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# Trends in C-Reactive Protein, D-Dimer, and Fibrinogen during Therapy for HIV-Associated Multidrug-Resistant Tuberculosis

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*Abstract.* HIV-positive adults on treatment for multi drug-resistant tuberculosis (MDR-TB) experience high mortality. Biomarkers of HIV/MDR-TB treatment response may enable earlier treatment modifications that improve outcomes. To determine whether changes in C-reactive protein (CRP), D-dimer, and fibrinogen were associated with treatment outcome among those with HIV/MDR-TB coinfection, we studied 20 HIV-positive participants for the first 16 weeks of MDR-TB therapy. Serum CRP, fibrinogen, and D-dimer were measured at baseline and serially while on treatment. At baseline, all biomarkers were elevated above normal levels, with median CRP 86.15 mg/L (interquartile range [IQR] 29.25–149.32), D-dimer 0.85 μg/mL (IQR 0.34–1.80), and fibrinogen 4.11 g/L (IQR 3.75–6.31). C-reactive protein decreased significantly within 10 days of treatment initiation and fibrinogen within 28 days; D-dimer did not change significantly. Five (25%) participants died after a median of 32 days. Older age (median age of 38*y* among survivors and 54*y* among deceased, $P = 0.008$) and higher baseline fibrinogen (3.86 g/L among survivors and 6.37 g/L among deceased, $P = 0.02$) were significantly associated with death. After adjusting for other measured variables, higher CRP concentrations at the beginning of each measurement interval were significantly associated with a higher risk of death during that interval. Trends in fibrinogen and CRP may be useful for evaluating early response to treatment among individuals with HIV/MDR-TB coinfection.

## INTRODUCTION

Tuberculosis (TB) remains the leading worldwide infectious cause of death,[1] driven in part by high mortality in HIV coinfected adults and by the emergence of strains of *Mycobacterium tuberculosis* resistant to both isoniazid and rifampicin (multidrug-resistant TB [MDR-TB]).

New molecular diagnostics rapidly identify drug resistance but presently provide limited information on susceptibility profiles of the infecting strain of *M. tuberculosis*. The Xpert MTB/Rif, the most widely used rapid molecular test, provides information on rifampicin resistance only.[2] Line probe assays (LPAs) directly on sputum can provide more information but have low sensitivity in smear-negative disease,[3] which is common in HIV-associated TB.[4] Mycobacterial cultures on sputum with indirect LPAs or phenotypic drug susceptibility testing (DST) can detect both first- and second-line drug resistance, but several weeks to months are required before results are available to guide therapy. Therefore, standardized second-line regimens are used to treat MDR-TB during the period between diagnosis and confirmation of drug susceptibility by culture-dependent methods, when risk of death is greatest.[5]

Mortality from HIV/MDR-TB coinfected patients is highest within the first 60 days of therapy.[3] However, there are presently no clinically useful early markers of effective therapy.[6] The earliest the World Health Organization recommends monitoring sputum smear microscopy for acid-fast bacilli is at the completion of 2 months of treatment,[7] whereas mortality at 2 months is already very high in certain populations and settings.[5] In addition, many HIV-coinfected individuals are smear negative at the time of TB diagnosis,[8] limiting the effectiveness of smear monitoring among these coinfected patients at highest risk of death. Earlier biomarkers of treatment response could identify individuals not responding rapidly to therapy, allow for earlier modification of ineffective treatment, and potentially prevent deaths.

Such biomarkers would be most valuable if they could be immediately used by clinicians at patient bedsides in high-burden, low-resource settings. We therefore studied candidate markers of early MDR-TB treatment response, which are available in routine clinical practice in South Africa, and available on point-of-care platforms in the developed world.[9]

C-reactive protein (CRP) is elevated in 93% of patients with HIV and TB coinfection at the time of diagnosis.[10] Once on therapy, studies of individuals without HIV coinfection and with drug-sensitive TB have shown reductions in CRP levels to be associated with increased 2-month culture conversion rates and less need for treatment extension.[11–14] Fibrinogen has also been shown to be elevated in HIV/TB coinfected patients[15,16] and to normalize within the first 2 months of therapy.[17,18] Elevated D-dimer has been associated with pulmonary TB[15] and HIV/TB coinfection,[19] and may presage death from pulmonary thromboembolic disease.[20] We conducted a study to prospectively evaluate these three candidate markers of treatment response among people living with HIV beginning treatment of MDR-TB.

## MATERIALS AND METHODS

Doris Goodwin Hospital (DGH) is a dedicated public MDR-TB treatment facility in KwaZulu-Natal, South Africa. It serves as the primary MDR-TB treatment site of the uMgungundlovu Health District. In 2015, the district had a case notification rate for TB of 678 per 100,000; 6.4% of all TB patients had rifampin resistance and 70.2% were HIV coinfected.[21]

We enrolled 20 consecutive HIV-positive patients admitted to DGH for initiation of MDR-TB therapy between September 2016 and March 2017. Inclusion criteria were as follows: 1) age

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greater than or equal to 18 years, 2) sputum positive for *M. tuberculosis* with rifampin resistance by molecular or phenotypic DST, 3) HIV seropositive, 4) able to attend clinic visits at DGH after discharge, and 5) willing to give informed consent for participation. Exclusion criteria were as follows: 1) known resistance at baseline to fluoroquinolones or kanamycin/amikacin/capreomycin, 2) initiation of HIV antiretroviral therapy (ART) within 12 weeks before initiating MDR-TB treatment, 3) pregnancy, and 4) prisoners.

After the informed consent process, venous blood was collected at baseline before treatment initiation, and at days 5, 10, 14, and 28, and weeks 8, 12, and 16 after treatment initiation, either while hospitalized or during regular clinic follow-up appointments. Blood was collected in vacuum blood collection tubes, stored at ambient temperature, and tested within 8 hours of collection. Samples were supplied to laboratory personnel with a coded participant identifier. Laboratory personnel were blinded to all other participant information. C-reactive protein was determined by immunoturbidimetric assay (Siemens Healthcare [Pty] Ltd., Halfway House Midrand, South Africa, normal range 0–5 mg/L), D-dimer was determined by reflectometric quantitative measurement (Roche Products [Pty] Ltd., Sandton, South Africa, normal range 0.1–0.5 μg/mL), and fibrinogen by immunologic method (Sysmex South Africa [Pty] Ltd., Johannesburg, South Africa, normal range 2–4 g/L), all according to manufacturer protocols. Thresholds for the upper limit of normal were set by the respective manufacturers. Hemoglobin, creatinine, albumin, and alkaline phosphatase results were obtained by review of participant records after tests were routinely performed by the South African National Health Laboratory Service.

Participant records were examined to determine demographic and additional medical information. Tuberculosis treatment was conducted according to local guidelines by department of health clinicians. Clinical staff were blinded to the results of the research assays. At the time of the study, MDR-TB patients were initiated on a standardized regimen, including moxifloxacin, kanamycin, and at least three additional agents.[22] Those with severe baseline hearing loss or renal impairment started a bedaquiline-based regimen and those developing severe side effects on fluoroquinolones or injectables were switched to a bedaquiline-based regimen, as per local guidelines.

Participants not on HIV ART at baseline were started on MDR-TB therapy first, and subsequently fast-tracked onto ART, as per South African guidelines.[23]

**Statistical analysis.** Comparisons between groups for continuous variables were tested with Kruskal–Wallis and for categorical variables by $\chi^2$ tests. The Benjamini–Hochberg procedure with a false discovery rate of 0.25 was used for multiple comparison correction.[24] A discrete time survival model[25,26] was used to describe the hazard of death during each time interval, controlling for age category of the patient (greater than or equal to 50 years versus less than 50 years), changing risk across time (linear and quadratic time effects), and temporally varying biomarker measurements for the patient. The model was fit using a binary variable (survival/death during each time interval for each patient) regression approach with the complementary log-log link function in R statistical software.[27] We corrected for multiple comparisons for the three separate biomarker measurement analyses using the Bonferroni adjustment. The analysis was iterated multiple times removing one participant at a time (i.e., a leave-one-out analysis) to test the sensitivity of our findings to inclusion of individual participants.

Cutoffs for continuous biomarkers were determined by the Youden index[28] of the receiver operating characteristic (ROC) curve. Laboratory clinical severity index (LCSI) was calculated as previously described.[29] Briefly, a score from 0 to 4 was assigned with one point for each abnormal value in hemoglobin, creatinine, albumin, or alkaline phosphatase, with cutoffs defined by our laboratory's standards, with hemoglobin of < 13 g/L, creatinine > 104 μmol/L, albumin < 35 g/L, and alkaline phosphatase > 128 IU/L considered abnormal.

Data were collected using REDCap electronic data capture tools hosted at Stanford University[30] and analyzed using Jupyter version 4.4.0 (jupyter.org) and R version 3.4.1 (r-project.org) using packages Tableone version 0.8.1, ggplot2 version 2.2.1,[31] and pROC version 1.10.0.[32]

**Ethics.** Written consent was obtained. The study was approved by the South African Medical Association Research Ethics Committee and Yale University Human Investigation Committee. All research was performed in accordance with relevant guidelines and regulations.

**Data availability.** The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

## RESULTS

**Study population.** Ninety-eight potential participants were screened for entry into the study. Of these, 64 were ineligible (24 started TB therapy before they could be approached for consent, 17 were HIV negative, nine were transferred in to the facility already on TB treatment, five were already enrolled in another study, five were prisoners, two had been started on ART in the 12 weeks before admission, and two were unable to provide informed consent because of altered mental state). Thirty-six individuals were approached for enrollment and 20 consented to participate. None of the participants withdrew consent at a later date and all were followed for at least 16 weeks or until death.

Most participants were male ($N = 13$), with median age of 41 years (interquartile range [IQR] 33–48*y*) (Table 1). Twelve had been treated previously for TB and two of these individuals had prematurely stopped their prior course of treatment. The median CD4 lymphocyte count was 234 cells per μL (IQR of 141–429 cells/μL), 12 were on ART and 10 of these individuals had a recent undetectable viral load measurement. Those not on ART at baseline were initiated at a median of 12.5 days after starting TB therapy (range 7–86 days). Participants were admitted to an inpatient unit at the initiation of therapy for a median of 32 days (range 5–140 days).

At baseline, almost all participants were anemic and hypoalbuminemic; 45% had an elevated alkaline phosphatase and 15% had baseline renal impairment. C-reactive protein, fibrinogen, and D-dimer were all elevated at baseline with a median CRP of 86.15 mg/L (upper limit of normal [ULN] of 5mg/L, IQR 29.25–149.32 mg/L), median fibrinogen of 4.11 g/L (ULN of 4 g/L, IQR 3.75–6.31 g/L), and median D-dimer of 0.85 μg/mL (ULN 0.5 μg/mL, IQR 0.34–1.80 μg/mL). When stratifying by disease severity, baseline CRP, fibrinogen, and d-dimer were not significantly different in groups with higher baseline smear grade (≥ 2) or in those who were baseline culture positive.

TABLE 1
Participant baseline characteristics

| | Category | Value | Normal range |
|---|---|---|---|
| *n* | | 20 | – |
| Gender (%) | Female | 7 (35.0) | – |
| | Male | 13 (65.0) | – |
| Race (%) | Indian | 1 (5.0) | – |
| | Black African | 19 (95.0) | – |
| Age (year) (median [IQR]) | | 41.95 [33.76, 48.93] | – |
| BMI (median [IQR]) | | 19.35 [16.23, 24.67] | – |
| ECOG (%) | 1 | 13 (65.0) | – |
| | 2 | 4 (20.0) | – |
| | 3 | 3 (15.0) | – |
| TB category (%) | New TB case | 8 (40.0) | – |
| | Prior history of TB | 10 (50.0) | – |
| | Treatment after default | 2 (10.0) | – |
| Sputum smear grade (%) | 0 | 12 (60.0) | – |
| | 1 | 1 (5.0) | – |
| | 2 | 3 (15.0) | – |
| | 4 | 4 (20.0) | – |
| CD4 count (cells/μL) (median [IQR]) | | 234.00 [141.75, 429.75] | – |
| Detectable viral load (%) | Detectable viral load on ART | 2 (10.0) | – |
| | Undetectable viral load on ART | 10 (50.0) | – |
| | Not on ART | 8 (40.0) | – |
| Hemoglobin (g/L) (median [IQR]) | | 10.05 [9.38, 11.33] | 13.0–17.0 |
| Creatinine (μmol/L) (median [IQR]) | | 72.50 [68.00, 85.25] | 64–104 |
| Albumin (g/dL) (median [IQR]) | | 24.00 [21.00, 28.50] | 35–52 |
| Alkaline phosphatase (IU/L) (median [IQR]) | | 125.00 [111.25, 145.00] | 53–128 |
| LCSI (%) | 2 | 11 (55.0) | – |
| | 3 | 7 (35.0) | – |
| | 4 | 2 (10.0) | – |
| CRP (mg/L) (median [IQR]) | | 86.15 [29.25, 149.32] | 0.0–5.0 |
| Fibrinogen (g/L) (median [IQR]) | | 4.11 [3.75, 6.31] | 2.00–4.00 |
| D-dimer (μg/mL) (median [IQR]) | | 0.85 [0.34, 1.80] | 0.1–0.5 |

ART = HIV antiretroviral therapy; BMI = body mass index; CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; LCSI = laboratory clinical severity index[29]; TB = tuberculosis.

**Trends.** While on therapy for MDR-TB, median CRP and fibrinogen levels decreased significantly, whereas D-dimer did not (Supplemental Figure 1). C-reactive protein fell significantly by day 10 of therapy and fibrinogen by day 28. The reductions were sustained beyond day 28, with median fibrinogen (but not CRP) reaching normal range.

**Outcomes.** After 4 months of follow-up, five of the 20 participants died (25%) at a median of 32 days after starting TB treatment (range 4–51 days).

At baseline, older age and higher baseline fibrinogen level were significantly associated with higher risk of death, after correction for multiple comparisons. Median age was 54 years (IQR 48–60*y*) among those dying during treatment and 38 years (IQR 32–44*y*) among survivors, $P = 0.008$. Median baseline fibrinogen was 6.37 g/L (IQR 6.05–7.50 g/L) for those dying and 3.86 g/L (IQR 3.68–4.33 g/L) for survivors, $P = 0.02$. Baseline CRP was elevated among those who died with a median of 117 mg/L (IQR 87.9–169.7 mg/L), but this was not statistically different from the baseline CRP among survivors (median 76.6 mg/L, IQR 17.8–145.7 mg/L), $P = 0.127$. Baseline D-dimer was similar in both survivors and nonsurvivors (Figure 1). Gender, race, body mass index, the Eastern Cooperative Oncology Group performance status, baseline smear positivity and grade, baseline culture positivity, CD4 lymphocyte count, initially being on HIV antiretrovirals, HIV viral load, hemoglobin, creatinine, albumin, and alkaline phosphatase were not predictive of outcome.

Results from the discrete time survival model suggest that patients with higher CRP values at the beginning of a discrete measurement interval are at higher risk of earlier death than those with lower CRP at the start of the time interval. All other factors being equal for two living patients at the start of a time interval, a patient whose CRP value is higher (by the interquartile range of CRP observed across all patients) had an estimated increase in the hazard of dying during that time interval of 193.88% (98.3% confidence interval [CI]: 3–735%) after Bonferroni adjustment. In our leave-one-out sensitivity analysis, average results across all models demonstrated a similar hazard of dying of 208% (95% CI: 23–65,121%). Only two of 127 models resulted in a 95% CI that included 0. Results also remained significant after Bonferroni correction.

The discrete time survival model did not show statistically significant associations between patients with higher fibrinogen or D-dimer at time interval start and hazard of dying during the time interval in either the Bonferroni adjusted or unadjusted analyses. For fibrinogen, larger interquartile values had an estimated increase in the hazard of dying by 171.08% (98.3% CI: –66–2,104%) and for D-dimer by 126.01% (98.3% CI: –50–922%) in the Bonferroni adjusted models. None of the models in the leave-one-out sensitivity analysis for fibrinogen or D-dimer had a 95% CI that excluded 0.

A reduction in CRP of less than 44% from initial levels by week 2 of treatment had a sensitivity of 100% and specificity of 71% for predicting death (ROC area under the curve of 0.74, 95% CI: 0.50–0.97).

In the subgroup of participants who initiated ART after starting TB therapy ($N = 8$), there was one death that occurred 18 days after ART initiation and 30 days after TB treatment initiation. Trends in CRP, D-dimer, and fibrinogen among

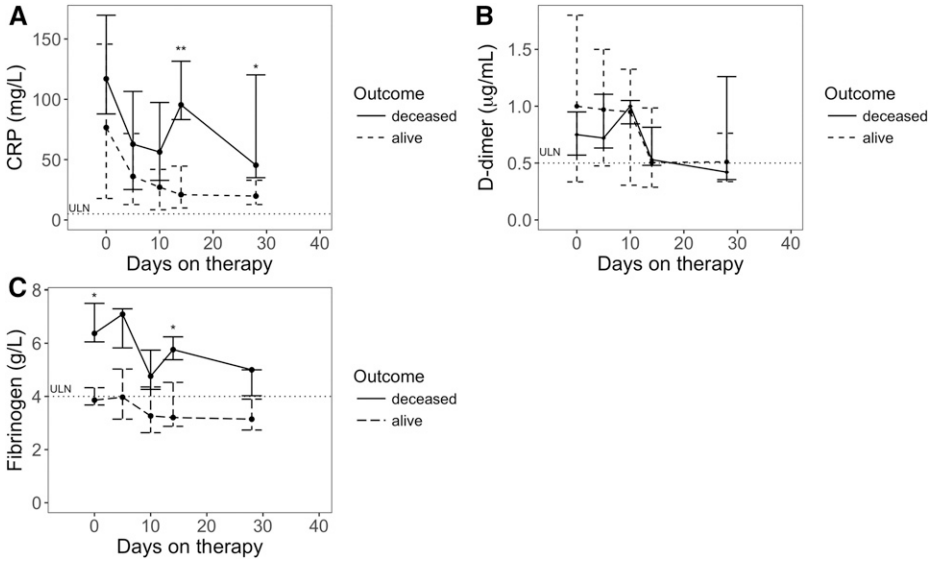


FIGURE 1. Outcome group trends while on multidrug-resistant tuberculosis (MDR-TB) therapy. Changes in serum (**A**) C-reactive protein (CRP), (**B**) D-dimer, and (**C**) fibrinogen in HIV-infected individuals while on therapy for MDR-TB, stratified by outcome. Lines are median response with error bars representing interquartile ranges. *Significant between group difference ($P < 0.05$ by Kruskal–Wallis test), **$P < 0.01$ by Kruskal–Wallis test. ULN = upper limit of normal.

those started on ART were similar to the full group, with no median rise after day 14.

## DISCUSSION

We conducted a study that prospectively followed a cohort of 20 participants with HIV and MDR-TB coinfection for the first 4 months of their therapy and found that individuals who had higher CRP concentrations at the start of a time interval had a significantly increased hazard of dying. The relative decrease in CRP in survivors was similar to that seen in other work by our group in people with HIV and drug-sensitive TB (manuscript in preparation) with a failure to reduce CRP by 44% at week 2, the most sensitive cutoff of predicting death. Baseline fibrinogen was also significantly higher in those who died.

Older age was a significant baseline predictor of death, a finding which has been reported by others in South Africa.[33] Other routinely collected clinical parameters were not significantly predictive of outcome.

Median CRP and fibrinogen rapidly declined on MDR-TB therapy, with CRP having a significant decrease by 10 days and fibrinogen by 28 days on treatment. The persistently elevated fibrinogen and CRP in those who died could have been a result of ineffective TB treatment, an unfavorable inflammatory response phenotype, coinfection with another opportunistic disease, or unrelated medical illness. Our results suggest that failure to normalize CRP and fibrinogen may be useful signals to prompt clinicians to risk stratify patients on therapy with the intention of pursuing further investigations or altering therapy. Potential clinical interventions could include strengthened adherence counseling and monitoring, rapid molecular drug sensitivity testing, addition of anti-TB agents, or additional screening for concomitant opportunistic infections. If therapy is found to be ineffective, earlier changes would not only improve outcomes but also could reduce the risk of generating additional resistance mutations and halt further drug-resistant TB transmission.[34]

D-dimer was elevated at the time of diagnosis for most participants but was not predictive of outcome. During the course of therapy, there was no significant difference between D-dimer trends in survivors and deaths, and overall, average D-dimer levels did not decline significantly.

Other routinely collected laboratory values (hemoglobin, creatinine, albumin, and alkaline phosphatase) measured at baseline were similar between the two groups, although abnormal in almost all participants. While studying patients with XDR-TB in the same setting, Shenoi et al.[29] developed a laboratory clinical severity index (LCSI) score. In our population, this score was not significantly predictive of outcome, most likely because all participants had baseline derangements in at least two of these four values and 45% had derangements in at least three, leaving little room for comparison.

Strengths of our study are that data were obtained by sequential recruitment of participants with confirmed rifampin-resistant TB at a public treatment site, who were treated with standardized regimens according to national guidelines. Treating physicians were blinded to CRP, D-dimer, and fibrinogen results. We note that this was a small study with limited statistical power and the results need to be followed up within larger cohorts. Additional studies are planned with larger enrollment to verify these findings.

Forty percent of our study's participants were not taking ART at baseline, and initiation of ART during MDR-TB treatment may have triggered immune reconstitution inflammatory syndrome (IRIS), complicating interpretation of observed biomarker trends. However, these markers are intended to identify patients failing to improve on therapy because of any mechanism, including IRIS, to prompt clinicians to investigate further. Some individuals did have mild downstream increases in markers after initiation of ART but median levels did not rise in this group.

## CONCLUSION

Our analysis of CRP and fibrinogen trends suggests that these biomarkers may predict mortality in HIV-positive adults on treatment of MDR-TB and should be further evaluated in larger studies.

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