4+ T-cell count ≥200 cells/uL.

In a sensitivity analysis excluding patients diagnosed with pulmonary or extrapulmonary TB during follow-up, the adjusted odds of being diagnosed with a non-TB opportunistic infection over follow-up for patients with elevated POC CRP was 1.54 (95% CI 0.86–2.75, p=0.14) times that of patients with non-elevated POC CRP.

DISCUSSION

Despite the widespread scale-up of ART, early mortality among PLWH initiating ART in sub-Saharan Africa remains high, as many patients entering care still present with advanced disease. Predictors of early mortality that can be measured using inexpensive and rapid POC tests have strong potential to reduce mortality by identifying patients at high risk of poor treatment outcomes. In this cohort of HIV-infected adults initiating ART in a high TB/HIV setting, we evaluated whether CRP, measured using a low-cost POC assay, was associated with death within three months. We found that elevated baseline POC CRP (≥8 mg/L) was associated with an increased risk of early death for patients without prevalent TB, independent of baseline CD4+ T-cell count and BMI. Furthermore, we found that elevated baseline POC CRP was independently associated with an increased odds of opportunistic infection within three months. These results suggest that pre-ART POC CRP testing may be a valuable tool for identifying patients at high risk of early morbidity and mortality.

Our findings are consistent with prior studies, which were largely case-control studies [5–8] conducted on stored specimens [5–12], showing an association between baseline CRP concentrations and HIV-associated morbidity and mortality in both resource-rich [5–7,9,10] and –limited [8,9,11,12] settings and among patients of varying CD4+ T-cell counts, irrespective of ART status. In resource-limited settings, where opportunistic infections such as TB and bacterial infections remain leading causes of death, prior studies have found elevated pre-ART CRP concentrations to be independently associated with HIV clinical progression (*i.e.,* development of WHO stage 3 and 4 disease) [9,11] and mortality [8–11] and that increasing levels of CRP decrease time-to-death [10]. Studies from resource-rich settings have reported similar findings [5–7,9], despite relatively healthier patient populations (*e.g.,* higher baseline median CD4+ T-cell counts) where death was largely due to non-infectious causes. Baseline CRP concentrations ≥5 and 10 mg/L [6,9,11] have been shown to be independently associated with opportunistic infections and predictive of mortality, while smaller elevations (CRP 1–3 mg/L) [10] have been associated with chronic

inflammation, including increased cardiovascular risk and HIV progression. Our study confirms these prior findings in a large cohort of ART-naïve patients using a POC CRP assay. We found that elevated pre-ART POC CRP concentrations (≥8 mg/L) among PLWH without prevalent TB was associated with an over 10-fold increase in three-month mortality rate (0.005 vs. 0.060 per 100 person-days) and identified 19/23 (83%) patients who died within three months. Pre-ART POC CRP ≥8 mg/L also correctly identified over half of patients diagnosed with an opportunistic infection during the same time period, of whom 24/86 (27.9%) were diagnosed with active pulmonary TB, despite negative baseline evaluations, and was found to be a stronger predictor of both death and opportunistic infection than even pre-ART BMI and CD4+ T-cell count. In routine settings, pre-ART POC CRP testing may therefore help clinicians identify patients requiring closer monitoring following ART initiation, repeat TB confirmatory testing, and/or more intensive investigations for non-TB diseases. Studies should evaluating the impact of pre-ART POC CRP testing on HIV-associated morbidity and mortality are now needed to accelerate uptake of this potentially important intervnetion.

As a non-specific marker of systemic inflammation, CRP has the potential to be used as a prognostic tool for identifying PLWH initiating ART with multiple potentially fatal infections. CRP has been more consistently and more strongly associated with early mortality and opportunistic infection among PLWH than other inflammatory markers, such as TNF-alpha and IL-6 [5–9], and, importantly, CRP is already available as a low-cost (<2 USD per test) rapid (results in 3 minutes) POC assay that could be easily implemented in resource-limited settings. Our results also confirm the prognostic value of high POC CRP concentrations. We found that among PLWH with elevated pre-ART POC CRP, patients with POC CRP ≥100 mg/L had a three-month mortality rate nearly two-times higher than patients with POC CRP concentrations 8–29 mg/L and 30–99 mg/L (0.090 vs. 0.057 and 0.055 deaths per 100 person-days, respectively). Prior studies evaluating causes of CRP elevations among people with and without HIV have consistently found marked elevations (CRP ≥100 mg/L) to be strongly associated with severe bacterial infections [18–20], which, if unrecognized, increase risk of early death. In contrast, active TB and severe non-bacterial infections (*e.g.,* fungal, viral) were associated with more modest elevations in CRP [18–20]. These results suggest that extremely high (≥100 mg/L) POC CRP concentrations may represent the presence of acutely fatal infection(s) for which increased vigilance and early consideration of empiric antibiotic therapy may be required.

Emerging literature supports using CRP testing to systematically screen PLWH initiating ART for active pulmonary TB [13–15,17,21,22]. Studies from high TB/HIV burden areas have demonstrated that baseline CRP concentrations strongly predicts prevalent TB [13,15,21,23] and that among TB/HIV patients, higher CRP concentrations are associated with higher mycobacterial load [13,21], disseminated TB [21], and greater mortality risk [21]. Our prior research in this setting identified POC CRP (using the same 8 mg/L cut-point) as the only tool to meet the WHO target product profile of an effective TB screening test [24], correctly identifying 90% of all culture-confirmed prevalent TB cases and 96% of all PLWH with Xpert-positive TB [13]. These results, in combination with our study findings, provide strong evidence to support the dual use of POC CRP concentrations ≥8

mg/L, both to screen for active TB and to identify those who test negative for TB in need of repeat TB testing and/or evaluation for non-TB infections.

Our study has a number of strengths. First, our findings are likely generalizable to other HIV programs in high TB/HIV burden areas as our study population is representative of patients with advanced HIV initiating ART. Second, all patients underwent comprehensive TB evaluation at baseline and we excluded all patients with prevalent pulmonary TB, which is known to cause elevations in CRP. As such, our study strengthens the growing body of evidence supporting CRP testing as a powerful predictor of early mortality and opportunistic infection. Third, CRP was prospectively measured using a simple and low-cost POC assay, maximizing the feasibility of implementing our screening strategy in other resource-limited settings and making our findings directly interpretable for clinical practice. If used in combination with pre-ART POC CD4 testing, POC CRP testing could provide clinicians with a more standardized and straightforward approach to identifying those patients at highest risk for early mortality (*i.e.* low CD4 count and elevated POC CRP), for whom intensive investigations for TB and non-TB disease and closer monitoring following ART initiation may be necessary. Finally, we had little loss to follow-up in our study population, and loss to follow-up did not differ between patients with and without elevated baseline POC CRP.

This study has several limitations. First, we restricted enrollment to patients with baseline CD4+ T-cell counts ≤350 cells/uL because early mortality risk and the need for tools to predict mortality are greatest in this population. Although prior studies from resource-rich settings enrolling PLWH with higher CD4+ T-cell counts have reported similar findings, future studies evaluating the association between elevated CRP and death among HIV-infected patients living in resource-limited settings with higher pre-ART CD4+ T-cell counts would be valuable, particularly as the median CD4+ T-cell count at ART initiation continues to rise over time. Second, our definition of prevalent TB included patients started on empiric TB treatment but with negative bacteriologic results; as such, we may have inadvertently excluded some TB-negative patients from our study. Our definition was intentionally stringent to ensure that our study population was very unlikely to contain any patients with prevalent pulmonary TB. Third, while we performed comprehensive pulmonary TB testing at baseline, we did not evaluate patients for extrapulmonary TB. Similarly, we did not perform comprehensive baseline or follow-up testing for non-TB infections, which may impact observed associations, nor did we perform additional tests for immune reconstitution inflammatory syndrome (IRIS), which is also a major cause of early mortality, particularly among PLWH with low pre-ART CD4+ T-cell counts. Future studies should directly assess the causes and significance of elevated CRP concentrations in HIV-infected patients without pulmonary TB, as well as specific causes of death.

In conclusion, high early mortality rates among PLWH initiating ART in resource-limited settings confirm an urgent need for inexpensive and accurate tools to identify patients at high risk for poor outcomes. Our findings therefore have important implications for global HIV clinical care and policy dedicated to reducing early mortality. Already available as a simple, low-cost and rapid POC test, pre-ART CRP testing could be used first as a TB screening tool for patients with advanced HIV and second to identify PLWH who test negative for TB who

require closer monitoring, repeat confirmatory TB testing, and/or additional investigations for non-TB opportunistic infections. These results suggest that POC CRP may be an important tool for reducing early mortality among PLWH initiating ART in resource-limited settings and should strongly be considered as part of a public health strategy for improving HIV outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Author roles: CY designed the study. FCS, EA, AOA, and MK oversaw the local collection of data. JK, SM, LA, and MN were responsible for obtaining clinical measurements and data collection. LHC and CY analyzed and interpreted the data. LHC drafted the manuscript. CY, CM, and AC critically revised the manuscript. All authors reviewed and approved the final manuscript.

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REFERENCES

1. WHO | Data and statistics. WHO http://www.who.int/hiv/data/en/ (accessed 20 Jul 2018).
2. WHO | Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. WHO http://www.who.int/hiv/pub/arv/arv-2016/en/ (accessed 23 Apr 2018).
3. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. AIDS 2008; 22:1897–1908. [PubMed: 18784453]
4. Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS 2015; 29:1987–2002. [PubMed: 26266773]
5. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med 2008; 5:e203. [PubMed: 18942885]
6. Rodger AJ, Fox Z, Lundgren JD, Kuller LH, Boesecke C, Gey D, et al. Activation and coagulation biomarkers are independent predictors of the development of opportunistic disease in patients with HIV infection. J Infect Dis 2009; 200:973–983. [PubMed: 19678756]
7. Boulware DR, Hullsiek KH, Puronen CE, Rupert A, Baker JV, French MA, et al. Higher levels of CRP, D-dimer, IL-6, and hyaluronic acid before initiation of antiretroviral therapy (ART) are associated with increased risk of AIDS or death. J Infect Dis 2011; 203:1637–1646. [PubMed: 21592994]
8. Ledwaba L, Tavel JA, Khabo P, Maja P, Qin J, Sangweni P, et al. Pre-ART levels of inflammation and coagulation markers are strong predictors of death in a South African cohort with advanced HIV disease. PLoS One 2012; 7:e24243. [PubMed: 22448211]
9. Balagopal A, Asmuth DM, Yang W-T, Campbell TB, Gupte N, Smeaton L, et al. Pre-cART Elevation of CRP and CD4+ T-Cell Immune Activation Associated With HIV Clinical Progression

in a Multinational Case-Cohort Study. J Acquir Immune Defic Syndr 2015; 70:163–171. [PubMed: 26017661]

10. Feldman JG, Goldwasser P, Holman S, DeHovitz J, Minkoff H. C-reactive protein is an independent predictor of mortality in women with HIV-1 infection. J Acquir Immune Defic Syndr 2003; 32:210–214. [PubMed: 12571532]
11. Drain PK, Kupka R, Msamanga GI, Urassa W, Mugusi F, Fawzi WW. C-reactive protein independently predicts HIV-related outcomes among women and children in a resource-poor setting. AIDS 2007; 21:2067–2075. [PubMed: 17885297]
12. Redd AD, Eaton KP, Kong X, Laeyendecker O, Lutalo T, Wawer MJ, et al. C-reactive protein levels increase during HIV-1 disease progression in Rakai, Uganda, despite the absence of microbial translocation. J Acquir Immune Defic Syndr 2010; 54:556–559. [PubMed: 20463585]
13. Yoon C, Semitala FC, Atuhumuza E, Katende J, Mwebe S, Asege L, et al. Point-of-care C-reactive protein-based tuberculosis screening for people living with HIV: a diagnostic accuracy study. Lancet Infect Dis 2017; 17:1285–1292. [PubMed: 28847636]
14. Yoon C, Chaisson LH, Patel SM, Allen IE, Drain PK, Wilson D, et al. Diagnostic accuracy of C-reactive protein for active pulmonary tuberculosis: a meta-analysis. Int J Tuberc Lung Dis 2017; 21:1013–1019. [PubMed: 28826451]
15. Shapiro AE, Hong T, Govere S, Thulare H, Moosa M-Y, Dorasamy A, et al. C-reactive protein as a screening test for HIV-associated pulmonary tuberculosis prior to antiretroviral therapy in South Africa. *AIDS* Published Online First: 28 5 2018. doi:10.1097/QAD.0000000000001902
16. Claus DR, Osmand AP, Gewurz H. Radioimmunoassay of human C-reactive protein and levels in normal sera. J Lab Clin Med 1976; 87:120–128. [PubMed: 1245780]
17. Yoon C, Semitala FC, Asege L, Katende J, Mwebe S, Andama AO, et al. Yield and efficiency of novel intensified tuberculosis case-finding algorithms for people living with HIV. Am J Respir Crit Care Med 2018.
18. Morley JJ, Kushner I. Serum C-reactive protein levels in disease. Ann N Y Acad Sci 1982; 389:406–418. [PubMed: 6953917]
19. Sage EK, Noursadeghi M, Evans HE, Parker SJ, Copas AJ, Edwards SG, et al. Prognostic value of C-reactive protein in HIV-infected patients with Pneumocystis jirovecii pneumonia. Int J STD AIDS 2010; 21:288–292. [PubMed: 20378904]
20. Landry A, Docherty P, Ouellette S, Cartier LJ. Causes and outcomes of markedly elevated C-reactive protein levels. Can Fam Physician 2017; 63:e316–e323. [PubMed: 28615410]
21. Lawn SD, Kerkhoff AD, Vogt M, Wood R. Diagnostic and prognostic value of serum C-reactive protein for screening for HIV-associated tuberculosis. Int J Tuberc Lung Dis 2013; 17:636–643. [PubMed: 23575330]
22. Yoon C, Davis JL, Huang L, Muzoora C, Byakwaga H, Scibetta C, et al. Point-of-care C-reactive protein testing to facilitate implementation of isoniazid preventive therapy for people living with HIV. J Acquir Immune Defic Syndr 2014; 65:551–556. [PubMed: 24346636]
23. Wilson D, Badri M, Maartens G. Performance of serum C-reactive protein as a screening test for smear-negative tuberculosis in an ambulatory high HIV prevalence population. PLoS ONE 2011; 6:e15248. [PubMed: 21249220]
24. WHO | High-priority target product profiles for new tuberculosis diagnostics. WHO http://www.who.int/tb/publications/tpp_report/en/ (accessed 16 Jul 2018).

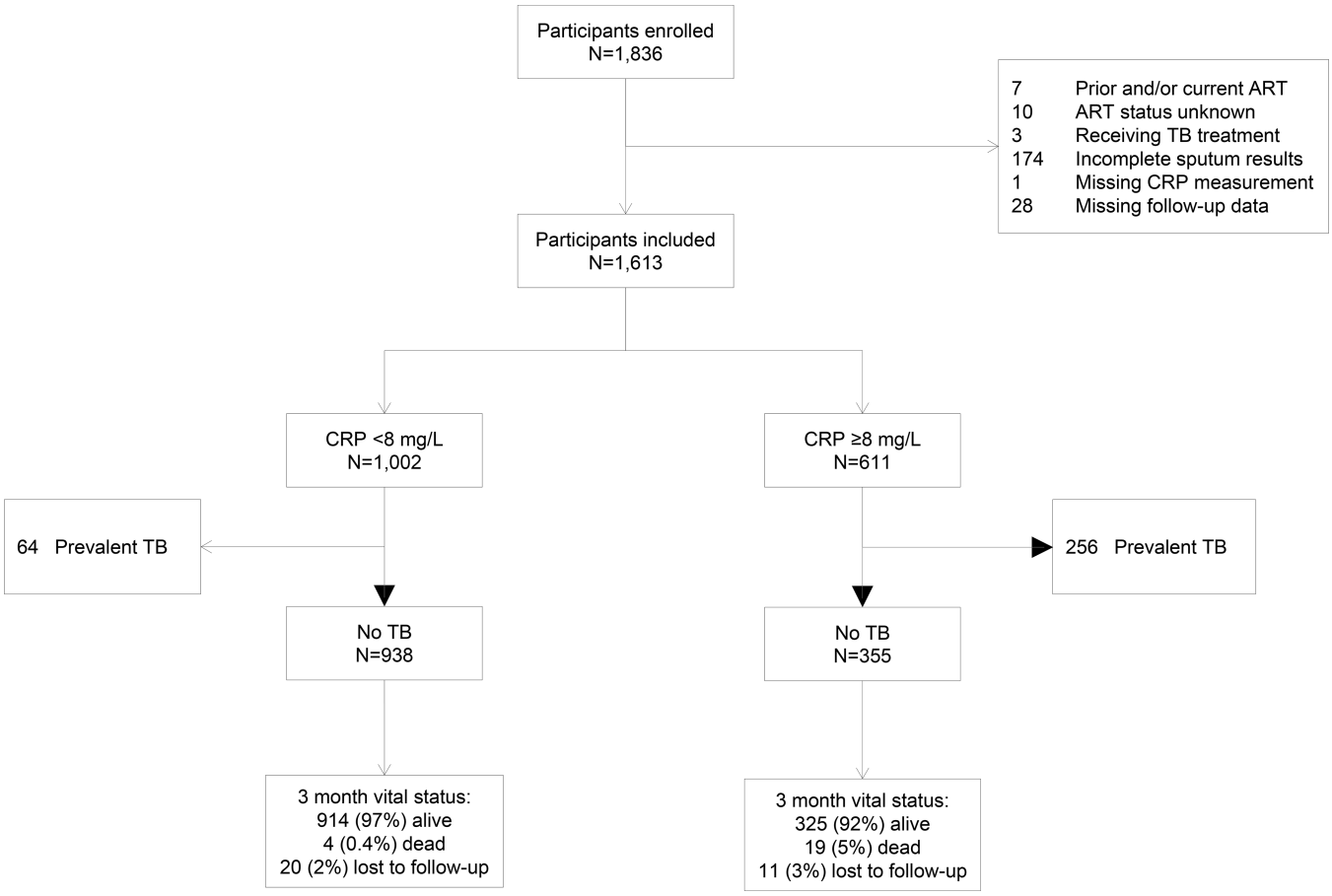

Figure 1. Study enrollment

We considered patients to have prevalent TB if active TB was diagnosed based on the results of microbiologic testing (mycobacterial culture, Xpert, sputum smear microscopy, or urine LAM) or if treatment was initiated within two weeks of enrollment based on clinical suspicion.

Abbreviations: ART, antiretroviral therapy; **TB,** tuberculosis; **CRP,** C-reactive protein

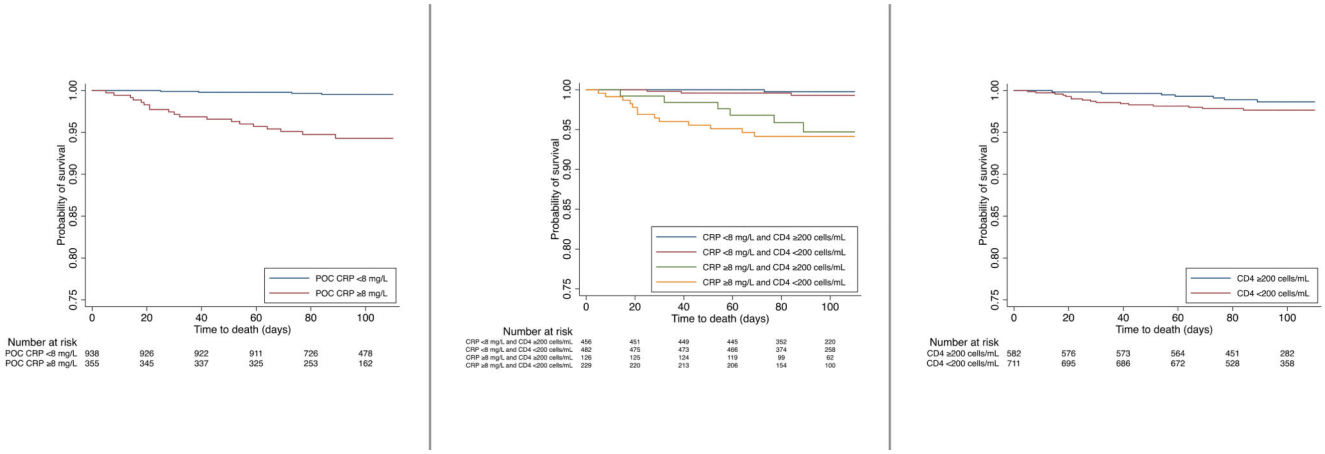

Figure 2. Kaplan-Meier survival curves

a) POC CRP ≥8 mg/L vs. <8 mg/L (log-rank p<0.001).

b) Baseline CD4 count ≥200 cells/uL vs. <200 cells/uL (log-rank p=0.15).

c) POC CRP ≥8 mg/L vs. <8 mg/L, stratified by baseline CD4 count (log-rank p<0.001)

Table 1.

Baseline demographic and clinical characteristics

Characteristic (%)	Total N=1,293	POC CRP <8 mg/L N=938	POC CRP ≥8 mg/L N=355	p-value*
Male	573 (44.3%)	377 (40.2%)	196 (55.2%)	<0.001
Age in years, median (IQR)	33 (27–40)	32 (26–40)	34 (27–40)	0.08
New to HIV care	902 (69.8%)	628 (67.0%)	274 (77.2%)	<0.001
Days from enrollment to ART initiation, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	<0.001
CD4 cells/uL, median (IQR)	181 (82–278)	195 (90–287)	146 (67–241)	<0.001
CD4 count				
<50 cells/uL	200 (15.5%)	135 (14.4%)	65 (18.3%)	<0.001
50–<200 cells/uL	511 (39.5%)	347 (37.0%)	164 (46.2%)	
200–350 cells/uL	582 (45.0%)	456 (48.6%)	126 (35.5%)	
BMI kg/m^2, median (IQR)	21.5 (19.4–24.3)	22.1 (19.7–24.7)	20.7 (18.6–23.3)	<0.001

Abbreviations: **POC CRP**, point-of-care C-reactive protein; **IQR,** interquartile range; **HIV,** human immunodeficiency virus; **uL,** microliters; **kg/m^2**,kilograms per square meter

*Based on Chi-squared test for binary outcomes or Wilcoxon rank-sum test for continuous outcomes

Table 2.

Unadjusted and adjusted hazard of death at three months among TB-negative patients initiating ART (N=1,293)

Characteristic	HR (95% CI)	p-value	aHR (95% CI)	p-value
POC CRP ≥8 mg/L	13.06 (4.44–38.39)	<0.001	10.87 (3.64–32.47)	<0.001
Male	2.00 (0.87–4.62)	0.11	1.29 (0.53–3.16)	0.58
Age	1.01 (0.96–1.05)	0.74	1.00 (0.95–1.05)	0.99
CD4 <200 cells/uL	1.91 (0.79–4.65)	0.15	1.13 (0.45–2.86)	0.79
BMI ≤18.5	4.24 (1.86–9.67)	0.001	2.84 (1.19–6.74)	0.02

Abbreviations: **TB,** tuberculosis; **ART,** antiretroviral therapy; **HR,** Hazard ratio; **CI,** Confidence interval; **aHR,** Adjusted hazard ratio; **POC CRP,** point-of-care C-reactive protein; **uL,** microliters

Table 3.

Unadjusted and adjusted odds of opportunistic infection over follow-up among TB-negative patients initiating ART (N=1,293)

Characteristic	OR (95% CI)	p-value	aOR (95% CI)	p-value
POC CRP ≥8 mg/L	2.34 (1.50–3.65)	<0.001	1.95 (1.23–3.07)	0.004
Male	1.56 (1.01–2.42)	0.05	1.31 (0.82–2.11)	0.26
Age	1.00 (0.98–1.02)	0.95	0.99 (0.96–1.02)	0.45
CD4 <200 cells/uL	2.88 (1.72–4.80)	<0.001	2.45 (1.45–4.15)	0.001
BMI ≤18.5	2.18 (1.33–3.58)	0.002	1.54 (0.92–2.59)	0.10

Abbreviations: **TB,** tuberculosis; **ART,** antiretroviral therapy; **OR,** Odds ratio; **CI,** Confidence interval; **aOR,** Adjusted odds ratio; **POC CRP,** point-of-care C-reactive protein; **uL,** microliters