1 Title: Trends in CRP, D-dimer and fibrinogen during therapy for HIV associated
2 multidrug resistant tuberculosis

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28 **Running Head:** On-treatment HIV/MDR-TB biomarker trends
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31   ABSTRACT

32   Background: HIV positive adults on treatment for multidrug-resistant tuberculosis (MDR-

33   TB) experience high mortality. Biomarkers of HIV/MDR-TB treatment response may

34   enable earlier treatment modifications that improve outcomes.

35   Methods: To determine whether trends in C-reactive protein (CRP), D-dimer and

36   fibrinogen predict treatment outcome among those with HIV/MDR-TB co-infection we

37   studied 20 HIV positive participants initiating therapy for MDR-TB. Serum CRP,

38   fibrinogen, and D-dimer were measured at baseline and serially while on treatment.

39   Results: At baseline, all biomarkers were elevated with median CRP 86.15 mg/L (IQR

40   29.25-149.32), D-dimer 0.85 µg/mL (IQR 0.34-1.80) and fibrinogen 4.11 g/L (IQR 3.75-

41   6.31). CRP decreased significantly within 10 days of treatment initiation and fibrinogen

42   within 28 days; D-dimer did not change significantly. 5 (25%) participants died. Older

43   age (median age of 38y among survivors and 54y among deceased, p=0.008) and

44   higher baseline fibrinogen (3.86 g/L among survivors and 6.37 g/L among deceased,

45   p=0.02) were significantly associated with death. Higher CRP concentrations at the

46   beginning of each measurement interval were significantly associated with a higher risk

47   of death during that interval.

48   Conclusion: Trends in fibrinogen and CRP may be useful for evaluating early response

49   to treatment among individuals with HIV/MDR-TB co-infection.

50   INTRODUCTION

51   Tuberculosis (TB) remains the leading worldwide infectious cause of death[1], driven in

52   part by high mortality in HIV co-infected adults and by the emergence of strains of *M.*

53   *tuberculosis* resistant to both isoniazid and rifampicin (multidrug resistant tuberculosis

54   [MDR-TB]). New diagnostics have been broadly deployed but significant population

55   level improvements in outcomes have not followed[2]. Especially concerning are the high

56   levels of early mortality (within 60 days) experienced by patients beginning therapy for

57   MDR-TB in South Africa, most of whom are HIV co-infected[3].

58   New molecular diagnostics have improved the ability to rapidly identify the presence of

59   drug-resistance but often provide only limited information about susceptibility profiles of

60   the infecting strain of *M. tuberculosis*. The Xpert MTB/Rif, currently the most widely

61   used rapid molecular test, provides information on rifampicin resistance only[4]. Direct

62   line-probe assays on sputum are also utilized for detecting first and second line drug

63   resistance but have low sensitivity in smear negative disease[5], which is common in HIV

64   associated tuberculosis[6]. More typically, several weeks to months are required before

65   phenotypic drug susceptibility testing (DST) or indirect line-probe assays are available

66   to guide therapy. Therefore, standardized second-line regimens are used during the

67   period between diagnosis and confirmation of drug susceptibility by culture dependent

68   methods, when risk of death is greatest[7].

69   There are currently no clinically useful early markers of effective therapy[8]. The earliest

70   World Health Organization (WHO) recommended monitoring is sputum smear

71   microscopy for acid-fast bacilli at the completion of two months of treatment[9]. However,

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72   mortality at two months is already very high in certain populations and settings[7] and

73   many HIV co-infected individuals are smear-negative at the time of TB diagnosis[10],

74   limiting the effectiveness of smear monitoring among these co-infected patients at

75   highest risk of death. Earlier biomarkers of treatment response could identify individuals

76   not responding rapidly to therapy, allow for earlier modification of ineffective treatment

77   and potentially prevent deaths.

78   Such biomarkers would be most valuable if they could be immediately used by clinicians

79   at patient bedsides in high burden, low resource settings. We therefore focused on

80   candidate markers of early MDR-TB treatment response which were available in routine

81   clinical practice in South Africa, and available on point-of-care platforms in the

82   developed world[11].

83   C-reactive protein (CRP) is elevated in 93% of patients with HIV and TB co-infection at

84   time of diagnosis[12]. Once on therapy, studies of individuals without HIV-coinfection and

85   with drug-sensitive TB have shown reductions in CRP levels to be associated with

86   increased two month culture conversion rates and less need for treatment extension[13–

87   16]. Fibrinogen has also been shown to be elevated in HIV-TB co-infected patients[17,18]

88   and to normalize within the first two months of therapy[19,20]. Elevated D-dimer has been

89   associated with pulmonary tuberculosis[17] and HIV/TB co-infection[21]. We conducted a

90   study to prospectively evaluate these three candidate markers of treatment response

91   among people living with HIV beginning treatment for MDR-TB.

92   METHODS

93   Doris Goodwin Hospital (DGH) is a dedicated public MDR-TB treatment facility in

94   KwaZulu-Natal, South Africa. It serves as the primary MDR-TB treatment site of the

95   uMgungundlovu Health District. In 2015, the district had a case notification rate for

96   tuberculosis of 678 per 100,000; 6.4% of all tuberculosis patients had rifampin

97   resistance and 70.2% were HIV co-infected[22].

98   We enrolled twenty consecutive HIV-positive patients admitted to DGH for initiation of

99   MDR-TB therapy between September 2016 and March 2017. Inclusion criteria were: 1)

100   age greater than or equal to 18 years; 2) sputum positive for *M. tuberculosis* with

101   rifampin resistance by molecular or phenotypic drug susceptibility testing; 3) HIV

102   seropositive; 4) able to attend clinic visits at DGH after discharge; 5) willing to give

103   informed consent for participation. Exclusion criteria were: 1) known resistance at

104   baseline to fluoroquinolones or kanamycin/amikacin/capreomycin; 2) initiation of HIV

105   antiretroviral therapy within 12 weeks prior to initiating MDR-TB treatment; 3)

106   pregnancy; 4) prisoners.

107   After the informed consent process, venous blood was collected at baseline before

108   treatment initiation, and at days 5, 10, 14 and 28, and weeks 8, 12 and 16 after

109   treatment initiation, either while hospitalized or during regular clinic follow-up

110   appointments. Blood was collected in vacuum blood collection tubes, stored at ambient

111   temperature and tested within 8 hours of collection. Samples were supplied to

112   laboratory personnel with a coded participant identifier. Laboratory personnel were

113   blinded to all other participant information. CRP was determined by immunoturbidimetric

114   assay (Siemens Healthcare (Pty) Ltd, S.A, normal range 0 to 5 mg/L), D-dimer was

115   determined by reflectometric quantitative measurement (Roche Products (Pty) Ltd, S.A,

116   normal range 0.1 to 0.5 µg/mL) and fibrinogen by immunologic method (Sysmex South

117   Africa (Pty) Ltd, S.A, normal range 2 to 4 g/L), all according to manufacturer protocols.

118   Thresholds for the upper limit of normal were set by the respective manufacturers.

119   Hemoglobin, creatinine, albumin and alkaline phosphatase results were obtained by

120   review of participant records after tests were routinely performed by the South African

121   National Health Laboratory Service.

122   Participant records were examined to determine demographic and additional medical

123   information. Tuberculosis treatment was conducted according to local guidelines by

124   department of health clinicians. Clinical staff were blinded to the results of the research

125   assays. At the time of the study, MDR-TB patients were initiated on a standardized

126   regimen, including moxifloxacin, kanamycin, and at least 3 additional agents[23]. Those

127   with severe baseline hearing loss or renal impairment started a bedaquiline-based

128   regimen, and those developing severe side-effects on fluoroquinolones or injectables

129   were switched to a bedaquiline-based regimen, per local guidelines.

130   Participants not on HIV antiretroviral therapy (ART) at baseline were started on MDR-

131   TB therapy first, and subsequently fast-tracked onto ART, per South African

132   guidelines[24].

133   Statistical Analysis

134   Comparisons between groups for continuous variables were tested with Kruskal-Wallis

135   and for categorical variables by chi-square tests. A discrete time survival model[25,26] was

136   used to describe the hazard of death during each time interval controlling for age

137   category of the patient (greater than or equal to 50 vs. less than 50 years), changing

138   risk across time (linear and quadratic time effects), and temporally varying biomarker

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139   measurements for the patient. The model was fit using a binary variable (survival/death

140   during each time interval for each patient) regression approach with the complementary

141   log-log link function in R statistical software[27]. Cutoffs for continuous biomarkers were

142   determined by the Youden index of the receiver operating characteristic (ROC) curve.

143   Laboratory clinical severity index was calculated as previously described[28]. A score from

144   0 to 4 was assigned with one point for each abnormal value in hemoglobin, creatinine,

145   albumin, or alkaline phosphatase, with cutoffs defined by our laboratory's standards,

146   with hemoglobin of < 13g/L, creatinine > 104 µmol/L, albumin < 35 g/L and alkaline

147   phosphatase > 128 IU/L considered abnormal.

148   Data were collected using REDCap electronic data capture tools hosted at Stanford

149   University[29], and analyzed using jupyter version 4.4.0 (jupyter.org) and R version 3.4.1

150   (r-project.org)[27] and with packages tableone version 0.8.1, ggplot2 version 2.2.1[30], and

151   pROC version 1.10.0[31].

152   Ethics

153   Written consent was obtained. The study was approved by the South African Medical

154   Association Research Ethics Committee and Yale University Human Investigation

155   Committee. All research was performed in accordance with relevant guidelines and

156   regulations.

157   Data availability

158   The datasets generated during and/or analyzed during the current study are available

159   from the corresponding author on reasonable request.

160

161   RESULTS

162   Study Population

163   98 potential participants were screened for entry into the study. Of these, 64 were

164   ineligible (24 started TB therapy before they could be approached for consent, 17 were

165   HIV negative, 9 were transferred in to the facility already on TB treatment, 5 were

166   already enrolled in another study, 5 were prisoners, 2 had been started on antiretroviral

167   therapy in the 12 weeks before admission, and 2 were unable to provide informed

168   consent due to altered mental state). 36 individuals were approached for enrollment and

169   20 consented to participate. None of the participants withdrew consent at a later date

170   and all were followed for at least 16 weeks or until death.

171   Most participants were male (n=13), with median age of 41 years (inter-quartile range

172   (IQR) 33 to 48y) (Table 1). 12 had been treated previously for tuberculosis and 2 of

173   these individuals had prematurely stopped their prior course of treatment. The median

174   CD4 cell count was 234 cells per μL (IQR of 141 to 429 cells/μL), 12 were on

175   antiretroviral therapy (ART), and 10 of these individuals had a recent undetectable viral

176   load measurement. Those not on ART at baseline were initiated at a median of 12.5

177   days after starting TB therapy (range 7 to 86 days). Participants were admitted to an

178   inpatient unit at the initiation of therapy for a median of 32 days (range 5 to 140 days).

179   At baseline, almost all participants were anemic and hypoalbuminemic; 45% had an

180   elevated alkaline phosphatase and 15% had baseline renal impairment. CRP, fibrinogen

181   and D-dimer were all elevated at baseline with a median CRP of 86.15mg/L (upper limit

182   of normal (ULN) of 5mg/L, IQR 29.25 to 149.32 mg/L), median fibrinogen of 4.11 g/L

183   (ULN of 4 g/L, IQR 3.75 to 6.31 g/L), and median D-dimer of 0.85 µg/mL (ULN 0.5

184   µg/mL IQR 0.34 to 1.80 µg/mL).

185   Trends

186   While on therapy for MDR-TB, median CRP and fibrinogen levels decreased

187   significantly while D-dimer did not (Supplementary Figure 1). CRP fell significantly by

188   day 10 of therapy, and fibrinogen by day 28. The reductions were sustained beyond day

189   28, with median fibrinogen (but not CRP) reaching normal range.

190   Outcomes

191   After four months of follow-up, 5 of the 20 participants died (25%) at a median of 32

192   days after starting TB treatment (range 4 to 51 days).

193   At baseline, older age and higher baseline fibrinogen level were significantly associated

194   with higher risk of death. Median age was 54 years (IQR 48 to 60y) among those dying

195   during treatment and 38 years (IQR 32 to 44y) among survivors, p=0.008. Median

196   baseline fibrinogen was 6.37 g/L (IQR 6.05 to 7.50 g/L) for those dying and 3.86 g/L

197   (IQR 3.68 to 4.33 g/L) for survivors, p=0.02. Baseline CRP was elevated among those

198   that died with a median of 117 mg/L (IQR 87.9 to 169.7 mg/L), but this was not

199   statistically different than the baseline CRP among survivors (median 76.6 mg/L, IQR

200   17.8 to145.7 mg/L), p=0.127. Baseline D-dimer was similar in both survivors and non-

201   survivors (Figure 1).

202   Hemoglobin, creatinine, albumin, and alkaline phosphatase were not significantly

203   different at baseline between survivors and non-survivors.

204   Results from the discrete time survival model suggest that patients with higher CRP

205   values at the beginning of a measurement interval had a significantly higher risk of

206   dying during that time interval. All other factors being equal for two living patients at the

207   start of a time interval, a patient whose CRP value is higher (by the interquartile range

208   of CRP observed across all patients) had an estimated increase in the hazard of dying

209   during that time interval of 194% (95% CI: 25% to 591%).

210   The discrete time survival model did not show statistically significant associations

211   between patients with higher fibrinogen or d-dimer at time interval start and hazard of

212   dying during the time interval. For fibrinogen, larger interquartile values had an

213   estimated increase in the hazard of dying by 171.08% (95% CI: -51.25% to 1407.23 and

214   for D-dimer by 126.01% (95% CI: -34.29% to 677.39%).

215   Failure to reduce CRP by 44% at week 2 had a sensitivity of 71% and specificity of

216   100% for predicting death (ROC area under the curve of 0.74, 95% CI 0.50 to 0.97).

217   DISCUSSION

218   We conducted a study that prospectively followed a cohort of 20 participants with HIV

219   and MDR-TB co-infection for the first 4 months of their therapy and found that

220   individuals who had higher CRP concentrations at the start of a time interval had a

221   significantly increased hazard of dying. The relative decrease in CRP in survivors was

222   similar to that seen in other work by our group in people with HIV and drug-sensitive TB

223   (manuscript in preparation) with a failure to reduce CRP by 44% at week 2 the most

224   sensitive cutoff of predicting death. Baseline fibrinogen was also significantly higher in

225   those that died.

226   Older age was a significant baseline predictor of death, a finding which has been

227   reported by others in South Africa[32]. Other routinely collected clinical parameters were

228   not significantly predictive of outcome.

229   Median CRP and fibrinogen rapidly declined on MDR-TB therapy, with CRP having a

230   significant decrease by 10 days, and fibrinogen by 28 days on treatment. The

231   persistently elevated fibrinogen and CRP in those who died could have been a result of

232   ineffective TB treatment, an unfavorable inflammatory response phenotype, coinfection

233   with another opportunistic disease, advanced HIV disease, or unrelated medical illness.

234   Our results suggest that failure to normalize CRP and fibrinogen may be useful signals

235   to prompt clinicians to risk stratify patients on therapy with the intention of pursuing

236   further investigations or altering therapy. Earlier effective therapy may improve

237   outcomes as well as reduce the risk of generating additional resistance mutations and

238   halt further drug resistant TB transmission[33].

239   D-dimer was elevated at time of diagnosis for most participants but was not predictive of

240   outcome. During the course of therapy there was no significant difference between D-

241   dimer trends in survivors and deaths and overall, average D-dimer levels did not decline

242   significantly.

243   Other routinely collected laboratory values (hemoglobin, creatinine, albumin, and

244   alkaline phosphatase) measured at baseline were similar between the two groups,

245   though abnormal in almost all participants. While studying patients with XDR-TB in the

246   same setting, Shenoi et al. developed a laboratory clinical severity index (LCSI)[28]. In our

247   population this score was not significantly predictive of outcome, most likely because all

248   participants had baseline derangements in at least two of these four values, and 45%

249   had derangements in at least three, leaving little room for comparison.

250   Strengths of our study are that data was obtained by sequential recruitment of

251   participants with confirmed rifampin-resistant TB at a public treatment site, who were

252   treated with standardized regimens according to national guidelines. Treating

253   physicians were blinded to CRP, D-dimer and fibrinogen results. We note that this was

254   a small study and the results will need to be followed up within larger cohorts.

255   Furthermore, 40% of our study's participants were not taking ART at baseline, and

256   initiation of ART that occurred during MDR-TB treatment may have triggered immune

257   reconstitution, complicating interpretation of observed biomarker trends.

258   CONCLUSION

259   Our analysis of CRP and fibrinogen trends suggests that these biomarkers may predict

260   mortality in HIV positive adults on treatment for MDR-TB and should be further

261   evaluated in larger studies.

262

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270   Acknowledgements

274   Contributions

275   PGTC, TC and DW conceived of and designed the study. PGTC collected the data.

276   PGTC and JLW analyzed the data. PGTC, TC, JLW and DW wrote the manuscript.

277   Conflicts

278   The authors have none to declare

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363

364 Tables/Figures

365 Table 1: Participant baseline characteristics

	Category	Value	Normal range
n		20	
Sex (%)	Female	7 (35.0)	
	Male	13 (65.0)	
Race (%)	Indian	1 (5.0)	
	Black African	19 (95.0)	
Age (years) (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

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| D-dimer (µg/mL) (median [IQR]) | 0.85 [0.34, 1.80] | 0.1-0.5 |

366   *BMI = Body mass index

367   †ECOG = Eastern Co-operative Oncology Group performance status
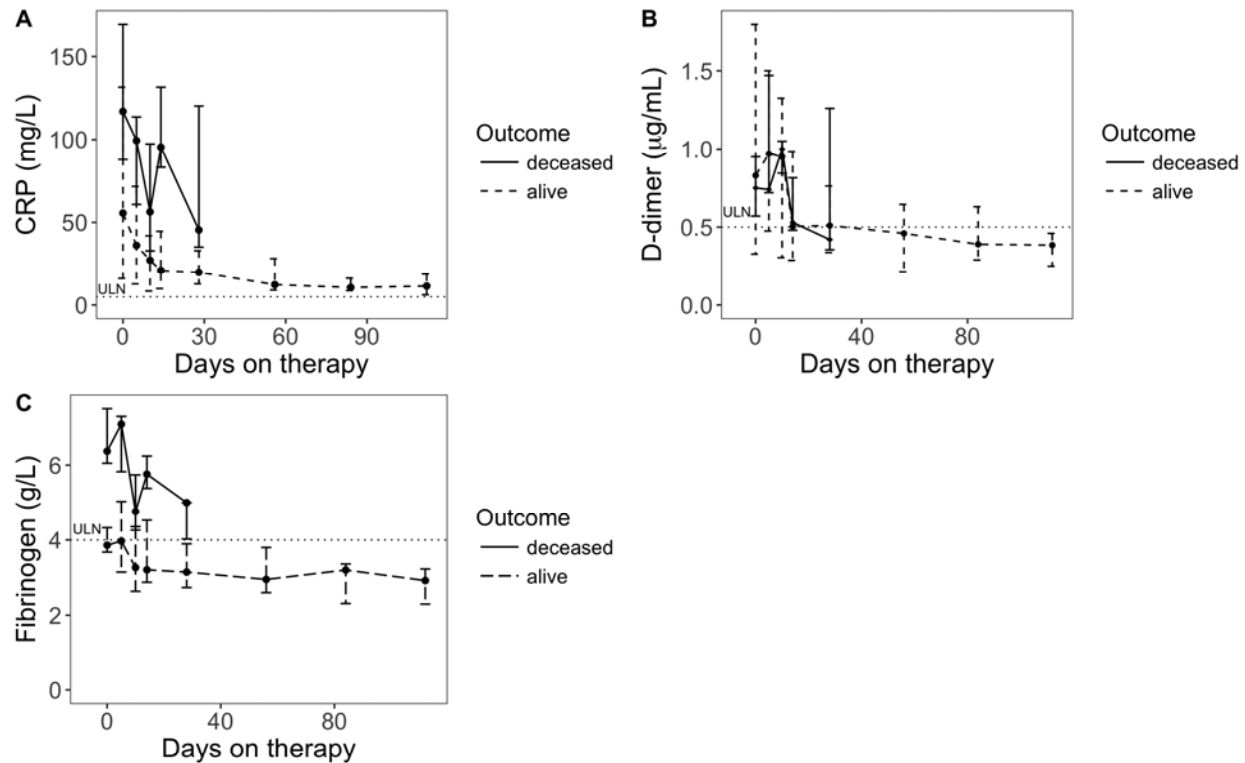
368   ‡ART = HIV antiretroviral therapy

369   §Laboratory clinical severity index[28]

370

371   Figure 1:
372

Figure 1: Outcome group trends while on MDR-TB therapy

Changes in serum a) 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 inter-quartile ranges.
ULN = Upper limit of normal

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375

376   Supplementary Figure 1:

377

Supplementary figure 1: Biomarker trends while on MDR-TB therapy
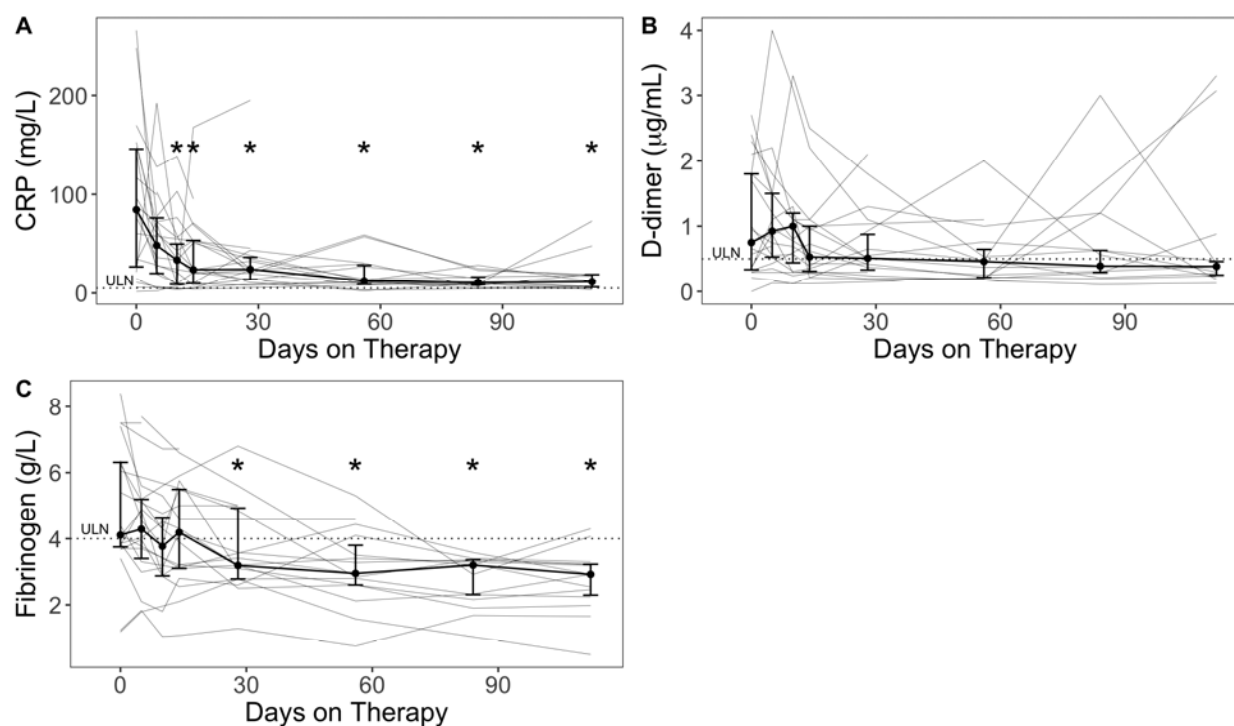
Changes in serum A) CRP, B) D-dimer and C) fibrinogen in HIV infected individuals on therapy for MDR-TB.
Light grey lines represent individual patient responses.
Black line is median response with error bars representing inter-quartile ranges.

* = Significant change from baseline (p < 0.05 by Kruskal-Wallis)
ULN = Upper limit of normal

378