Summer 8-7-2018

Hepatitis C and Risk of Adverse Treatment Outcomes among Patients with HIV and Multidrug-resistant Tuberculosis

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ABSTRACT

HEPATITIS C AND RISK OF ADVERSE TREATMENT OUTCOMES AMONG PATIENTS WITH HIV AND MULTIDRUG-RESISTANT TUBERCULOSIS

By

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July 19, 2018

BACKGROUND
Multidrug-resistant (MDR) tuberculosis (TB) is a public health emergency that causes substantial morbidity and mortality. Treatment of MDR-TB requires 9-24 months of second-line regimens, has poor success rates, and frequently results in harmful side effects. Hepatitis C virus (HCV) co-infection is a common comorbidity among patients with MDR-TB/HIV and contributes to acute and chronic liver conditions, potentially increasing the risk of hepatotoxicity and adverse treatment outcomes. The aim of this study was to estimate the association between HCV co-infection and adverse MDR-TB treatment outcomes among patients with MDR-TB and HIV.

METHODS
We conducted a retrospective cohort study among MDR-TB patients co-infected with HIV receiving clinical care from Médecins Sans Frontières (MSF) in Yangon, Myanmar during 2009-2017. Eligible patients included adults aged ≥18 years who had final MDR-TB treatment outcome and HCV status documented. HCV status was determined by OraQuick® antibody test. Treatment outcome was classified as favorable (cured and treatment completed) or adverse (default, failed, died, not evaluated).

RESULTS
Among patients with MDR-TB and HIV (n=220), the overall treatment success rate was 65% (95%CI 59 – 71%) and 8% (95%CI 5-12%) had HCV. Co-infection with HCV was not significantly associated with adverse treatment outcome in unadjusted (OR 1.33, 95%CI 0.49 – 3.65) or adjusted analyses (aOR 1.43, 95%CI 0.50 – 4.03).

CONCLUSION
Whether patients with HIV/HCV co-infection require altered MDR-TB treatment regimens remains an important gap in knowledge. Additional research is needed to determine the relationship between the extent of hepatotoxicity due to HCV co-infection, interaction with second-line TB medications, and risk of poor MDR-TB treatment outcomes among patients with and without HIV.

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M.B., B.S. University of Medicine 1 – Yangon

A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment
of the
Requirements for the Degree

MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA
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APPROVAL PAGE

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ACKNOWLEDGMENTS

I would like to express my sincere gratitude to my thesis committee and a special thank you to Dr. Matthew Magee for his guidance and support throughout the research. I also would like to acknowledge Dr. Anita Mesic and MSF team in Myanmar for granting the dataset for analysis. Moreover, I would like to thank U.S. Department of State for awarding me Fulbright scholarship to pursue a master degree in U.S. Finally, I am thanking to my family and my wife for their unconditional love and support throughout my study away from home.

Author's Statement Page

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CHAPTER I

INTROUDCTION

1.1 Background

The global ambition to end the tuberculosis (TB) epidemic is determined by the End-TB Strategy. This global target is set for 2035 when the End-TB goals state mortality rates should have a 95% reduction compared to 2015, and reduction of TB incidence rate <10 per 100,000 population. To achieve the global End-TB targets, priority indicators are to reach TB treatment coverage and success rate to ⩾ 95% and to reduce case fatality ratio (CFR) to < 5%. Although some progress has been made in achieving global targets, key challenges like multidrug-resistant tuberculosis (MDR-TB) and lack of funding prohibit full realization of these End-TB goals (World Health Organization, 2014).

In 2016 the global TB incidence was estimated at 10.4 million people and accounted for approximately 1.3 million deaths and an additional 0.4 million deaths among HIV-positive people. MDR-TB is a form of TB resistant to at least two of the most potent anti-TB drugs (rifampicin and isoniazid), and the 2016 MDR TB incidence was 490,000 (World Health Organization, 2017c). The global prevalence of hepatitis C virus (HCV) infection was 71 million people in 2015, and almost 400,000 die annually due to chronic HCV infection (World Health Organization, 2017b).

Myanmar is included in 30 high burden countries (HBC) with overlapping TB, MDR-TB and HIV/TB epidemics (World Health Organization, 2015). In Myanmar, the overall incidence of MDR-TB and RR-TB was 13,000 (8,800 – 18,000) in 2016. Among them, only 1,497 MDR/RR-TB cases were started on second-line treatment in 2014, and the success rate was estimated to have 80% (World Health Organization, 2017a). The rate of HCV was 2% among

healthy individuals, and 27% in patients with acute and chronic liver conditions in Myanmar in 2001 (Nakai, Win, Oo, Arakawa, & Abe, 2001).

Treatment of MDR-TB is available, but it requires substantially longer duration (9 – 24 months) with more expensive second-line toxic drugs (Marks et al., 2014) and the treatment is less effective than the treatment of drug-sensitive TB (Micheletti, Kritski, & Braga, 2016). Moreover, there are multiple side-effects of MDR-TB treatment for patients ranging from self-limiting reactions like arthralgia (aching or pain in the joints) and dermatological complications (Yang et al., 2017) to life-threatening toxicities such as nephrotoxicity, cardiotoxicity, and hepatotoxicity (Ramachandran & Swaminathan, 2015). HCV infection frequently results in chronic liver disease with causes persistent liver cell damage leading to cirrhosis and hepatocellular carcinoma. HCV co-infection is common among HIV patients (Platt et al., 2016), and TB patients. The triad of HCV, HIV, and TB promotes the additional risk of drug-induced liver injury during the TB treatment in HIV population (Kwon et al., 2007). Given the increased risk of MDR-TB treatment on hepatotoxicity, HCV co-infection may augment the risk of liver disease during the treatment, leading to a higher chance of adverse MDR-TB treatment outcomes.

MDR-TB treatment success rates are not as favorable as drug-sensitive TB. According to MDR-TB outcome analysis by Falzon et al. (Falzon et al., 2015), the treatment outcome among 23 high TB burden countries has a median success rate of 53% (IQR 40% - 70%). Many factors are associated with adverse treatment outcome particularly HIV co-infection (Farley et al., 2011) and chronic HCV co-infection (Kikvidze & Ikiashvili, 2014). Studies found that drug-induced hepatotoxicity in TB and MDR-TB treatment was associated with HCV co-infection (Lee et al., 2016; Lomtadze et al., 2013). There were also other studies on MDR-TB treatment outcome

which suggested that mortality rate during TB treatment was higher among individuals living with HIV (Isaakidis et al., 2015). However, the impact of HCV infection on MDR-TB treatment outcomes in the context of HIV co-infection is still needed to elaborate.

1.2 Gap and Purpose of Study

Current knowledge on MDR-TB outcomes among patients with HCV and HIV infection is limited. Improved knowledge regarding the role of HCV in adverse MDR-TB outcome in patients with HIV may inform future clinical HIV-TB guidelines including how to monitor side effects, and risk stratification. Mortality due to MDR-TB is high even with the proper treatment (Chung-Delgado, Guillen-Bravo, Revilla-Montag, & Bernabe-Ortiz, 2015; Gandhi et al., 2012). Even incremental improvements in MDR-TB treatment outcomes may substantially improve clinical care for high HIV/TB burden countries like Myanmar. Therefore, in the cohort of HIV patients with MDR-TB in Myanmar, the aims of our study are to

1) Determine socioeconomic, clinical and laboratory characteristics associated with HCV infection;
2) Determine the association between HCV comorbidity and adverse MDR-TB treatment outcomes.

CHAPTER II

REVIEW OF LITERATURE

2.1 Multidrug-Resistant Tuberculosis

Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis (TB) caused by the same mycobacteria organism but molecularly resistant to two of the most potent anti-TB agents, rifampicin and isoniazid. Since anti-TB drugs have been used for decades, drug resistance has been documented in every country where inappropriate practice of anti-TB treatment is present; such as incorrect prescription by healthcare providers, poor quality drugs, and patients' adherence to the treatment (World Health Organization, 2017c). The molecular mechanisms of drug-resistant TB depend on different developments such as the genetic basis of resistance, mutation rate, mutation type and hetero-resistant and preexisting mutants (Gillespie, 2002), which results in different categories of drug resistance including (1) monoresistance – resistant only to one first-line anti-TB drug, (2) polydrug resistance – resistant to more than one first-line anti-TB drug other than isoniazid and rifampicin, (3) multidrug resistance or MDR-TB – resistant to at least both isoniazid and rifampicin, (4) extensive drug resistance or XDR-TB – resistant to fluoroquinolone and at least one of injectable drugs in addition to multidrug resistance, (5) rifampicin resistance or RR-TB – resistant only to rifampicin with or without resistance to other anti-TB drugs (World Health Organization, 2013).

Treatment of MDR-TB is possible, but only 22% of global MDR-TB/RR-TB patients (130,000 of 600,000) received the treatment in 2016 (World Health Organization, 2017c). The MDR-TB treatment requires a long duration ranging 9 – 24 months (World Health Organization, 2016) of expensive antibiotic courses (Kang et al., 2006; Marks et al., 2014; Schnippel et al., 2013), but they are more toxic and less effective (Micheletti et al., 2016) than the drugs used to

treat drug-susceptible TB. In addition, side-effects of MDR-TB treatment affect different systems of the human body – ototoxicity, psychiatric disorder, gastrointestinal disturbance, arthralgia, hepatitis, epileptic seizures and dermatological complications (Torun et al., 2005; Yang et al., 2017). The minor side-effects such as skin reaction, arthralgia, and gastrointestinal upsets are common and easily manageable by symptomatic treatment. However, some severe toxicities such as nephrotoxicity, cardiotoxicity, gastrointestinal toxicity, central nervous system toxicity due to certain drugs are life-threatening (Ramachandran & Swaminathan, 2015). Side-effects were mostly experienced in 37% to 99% of patients receiving treatment (J. C. Brust et al., 2013; Yang et al., 2017) that can lead to sporadic treatment interruption, potentially increasing the risk of poor treatment outcome (Podewils, Gler, Quelapio, & Chen, 2013).

2.2 Outcome of Multidrug-Resistant Tuberculosis treatment

The World Health Organization has classified the treatment outcome for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment as cured, treatment completed, treatment failed, died, lost to follow-up or not evaluated – defining treatment success as the sum of cured and treatment completed (World Health Organization, 2013). The median success rate of MDR-TB treatment among 23 countries out of 30 high TB burden countries (World Health Organization, 2017a) was 53% (IQR 40 – 70%) (Falzon et al., 2015) a rate that is far below the target set for Global Plan to stop TB 2011 – 2015 in which the treatment success rate among confirmed MDR-TB cases should be $\geqslant$75%. The overview of adverse outcome among high burden countries was 11% (8 – 17) died, 8% (2 – 11) had treatment failure, 13% (8 – 18) were lost to follow up, and 4% (1 – 14) were not evaluated (Falzon et al., 2013).

There are different factors associated with MDR-TB treatment success such as being female, improvement on radiological findings (Jain, Desai, Solanki, & Dikshit, 2014), non-HIV patients, sputum smear-negative at baseline, without prior DR-TB (Bastos et al., 2017), use of individualized treatment regimen (Kibret, Moges, Memiah, & Biadgilign, 2017) and use of fluoroquinolone, aminoglycoside, and Group IV MDR-TB drugs (Anderson et al., 2013; Isaakidis et al., 2015). Importantly, adverse treatment outcome is associated with many host-related factors such as male sex, older age, prior TB treatment (Xu et al., 2018), having HIV co-infection, low baseline body weight (i.e., < 45 kg) (Farley et al., 2011), chronic viral hepatitis C co-infection (Kikvidze & Ikiashvili, 2014), lung cavitation at baseline chest X-ray (Ahmad et al., 2015), and resistance to ofloxacin and streptomycin (Basit et al., 2014). In addition, higher mortality among MDR-TB patient is associated with the used of anti-retroviral therapy (ART) before initiation of MDR-TB treatment (Umanah, Ncayiyana, Padanilam, & Nyasulu, 2015), and CD4 count ≤100 cells/mm3 (J. C. M. Brust et al., 2018). Therefore, it is important to address the determining factors to understand adverse and successful treatment outcomes.

2.3 Hepatitis C

The first antibody test to HCV became available in 1989 when it was discovered that non-A non-B hepatitis was predominantly caused by HCV (H. J. Alter et al., 1989). The World Health Organization has defined HCV as a bloodborne virus, commonly transmitted through sharing injection materials, reuse and inadequate sterilization of medical equipment, and transfusion of unscreened blood (World Health Organization, 2017d). Although the transmission of HCV was recognized primarily as blood contact, there are other route of transmission such as sexual transmission (Dienstag, 1997), transmission from mother to infant (Ohto et al., 1994), use

of folk remedies such as acupuncture and vacuuming (Kiyosawa et al., 1994), and tattoo and body piercing (Tohme & Holmberg, 2012). The estimated global prevalence of HCV infection was 2.2% (Global Burden Of Hepatitis, 2004), however due to the lack of data from many countries, WHO estimated 71 million people have chronic hepatitis C infection, accounting for 1.34 million deaths in 2015 (World Health Organization, 2017b).

Acute HCV infection is usually mild and the transition of acute to chronic hepatitis C is sub-clinical. Acute HCV infection can be resolved but most frequently progresses to chronic hepatitis (Grebely et al., 2014; Yeung, To, King, & Roberts, 2007). Chronic HCV infection is a slowly progressing disease with persistent liver inflammation leading to cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC). Globally, chronic HCV contributed to 27% of hepatic cirrhosis and 25% of HCC (Perz, Armstrong, Farrington, Hutin, & Bell, 2006). However, with the development of direct-acting antiviral (DAA), HCV treatment is more available and providing the promising results (Cotte et al., 2016; Sulkowski et al., 2014). Despite these advancement, the epidemiological studies on HCV and its interaction on different diseases especially patients with HIV and TB are still needed to explore.

2.4 Tuberculosis/ Multidrug-Resistant Tuberculosis and Hepatitis C in HIV population

Approximately 30% of HIV patients are co-infected with Hepatitis C virus (M. J. Alter, 2006; Platt et al., 2016) due to shared routes of transmission. With the improvement in HIV treatment and increase survival of HIV patient, it has emerged as that the liver complication by HCV infection is being a threat to survival of HIV patients. Studies found that HIV infection accelerate the liver disease progression in patients co-infected with HCV (Hernandez & Sherman, 2011). Tuberculosis is more prevalent in HIV population due to weaken immune

system of the host. The pool prevalence of TB/HIV co-infection was 23.51% (95% CI 20.91 – 26.11) with highest among African countries with 31.25% and lowest in United States with 14.84% (Gao, Zheng, & Fu, 2013). Medicines used to treat TB have hepatotoxic potential (Yew & Leung, 2006). Studies have frequently reported drug-induced hepatotoxicity during TB treatment among individuals with HCV co-infection (Kwon et al., 2007; Lomtadze et al., 2013).

2.5 Summary

The literature review of previous studies highlights –

- MDR-TB treatment requires the use of second-line drugs for long periods of time, and side effects of its treatment are common and serious.
- Adverse TB treatment outcomes are common among patients with MDR-TB.
- Knowledge about the impact of HCV infection on MDR TB treatment is lacking, especially among patients with HIV.

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CHAPTER III

MANUSCRIPT

Introduction

Tuberculosis (TB) is one of the top 10 causes of death worldwide. Multidrug-resistant tuberculosis (MDR-TB), a form of TB that is resistant to two of the most effective first-line anti-TB drugs – rifampicin and isoniazid, is a global public health crisis. In 2016, the worldwide prevalence of MDR-TB was 4% among new TB cases and 19% among retreatment cases [1]. Compared to drug susceptible TB, treatment of MDR-TB is substantially longer (i.e. 9 to 24 months) [2], requires more expensive and toxic drugs and has a high mortality rate [3, 4]. In addition, hepatitis co-infection is a common comorbidity in patients with TB [5], potentially increasing the risk of hepatoxicity and mortality during TB treatment [6-8]. For example, hepatitis C virus (HCV) causes acute and chronic liver conditions and is associated with adverse TB treatment outcomes [9-11]. Given the increased risk of MDR-TB treatment on hepatotoxicity [12], HCV co-infection may augment the risk of liver disease during TB treatment leading to even greater risk of adverse MDR-TB treatment outcome.

MDR-TB treatment success rates vary by region, but the median treatment success rate is only 53% (IQR 40 – 70%) in high TB burden countries [13-15]. Many patient factors contribute to adverse MDR-TB treatment outcomes, but HIV co-infection is of particular concern given its link to TB incidence [16] and high mortality during TB treatment [17, 18]. With a potential link between HCV and HIV among patients with drug-resistant TB [19], it is important to understand the impact of HCV on MDR-TB treatment outcomes in the context of patients with HIV.

Further epidemiologic data on the role of HCV on adverse MDR-TB outcomes are needed to improve treatment guidelines for patients receiving second line anti-TB medicines

with multiple risk factors for hepatotoxicity. Improved knowledge regarding the role of HCV on adverse MDR-TB treatment outcome in patients with HIV may inform future clinical HIV-TB guidelines including side effects monitoring and risk stratification for patients. Mortality due to MDR-TB is high even with the proper treatment [3, 4]. Therefore, even incremental improvements in MDR-TB treatment outcomes may substantially improve clinical care for high HIV/TB burden countries like Myanmar. In this context, we aimed to analyze the association between HCV infection and adverse MDR-TB outcome among patients with MDR-TB and HIV.

Methods

Study design

We performed a retrospective cohort study using previously collected data from the Médecins Sans Frontières (MSF – Doctors without Borders) HIV clinic in Myanmar during 2009-2017. Participants were registered at the time of TB diagnosis and followed during standard MDR-TB and HIV treatment.

Setting and participants

In Myanmar, MDR-TB treatment became available in 2009 with a National Tuberculosis Program (NTP) and MSF initiated a pilot treatment project in Yangon. Following the pilot, a Programmatic Management of Drug-resistant Tuberculosis (PMDT) program was extended in 2012 to accelerate the MDR-TB treatment program throughout Myanmar.

Eligible patients for the study included all adults aged ≥18 years receiving HIV treatment at MSF Myanmar who had MDR-TB diagnosed by Xpert MTB/RIF test and were confirmed by sputum culture and conventional drug sensitivity test (DST). Solid or liquid sputum culture (Lowenstein-Jensen media or Mycobacterium Growth Indicator Tube) were used to confirm

Xpert MTB/RIF results and drug resistance patterns. Patients without a final TB treatment outcome or unknown HCV status were excluded.

Measures and definitions

The primary outcome of the study was MDR-TB treatment outcome which was defined according to WHO categories of cured, treatment completed, treatment failed, died, lost to follow-up, and not evaluated [20]. We defined the primary outcome dichotomously as adverse (default, failed, died, not evaluated) or favorable (cured, completed).

The study's primary exposure was HCV status, classified as positive or negative based on OraQuick® hepatitis C antibody test, a point-of-care test used to detect HCV infection. After Hepatitis C treatment guideline had implemented in 2015, all HIV patients were routinely tested with OraQuick® at the clinic laboratory by laboratory technicians.

Other covariates of interest included demographic and socioeconomic characteristics which were assessed during the clinical consultation. Clinical symptoms of TB, and HIV were examined by physicians during clinic visits. Routine laboratory tests such as CD4 count, complete blood count, and other tests for MDR-TB side effects such as liver function tests were performed in MSF reference laboratories and recorded in the database accordingly.

Statistical methods

We used chi-square and Fisher's exact tests to examine the bivariate association between categorical variables and 1) HCV status and 2) adverse MDR-TB outcome. The association between both HCV and MDR-TB outcome with continuous variables such as age, BMI, CD4 count, and laboratory tests were assessed using Wilcoxon rank sum test. Multivariable logistic regression models were used to estimate the adjusted association between HCV and MDR-TB

treatment outcome. A two-sided p-value <0.05 was considered statistically significant in all analyses. SAS 9.4 (Cary, NC) was used to perform all analyses.

Ethical approval

Georgia State University and MSF Institutional Review Boards reviewed and approved the study's protocol.

Results

Participant characteristics

During the study period, a total of 454 patients registered in the MDR-TB treatment program and 387 patients (85%) initiated MDR-TB treatment with second-line drugs. Of these, 308 (68%) patients had MDR-TB final treatment outcome recorded and 220 with known HCV status were included in the analysis (Figure 4.1). Among the 220 patients in our analyses, 8% (N=17) were HCV positive, among them the median age was 35 years (IQR 30 – 40) and the majority (67%, N=148) were male.

Clinical and laboratory characteristics associated with HCV among MDR-TB patients with HIV (Table 3.1)

Out of 220 patients with HCV test results, the majority of patients had pulmonary TB – 93% (N=185) in HCV negative group and all 100% (N=17) in HCV positive group (P=0.61). Also, most of the cases were retreatment cases: 63% (N=125) among HCV negative and (71% (N=12) among HCV positive were previously treated for TB (P=0.52). Regarding HIV clinical stage to define the severity of HIV infection, 63% (N=121) were in stage 3 and 37% (N=72) were in stage 4 among HCV negative patients, while 59% (N=10) were stage 3 and 41% (N=7)

stage 4 in HCV positive group (P=0.75). Almost all patients received HIV treatment – 95% (N=193) of HCV negative and 94% (N=16) HCV positive were on treatment for HIV (P=0.60). Cotrimoxazole preventive therapy (CPT) prior to MDR-TB treatment initiation was more common among HCV negative patients (87%) compared to HCV positive patients (62%) (P=0.02). Regarding TB laboratory results, 58% (N=117) of HCV negative patients were sputum AFB smear-positive, and 76% (N=13) among HCV positive patients were smear-positive (P=0.13). CD4 counts were non-significantly higher in HCV positive patients (median 261 cells/µL; IQR 148 – 414) compared to HCV negative patients (median 144 cells/µL; IQR 63 – 274) (P=0.06). Alanine aminotransferase (ALT) levels were not significantly different comparing HCV positive patients (median 26.5 IU/L; IQR 22.1 – 31.3) and HCV negative patients (median 25.6 IU/L; IQR18.1 – 40.85) (P=0.97).

Factors associated with adverse MDR-TB treatment outcome (Table 3.2)

Among study participants 35% (N=77) had an adverse outcome while 65% (N=143) had a favorable treatment outcome. Among patients with pulmonary TB, 34% (68/202) had an adverse treatment outcome, and in patients with extrapulmonary, 46% (6/13) had an adverse outcome (P=0.38). Regarding previous TB treatment history, 43% (34/79) of new cases and 30% (42/137) of retreatment cases had adverse treatment outcomes (P=0.07). HIV clinical stage and anti-retroviral therapy provided a difference in MDR-TB treatment outcome. Nearly one-third (32%) of patients receiving HIV treatment had adverse outcomes, while the majority (91%) of those without HIV treatment had adverse MDR-TB treatment outcomes (P=<0.01). The proportion of patients with cotrimoxazole prophylaxis at enrollment who had adverse outcome was non-significantly greater 36% (63/177) compared to those without prophylaxis 29% (9/31)

(P=0.48). Regarding TB laboratory results, 32% (41/130) of patients who were sputum smear positive had adverse outcome compared to 40% (36/90) with smear negative or non-conclusive had an adverse outcome (P=0.20). The median CD4 count was different by treatment outcome: among those with adverse outcomes the median CD4 count was 138.5 cells/μL (IQR 64 – 256) compared to 173.5 cells/μL (IQR 83 – 365) among those with favorable treatment outcomes (P=0.41).

Association between HCV and adverse MDR-TB outcome (Table 3.3)

In an unadjusted model, the odds of adverse treatment outcome among patients with HCV infection was 1.33 (95% CI 0.49 – 3.65) times the odds of those without HCV (Table 3). In a model adjusted for age and gender, the odds ratio of adverse treatment outcome comparing those with HCV to those without was 1.31 (95% CI 0.47 – 3.61). Additional models adjusted for age, gender, and illicit drug use (aOR 1.28 95% CI 0.25 – 6.50) and for previous TB treatment history, age, and gender (aOR 1.43 95% CI 0.50 – 4.03) did not substantially change the estimated association between HCV and adverse MDR-TB treatment outcome.

Discussion

This study assessed the relationship between HCV and adverse MDR-TB treatment outcomes among patients with HIV co-infection in Myanmar. We observed a high proportion of adverse MDR-TB outcomes among patients with HIV—overall more than one-third of patients failed, died, or were lost to follow up during second-line TB treatment. We did not detect a significant difference in the proportion of patients with and without HCV who had adverse outcomes.

The treatment outcome for MDR-TB tuberculosis varies widely among high TB burden countries, with a median treatment success rate of 53% and IQR 40 – 70% [13] which is greatly lower than the goal of 75% posed by the WHO Global Plan to End TB [21]. In our study, the overall treatment success rate was 65%, with 55% cured and 10% completed. Unexpectedly, in our patient population, the proportion achieving treatment success among HCV negative patients was similar to those with HCV infection. However, the HCV positive group had a slightly lower success rate with a considerable proportion (29%) of patients with the outcome not evaluated.

Although not the objective of our study, we found that HIV treatment at the time of registration into the MDR-TB program predicted treatment success. Unlike our findings, previous studies of MDR-TB patients with HIV have reported higher mortality among those using ART at the time of TB treatment [22], likely due to immune reconstitution inflammatory syndrome (IRIS). The majority (62%) of patients with MDR-TB in our study were retreatment cases, therefore IRIS was more likely to have occurred during the initial TB disease treatment.

This study was subject to a number of limitations. First, the study population only included half of all registered MDR-TB patients because of incomplete testing for HCV antibodies and therefore the study sample size was underpowered to test our hypothesis. Moreover, standard testing for HCV began in 2015 after the MDR-TB program had been on-going. Consequently, a large proportion of patients in our study only had HCV test results performed after the initiation of MDR-TB treatment. However, because HCV and HIV may have similar modes of transmission [23, 24], it is likely a large proportion of patients were co-infected with HCV and HIV at the time of MDR-TB treatment. Third, the quality of data is another limitation of the study. Patients' history, clinical symptoms and medical examination were collected by physicians but there were no quality control mechanisms in place to ensure data

were complete. Fourth, most of the patient risk factors were self-reported, and therefore several behavioral predictors of poor MDR-TB outcome (i.e., smoking, alcohol use, and illicit drug use [25-28]) were likely under reported. Liver function tests such as serum bilirubin, alanine amino transferase (ALT), aspartate amino transferase (AST) are standard of care [29] in MSF Myanmar. However, missing data prohibited the classification of hepatotoxicity in our patients. Last, we were unable to differentiate between acute and chronic HCV infection as the point-of-care test used to measure HCV did not provide HCV RNA confirmation.

Despite limitations, this is the first study resulting from a pilot MDR-TB treatment project at MSF and serves to describe the initial treatment outcomes of MDR-TB patients co-infected with HIV and HCV in Myanmar. Importantly, as our study used data from the first MDR-TB treatment program from Myanmar at the time, patients from several regions were included. Therefore, we believe the results of the study are widely generalizable to patients with MDR-TB and HIV in the country of Myanmar.

Conclusion

There is a growing concern that poor MDR-TB treatment outcomes will greatly inhibit the EndTB strategy. Our initial findings from Myanmar point to a high rate of MDR-TB treatment failure in patients with HIV and suggest that additional work is needed to understand the relationship between HCV, hepatotoxicity, and poor TB outcomes among patients with MDR-TB and HIV.

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Table 3.1: Demographic, clinical, and laboratory characteristics of patients with MDR-TB by Hepatitis C infection status

Participant Characteristics	Hepatitis C Negative N= 203 (92%)	Hepatitis C Positive N= 17 (8%)	Total N= 220	P * Value
Demographic characteristics				
Age				
Median (IQR)	35 (30 – 40)	36 (32 – 41)	35 (30 – 40)	0.35 [a]
Gender				
Female	69 (34)	3 (18)	72 (33)	0.17
Male	134 (66)	14 (82)	148 (67)	
Marital status				
Not Disclosed	17 (8)	1 (6)	18 (8)	0.23 [b]
Married	102 (50)	7 (41)	109 (50)	
Single	46 (23)	5 (29)	51 (23)	
Divorced	10 (5)	2 (12)	12 (5)	
Widowed	20 (10)	0	20 (9)	
Separated	8 (4)	2 (12)	10 (5)	
Employment				
Not Disclosed	44 (22)	1 (6)	45 (20)	0.15 [b]
Employed	50 (25)	4 (24)	54 (24)	
Pensioner	0	0	0	
Student	0	0	0	
Unemployed	86 (42)	8 (47)	94 (43)	
Housework	8 (4)	0	8 (4)	
Others	15 (7)	4 (24)	19 (9)	
Risk Factors				
Prison				
Not been in Prison	195 (96)	16 (94)	211 (96)	0.70
Ever been in Prison	8 (4)	1 (6)	9 (4)	
Alcohol use				
No	190 (96)	16 (94)	206 (94)	0.53 [b]
Yes	8 (4)	1 (6)	9 (4)	
Missing	5	0	5 (2)	
Illicit Drug use				
No	81 (40)	7 (41)	88 (40)	**< 0.01** [b c]
Yes	0	2 (12)	2 (1)	
Missing	122 (60)	8 (47)	130 (59)	
Tobacco use				
No	190 (94)	15 (88)	205 (93)	0.33 [b]
Yes	13 (6)	2 (12)	15 (7)	

Participant Characteristics	Hepatitis C Negative N= 203 (92%)	Hepatitis C Positive N= 17 (8%)	Total N= 220	P * Value
Homeless				
No	201 (99)	17	218 (99)	1.00 [b]
Yes	2 (1)	0	2 (1)	
Migrant				
No	202 (99)	17	219 (99)	1.00 [b]
Yes	1 (1)	0	1 (1)	
Prostitution				
No	200 (99)	17	217 (99)	1.00 [b]
Yes	3 (1)	0	3 (1)	
Clinical characteristics				
Site of TB				
Pulmonary	185 (93)	17	202 (92)	0.61 [b]
Extra-pulmonary	13 (7)	0	13 (6)	
Missing	5		5 (2)	
TB treatment history				
New Case	74 (37)	5 (29)	79 (36)	0.75 [b]
Failure	47 (23)	6 (35)	53 (24)	
Relapse	71 (35)	6 (35)	77 (35)	
Treatment	5 (2)	0	5 (2)	
interrupted	2 (1)	0	2 (1)	
Unknown	4 (2)		4 (2)	
Previous TB history				
New Case	74 (36)	5 (29)	79 (36)	0.52
Retreatment Case	125 (62)	12 (71)	137 (62)	
Missing	4 (2)	0	4 (2)	
HIV clinical stage				
Stage 3	121 (63)	10 (59)	131 (60)	0.75
Stage 4	72 (37)	7 (41)	79 (39)	
Missing	10	0	10 (5)	
HIV treatment				
No	10 (5)	1 (6)	11 (5)	0.60 [b]
Yes	193 (95)	16 (94)	209 (95)	
Cotrimoxazole prophylaxis at enrollment				
No	25 (12)	6 (38)	31 (14)	**0.02** [b]
Yes	167 (82)	10 (62)	177 (80)	
Missing	11 (6)	1	12 (6)	

Participant Characteristics	Hepatitis C Negative N= 203 (92%)	Hepatitis C Positive N= 17 (8%)	Total N= 220	P * Value
BMI				
Median (IQR) (N = 186)	17.1 (15.5 – 18.6)	16.65 (14.05 – 18)	17.05 (15.4 – 18.6)	0.24 [a]
Clinical Symptoms				
Fever				
No	113 (56)	12 (71)	125 (57)	0.23
Yes	90 (44)	5 (29)	95 (43)	
Sweat				
No	162 (80)	16 (94)	178 (81)	0.21 [b]
Yes	41 (20)	1 (6)	42 (19)	
Dry cough				
No	180 (89)	15 (88)	195 (87)	1.00 [b]
Yes	23 (11)	2 (12)	25 (13)	
Productive cough				
No	121 (60)	9 (53)	130 (59)	0.59
Yes	82 (40)	8 (47)	90 (41)	
Blood spitting				
No	197 (97)	17	214 (97)	1.00 [b]
Yes	6 (3)	0	6 (3)	
Chest Pain				
No	172 (85)	16 (94)	188 (85)	0.48 [b]
Yes	31 (15)	1 (6)	32 (15)	
Loss of Appetite				
No	126 (62)	11 (65)	137 (62)	0.83
Yes	77 (38)	6 (35)	83 (38)	
Weight Loss				
No	126 (62)	11 (65)	137 (62)	0.83
Yes	77 (38)	6 (35)	83 (38)	
Dyspnea				
No	149 (73)	14 (82)	163 (74)	0.57 [b]
Yes	54 (27)	3 (18)	57 (26)	

Participant Characteristics	Hepatitis C Negative N= 203 (92%)	Hepatitis C Positive N= 17 (8%)	Total N= 220	P * Value
Laboratory characteristics				
Sputum smear result				
Not conclusive	6 (3)	0	6 (3)	0.41
Negative	68 (36)	4 (24)	72 (33)	
Positive	117 (61)	13 (76)	130 (59)	
Missing	12	0	12 (5)	
Sputum smear result				
Negative & non-conclusive	86 (42)	4 (24)	90 (41)	0.13
Positive	117 (58)	13 (76)	130 (59)	
CD4 count (cells/μL)				
Median (IQR) (N = 120)	144 (63 – 274)	261 (148 – 414)	161 (73 – 296)	0.06 [a]
ALT (IU/L)				
Median (IQR) (N = 93)	25.6 (18.1 – 40.85)	26.5 (22.1 – 31.3)	26 (18.2 – 40.4)	0.97 [a]
Primary outcome variable				
MDR-TB Treatment outcome ^				
Completed	20 (10)	1 (6)	21 (10)	**0.03** [b]
Cured	113 (55)	9 (53)	122 (55)	
Defaulter	22 (11)	0	22 (10)	
Died	30 (15)	1 (6)	31 (14)	
Failure	2 (1)	1 (6)	3 (1)	
Not evaluated	16 (8)	5 (29)	21 (10)	
MDRTB Treatment outcome				
Favorable	133 (66)	10 (59)	143 (65)	0.58
Adverse	70 (34)	7 (41)	77 (35)	

Abbreviation: IQR – interquartile range, BMI – Body Mass Index, ALT – alanine aminotransferase, MDRTB – Multidrug-resistant Tuberculosis

* chi-square test with 2-sided probability

a Wilcoxon Scores (Rank Sums)

b Fisher's Exact Test

c included the missing values

^ WHO definition framework for TB treatment outcome

Table 3.2: Factors associated with MDR-TB treatment outcome and HCV infection, univariate analysis

Participant Characteristics	Adverse Treatment outcome N= 77 (35%)	Favorable Treatment Outcome N= 143 (65%)	Total N= 220	P value *
Primary exposure variable				
Hepatitis C Negative	70 (34)	133 (66)	203 (92)	0.58
Hepatitis C Positive	7 (41)	10 (59)	17 (8)	
Demographic Characteristics				
Age, years				
Median (IQR)	35 (31 – 41)	35 (30 – 40)	35 (30 – 40)	0.96 [a]
Gender				
Female	24 (33)	48 (67)	72 (33)	0.72
Male	53 (36)	95 (64)	148 (67)	
Marital status				
Not Disclosed	9 (50)	9 (50)	18 (8)	0.16
Married	33 (30)	76 (70)	109 (50)	
Single	21 (41)	30 (59)	51 (23)	
Divorced	3 (25)	9 (75)	12 (5)	
Widowed	5 (25)	15 (75)	20 (9)	
Separated	6 (60)	4 (40)	10 (5)	
Employment				
Not Disclosed	18 (40)	27 (60)	45 (20)	0.36
Employed	22 (41)	32 (59)	54 (25)	
Pensioner			0	
Student			0	
Unemployed	26 (28)	68 (72)	94 (43)	
Housework	4 (50)	4 (50)	8 (4)	
Others	7 (37)	12 (63)	19 (9)	
Risk Factors				
Prison risk factor				
Not been in Prison	75 (36)	136 (64)	211 (96)	0.50 [b]
Ever been in Prison	2 (22)	7 (78)	9 (4)	
Alcohol use				
No	73 (35)	133 (65)	206 (94)	1.00 [b]
Yes	3 (33)	6 (67)	9 (4)	
Missing	1	4	5 (2)	
Illicit Drug use				
No	31 (35)	57 (65)	88 (40)	1.00 [b]
Yes	1 (50)	1 (50)	2 (1)	
Missing	45 (35)	85 (65)	130 (59)	

Participant Characteristics	Adverse Treatment outcome N= 77 (35%)	Favorable Treatment Outcome N= 143 (65%)	Total N= 220	P value *
Tobacco use				
No	72 (35)	133 (65)	205 (93)	0.89
Yes	5 (33)	10 (67)	15 (7)	
Homeless				
No	77 (35)	141 (65)	218 (99)	0.54 [b]
Yes	0	2 (100)	2 (1)	
Migrant				
No	76 (35)	143 (65)	219 (99)	0.35 [b]
Yes	1 (100)	0	1 (1)	
Prostitution				
No	75 (35)	142 (65)	217 (99)	0.28 [b]
Yes	2 (67)	1 (33)	3 (1)	
Clinical Characteristics				
Site of TB				
Extra-Pulmonary	6 (46)	7 (54)	13 (6)	0.38 [b]
Pulmonary	68 (34)	134 (66)	202 (92)	
Missing	3	2	5 (2)	
Previous TB treatment	34 (43)	45 (57)	79 (36)	0.34 [b]
New Case	15 (28)	38 (72)	53 (24)	
Failure	24 (31)	53 (69)	77 (35)	
Relapse	2 (40)	3 (60)	5 (2)	
Treatment interrupted	1 (50)	1 (50)	2 (1)	
Unknown	1	3	4 (2)	
Previous TB treatment	34 (43)	45 (57)	79 (36)	0.07
New Case	42 (30)	95 (70)	137 (62)	
Retreatment Case	1	3	4 (2)	
HIV clinical stage				
Stage 3	47 (36)	84 (64)	131 (60)	0.41
Stage 4	24 (30)	55 (70)	79 (36)	
Missing	6	4	10 (4)	
HIV treatment				
No	10 (91)	1 (9)	11 (5)	**< 0.01** [b]
Yes	67 (32)	142 (68)	209 (95)	

Participant Characteristics	Adverse Treatment outcome N= 77 (35%)	Favorable Treatment Outcome N= 143 (65%)	Total N= 220	P value *
Cotrimoxazole prophylaxis at enrollment				
No	9 (29)	22 (71)	31 (14)	0.48
Yes	63 (36)	114 (64)	177 (80)	
Missing	5	7	12 (6)	
BMI				
Median (IQR) (N = 186)	17.1 (15.6 – 18.8)	17 (15.4 – 18.5)	17.05 (15.4 – 18.6)	0.77 [a]
Clinical Symptoms				
Fever				
No	40 (32)	85 (68)	125 (57)	0.28
Yes	37 (39)	58 (61)	95 (43)	
Sweat				
No	58 (33)	120 (67)	178 (81)	0.12
Yes	19 (45)	23 (55)	42 (19)	
Dry cough				
No	68 (35)	127 (65)	195 (87)	0.91
Yes	9 (36)	16 (64)	25 (13)	
Productive cough				
No	50 (38)	80 (62)	130 (59)	0.20
Yes	27 (30)	63 (70)	90 (41)	
Blood spitting				
No	73 (34)	141 (64)	214 (97)	0.19 [b]
Yes	4 (67)	2 (33)	6 (3)	
Chest Pain				
No	66 (35)	122 (65)	188 (85)	0.94
Yes	11 (34)	21 (66)	32 (15)	
Loss of Appetite				
No	51 (37)	86 (63)	137 (62)	0.37
Yes	26 (31)	57 (69)	83 (38)	
Weight Loss				
No	50 (37)	87 (63)	137 (62)	0.55
Yes	27 (33)	56 (67)	83 (83)	

Participant Characteristics	Adverse Treatment outcome N= 77 (35%)	Favorable Treatment Outcome N= 143 (65%)	Total N= 220	P value *
Dyspnea				
No	62 (38)	101 (62)	163 (74)	0.11
Yes	15 (26)	42 (74)	57 (26)	
Laboratory Characteristics				
Smear result				
Not conclusive	1 (17)	5 (83)	6 (3)	0.42 [b]
Negative	28 (39)	44 (61)	72 (33)	
Positive	41 (32)	89 (68)	130 (59)	
Missing	7	5	12 (5)	
Smear result				
Negative & non-conclusive	36 (40)	54 (60)	90 (41)	0.20
Positive	41 (32)	89 (68)	130 (59)	
CD4 count (cells/µL)				
Median (IQR) (N = 120)	138.5 (64 – 256)	173.5 (83 – 365)	161 (73 – 296)	0.41 [a]
ALT (IU/L)				
Median (IQR) (N = 93)	21.3 (18.2 – 30.8)	28 (18.5 – 42.55)	26 (18.2 – 40.4)	0.20 [a]

Abbreviation: IQR – interquartile range, BMI – Body Mass Index, ALT – alanine aminotransferase, MDRTB – Multidrug-resistant Tuberculosis
* chi-square test with 2-sided probability
a Wilcoxon Scores (Rank Sums)
b Fisher's Exact Test

Table 3.3: Association between HCV and adverse MDR-TB treatment outcomes, multivariate analysis (N=220)

Participant Characteristics	**Adverse Treatment Crude OR (95%CI)**	**Model 1 Adjusted OR (95%CI)**	**Model 2 Adjusted OR (95%CI)**	**Model 3 Adjusted OR (95%CI)**
Hepatitis C				
Negative	1	1	1	1
Positive	1.33 (0.49 – 3.65)	1.31 (0.47 – 3.61)	1.43 (0.50 – 4.03)	1.28 (0.25 – 6.50)

Model 1 adjusted for age and gender
Model 2 adjusted for age, gender, smear result, and history of previous TB treatment
Model 3 adjusted for age, gender, and illicit drug use

Figure 4.1 Participant selection of the study