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Research Article

Treatment Outcomes of Drug Resistant TB and Hepatitis B and C Virus Co-Infection in a Nigerian DR-TB Treatment Center

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Abstract

Background: Literature surrounding the burden of and factors associated with hepatitis B virus (HBV) and hepatitis C virus (HCV) infection in persons with drug resistant tuberculosis (DR-TB) disease remains limited especially in the developing countries that have high DR-TB and viral hepatitis burden. DR-TB and viral hepatitis infections are quite common in the developing world especially Nigeria. As both are so common, co-infection is commonly encountered in clinical practice. However, since anti-tuberculosis therapy (ATT) can be hepatotoxic in around 10% of patients, the occurrence of hepatotoxicity can complicate management especially in the presence of already compromised liver function due to HBV/HCV co-infection. Therefore, co-infection of DR-TB and HBV/HCV is an important public health issue. There has not been any concerted effort of note to bring to public notice this dreadful occurrence and hence a coordinated management approach in the national treatment guidelines for DR-TB or viral hepatitis is still lacking. This article reviews the epidemiology and management of co-infection with DR-TB, Viral Hepatitidis and hepatotoxicity due to second line anti-tuberculous drugs (SLD) with its effect on treatment.

Method: DR-TB and viral hepatitis data from DR-TB register at Abubakar Tafawa Balewa University Teaching Hospital DR-TB treatment center was used as the primary data source, the proportion of adults diagnosed with DR-TB and viral hepatitis B, Hepatitis C or both from 2014 to 2017 was obtained, the data was analyzed and proportion of DRTB, HBV, HCV burden were expressed as percentage and treatment outcome were compared outcome during and on upon completion of intensive phase of treatment for liver toxicity using derangement in liver function (LFT) from baseline. The impact of viral hepatitis and second line ATT drugs induced hepatitis on DRTB treatment and associated mortality was described.

Results: There were 137 patient that were diagnosed to have MDR-TB using the molecular assay by Xpert MTB/RIF machine and all patient were screened for HBV and HCV on enrolment for treatment based on the National tuberculosis control program of Nigeria. Most patients with DR-TB and viral Hepatitis were between the age group of 18 - 25 years. About 4.3% of the patient were positive for HBV and 2.2% for HCV infection, < 1% of the DR-TB patients had both HCV and HBV respectively infection, The proportion of HIV/DR-TB co infection was found to be 12.45 ($p > 0.005$) and less than 1% had DR-TB, HIV and HBV co-infection with about 100% mortality among this group. There was no statistically significant difference in treatment outcome among patient with DR-TB and those with any form of Hepatitis except those with additional HIV co-morbidity, 35% are at different phases of treatment and 38% have completed treatment awaiting outcome and about 30% have been declared cured, 3% mortality and 2% were lost to follow up (LTFU). Mortality was higher among Hypokalaemia related events than patient with viral Hepatitidis.

Conclusion: In this study, we found that patients with DR-TB/HBV/HCV co-infection were more susceptible to developing drug induced liver injury and having poor outcomes during DR-TB treatment compared to non-co-infected patients. HIV co-infection was associated with increase mortality, however, we found no significant mortality among HBV/ or HCV co-infected DR-TB patient, these findings highlights the importance of hepatitis testing and providing additional support to DR-TB patients with viral hepatitis infection.

Keywords: *Hepatitis B Virus (HBV); Hepatitis C Virus (HCV); Drug Resistant Tuberculosis (DR-TB); Anti-Tuberculosis Therapy (ATT)*

Abbreviations

ADR: Adverse Drug Reaction; ATBUTH: Abubakar Tafawa Balewa University Teaching Hospital; ATT: Anti Tuberculous Treatment; DST: Drug sensitivity Testing; FQ: Fluroquinolones; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; LPA: Line Probe Assay; MDR-TB: Multidrug Resistant Tuberculosis; RR: Rifampicin Resistant; DR-TB: Drug Resistant Tuberculosis; NTBLCP: National Tb Leprosy Control Program; WHO: World Health Organization; XDR-TB: Extensively Drug Resistant Tb; Mfx: Moxifloxacin; Bdq: Bedaquiline; Lzd: Linezolid; Cfz: Clofazimine; PAS: Para Amino Salicylic Acid; H^h: High Dose Isoniazid; Z: Pyrazinamide; LFT: Liver Function Test; AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; ULN: Upper Limit of Normal; XPERT/MTB/RIF: Expert Mycobacterium/Rifampicin Assay

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, the two most powerful, first-line anti-TB drugs. MDR-TB is treatable and curable by using second-line drugs however, second-line treatment options are limited and require extensive chemotherapy (9 to 24 months of treatment) with medicines that are expensive and toxic. In some cases, more severe drug resistance can develop extensively drug-resistant TB (XDR-TB), it is a more serious form of MDR-TB caused by bacteria that do not respond to the most effective second-line anti-TB drugs, often leaving patients without any further treatment options [1].

The emergence of DRTB, and particularly multi drug resistance Tuberculosis (MDR-TB) has become a significant public health problem in a number of countries and an obstacle to effective global TB control [1]. With the increasing accessibility to Xpert MTB/Rif assay there has been steady increase in cases of Drug Resistant Tb (DR-TB) across the states in Nigeria [1,2].

In 2015, there were an estimated 480 000 new cases of multidrug-resistant TB (MDR-TB) and an additional, 100 000 people with Rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR-TB treatment [1]. Worldwide majority of these cases are in Eastern Asia, India, China and the Russian Federation accounted for 45% of the combined total of 580 000 cases [1]. There has been 250, 000 thousand reported death as a result of DR-TB with 4.3% (3.2 - 5.4) among new cases and 25% (19 - 31) among previously treated cases with multidrug resistant tuberculosis and rifampicin resistant (MDR/RR). One case of Extremely Drug resistant (XDR-TB) was confirmed and started on treatment, about 50,274 patient were notified and tested for Rifampicin resistance 40% among new cases 64% among previously treated cases with a median prevalence of 7%, thus reflecting the failure of the programmed designed to ensure complete cure of patient with Tb [1]. Drug resistance in *M. tuberculosis* isolates arises from spontaneous genetic mutations and can be enhanced by poor adherence of patients to anti-TB drugs [3]. Multidrug resistant TB (MDR-TB) portrays a great challenge to treatment interventions while XDR-TB is much more difficult to treat with associated adverse drug reaction (ADR) [4].

Nigeria moved from 4^{th} position in 2007 to 10^{th} in 2012 among the 22 high Tb burden countries in the world and from 1^{st} to 4^{th} highest TB burden in Africa [1]. About 4,700 MDR-TB cases were estimated which constitute 3 - 5% of all cases of Tb with estimated 4.3% among new cases and about 23% among retreatment Tb cases [4].

In Nigeria the National Tuberculous Leprosy Control Program (NTBLCP) endorsed the WHO 2013 policy update that recommends Xpert MTB/RIF as initial diagnostic test in all adults and children with signs and symptoms of TB [5].

NTBLCP also recently endorsed the WHO 2016 policy that recommends the use of GenoType MTBDR*s l* Version 2 Line Probe Assay (SL LPA) for patients with confirmed RR-TB regardless of the sputum smear result as initial test to detect resistance to fluoroquinolones (FQs) and second-line injectable drugs (SLIDs) [5].

There are eight TB reference laboratories with the capacity to perform baseline culture/DST and the first line LPA in Nigeria, currently four laboratories have additional testing capacity for the second line culture/DST and second line LPA [5].

Recommended treatment for DR-TB is a shorter and individualized regimen, this is the WHO recommended regimen for DR-TB patients based on eligibility criteria [6]. For shorter regimen the total duration is 9 - 12 months: Intensive phase of 4 - 6 months and continuation phase of 5 months - Intensive phase of 4 - 6 Km-Mfx-Cfz-Pto-Z-E-H^h, continuation phase of 5 Mfx-Cfz-E-Z with vitamin B6 For individualized regimen which is for patients with DR-TB who are not eligible for treatment with the shorter regimen. The total duration is 20 months or longer for regimen designed based on the most recent DST results of the patient and history of previous drug use and/or exposure. Standard duration of the intensive phase will be at least 6 months and duration of the continuation phase will be at least 14 months. Pre-XDR TB (resistant to second line injectable Intensive phase 6 Mfx-Bdq-Lzd-Cfz-PAS-H^h-Z, continuation phase 14 Bdq(6)-Lzd-Cfz-PAS-Z [6]. Pre-XDR TB (resistant to fluoroquinolones intensive 6 Cm/Km-Bdq-Lzd-Cfz-PAS-H^h-Z, continuation phase 14 Bdq(6)-Lzd-Cfz-PAS-Z.

XDR-TB intensive phase 6 Cm/Dlm-Bdq-Lzd-Cfz-PAS-H^h-Z, continuation phase 14 Bdq(6)-Lzd-Cfz-PAS-Z [6].

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XDR-TB intensive phase 6 Cm/Dlm-Bdq-Lzd-Cfz-PAS-H^h-Z, continuation phase 14 Bdq(6)-Lzd-Cfz-PAS-Z [6].

Hepatotoxicity is the major side effect of this highly effective ATT and can occur as a comorbidity with viral hepatitidis [7]. ATT-hepatotoxicity results in significant morbidity and even mortality, due to acute liver failure. Also these events lead to a substantial financial burden because of additional outpatient visits, tests, and additional hospitalization in case of severe reactions. Hepatotoxicity leads to interruption, modification or non-adherence; eventually this results in treatment failure, relapse, and drug-resistance. Modification of therapy results in the use of less effective, second-line drugs, leading to a suboptimal response to the therapy and prolongation of the therapy, with attendant challenges to compliance. Definition of hepatotoxicity varies from alanine aminotransferase (ALT) > thrice the upper normal limit (X ULN) with symptoms, > 5x ULN with/without symptoms, to > 10 X ULN in various series [7].

There are no data on the management of DR-TB and hepatitis B and C related liver disease.

Hepatitis B virus (HBV) and HCV co-infection is commonly found in HBV-endemic countries in Asia, sub-Saharan Africa and South America. Up to 25% of HCV infected persons may be co-infected with HBV in some areas [8].

Groups at increased risk of infection with HBV and HCV are also at risk of infection with TB/ DR-TB. This is common in many countries where blood and blood products are not properly screened routinely [8]. This study looked into the burden associated with TB/DRTB comorbidity with viral hepatitidis and its possible outcome.

Objective of the Study

The objective of this study include:

- To determine the presence of viral hepatitis among DRTB patients on SLD.
- To determine the drug induced hepatotoxicity associated with SLD.
- To determine the burden and mortality associated with viral hepatitis with SLD induced hepatotoxicity.
- To determine the outcome of treatment among DRTB and viral hepatitidis co infection.

Methodology

Data was extracted from all patients diagnosed with MDR-TB hospitalized at DR-TB treatment center of Abubakar Tafawa Balewa University Teaching Hospital (ATBUTH) Bauchi, Nigeria from January 2014 to December 2017. All the patients were registered for intensive phase of MDR-TB treatment on in-patient bases. All patients included in the analysis were diagnosed using the Gene Xpert Cepheid 4 module machine. Any MDR-TB patients registered for intensive phase of treatment who lack base line viral screening for HBV, HCV, liver function test or lost to follow up; transferred out during the intensive phase of the treatment were excluded from the analysis.

DR-TB and viral hepatitis data from DR-TB register at Abubakar Tafawa Balewa University Teaching Hospital DR-TB treatment center was used as the primary data source document. The proportion of adults diagnosed with DR-TB and viral hepatitis B, Hepatitis C or both from 2014 to 2017 was obtained, the proportion of such burden was expressed as percentages and the outcome during and on completion of treatment was analyzed. Comparison of derangement in liver function (LFT) from baseline and the impact of viral hepatitis; second line ATT drugs induced hepatitis; and effect on DR-TB treatment on completion of treatment and associated mortality was made.

A proforma was used to extract data from a 'Standardized' MDR-TB treatment registers; and patient level data and laboratory records were also extracted for analysis.

Data analysis

Results were presented as frequencies of viral hepatitidis among DR-TB patients, baseline and follow up laboratory values for LFT were presented as tables. Significance level was set a p value of less than 0.05 and CI of 95%. Fisher's exact test was used to compare proportions. Adjustment was made for confounders using negative binary regression

Ethical approval

This was obtained from the ethical committee of the ATBU Teaching Hospital treatment center where this study was conducted.

Data management

Data collected from MDR-TB register was coded and entered into SPSS software for analysis. Access to the data stored in the computer was limited through a secured password.

Results

There were 137 patients that were diagnosed to have MDR-TB using the molecular assay by Xpert MTB/RIF machine. There were 67% male cases compared to 33% female cases diagnosed with MDR-TB (Table 1). All patients were screened for HBV and HCV on enrolment for treatment based on the National Tuberculosis Control Program of Nigeria. Most patients with DR-TB were between the age group of 26 - 35 years (Table 1). About 4.3% of the patients were positive for HBV and 2.2% for HCV infection respectively. Less than 1% of the DR-TB patients had both HCV and HBV infection (Figure 1). The proportion of HIV/DR-TB co infection was found to be 12.45 ($p > 0.005$), less than 1% had DR-TB, HIV and HBV co-infection with about 100% mortality among this group.

Patient with HBV, HCV co-infection showed a decline in the AST and ALT from the baseline, however there was no increase in > 5 folds above upper limit of normal throughout the treatment period (Table 2).

Age grp	Male	Female	Total
15 - 25	18	10	28
26 - 35	33	15	48
36 - 45	19	7	26
46 - 55	12	8	20
> 55	10	5	15

Table 1: *Age distribution of DR-TB Patients.*

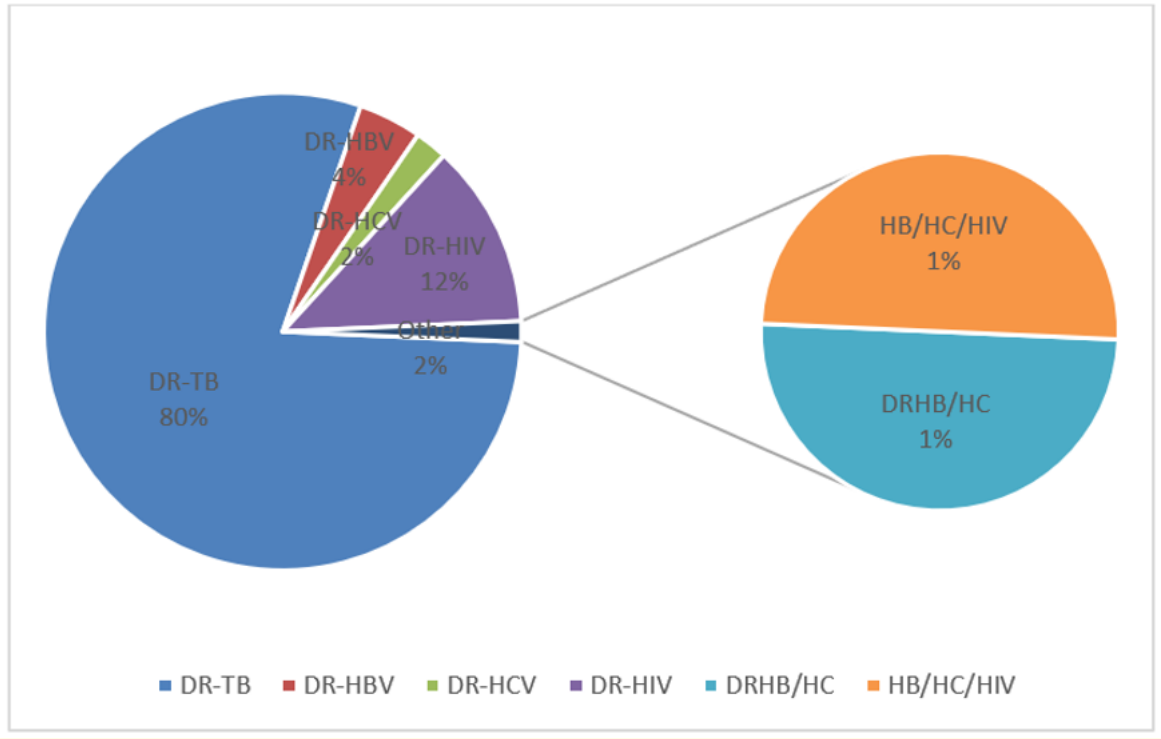

Figure 1: *Percentage viral co-infection among DR-TB Patient.*

	pro	Alb g/I	AST u/I	ALT u/I	DBIL u/I	TBIL
BL	62	35	12	13	3.0	12
M1	64	40	42	47	4.0	13
M2	60	30	58	60	4.1	16
M3	72	45	22	38	3.8	11
M4	73	46	18	20	3.6	10

Table 2: *Average LFT parameters among DRTB, HBV, HCV co-infected patients.*

There was no statistically significant difference in treatment outcome among patient with DR-TB and those with any form of Hepatitis except those with additional HIV co-morbidity. Thirty five percent (35%) are at different phases of treatment and 38% have completed treatment awaiting outcome and about 30% have been declared cured, where as 2% of the study patients were lost to follow up (LTFU), 2% were transferred out and 3% died during the course of treatment, However there were no cases of treatment failure recorded (Figure 2).

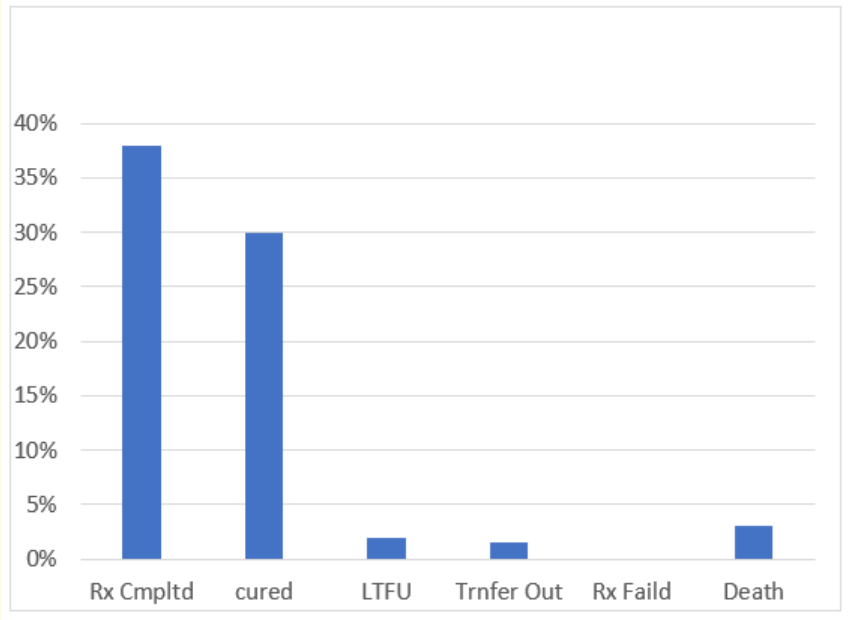

Figure 2: *Treatment outcomes.*

Discussion

Hepatotoxicity is the major adverse effect of three of the first-line anti-TB agents: isoniazid (INH), rifampin (RIF), and pyrazinamide (PZA). Underlying liver disease may increase the risk of developing drug-induced hepatotoxicity and there is concern that HCV and/or HIV co-infection may increase the risk of anti-TB drug-induced hepatotoxicity [9]. Few studies have examined the impact of HBV and HCV infection on incident hepatotoxicity during SLD treatment for DR-TB treatment [9,10]. There remains very limited data on the impact of chronic viral hepatitis on the risk of incident anti-TB drug induced hepatotoxicity, there is a growing concern that underlying chronic liver disease caused by viral hepatitis might increase the risk of SL anti-TB drug-induced hepatotoxicity [9,10]. In this study, we found that patients with DR-TB/HBV/HCV co-infection were more susceptible to developing drug induced liver injury and having poor outcomes during DR-TB treatment compared to non-co-infected patients.

In our study there were 6.5% of subjects with a normal baseline ALT level developed hepatotoxicity during the treatment, indicating an important increase from baseline ALT and AST level during the 4 months of intensive phase of SL anti-TB therapy.

There were 137 patient that were diagnosed to have MDR-TB using the molecular assay by Xpert MTB/RIF machine. All patient were screened for HBV and HCV on enrolment for treatment based on the National tuberculosis control program of Nigeria. Most patients with

DR-TB and viral Hepatitis were between the age group of 18 - 25 years. In this study 4.3% of the patient were positive for HBV and 2.2% have HCV infection, < 1% of the DR-TB patients had both HCV and HBV infection.

The patients were at various stage of treatment at the end of this study, 35% are at different phases of treatment and 38% have completed treatment awaiting outcome and about 30% have been declared cured, where as 2% of the study patients were lost to follow up (LTFU), 2% were transferred out and 3% died during the course of treatment, However there were no cases of treatment failure recorded.

The proportion of HIV/DR-TB co infection was found to be 12.45 ($p > 0.005$), less than 1% had DR-TB, HIV and HBV co-infection with about 100% mortality among this group.

Patient with HBV, HCV co-infection showed a decline in the AST and ALT from the baseline, however there was no increase in > 5 folds above upper limit of normal throughout the treatment period. Patients on anti-TB therapy with chronic HBV co-infection are more susceptible to developing liver failure and having poor outcomes during anti-TB treatment [11,12]. We found out that co-infection with viral infection was associated with increase morbidity, and HIV in particular was associated with increase mortality, HBV and HCV infection was however not associated with significant mortality during the intensive phase of treatment.

It is important to perform HBV screening before starting anti-TB therapy, ideally at the time of diagnosis of the condition requiring SL anti-TB treatment, cases, in which an HBV core-positive profile is only reflected after HBV infection (anti-HBcAb-positive and HBsAg-negative), so-called occult HBV infection [8], the positive results could also reflect passively acquired antibodies from recent blood products or may rarely be due to nonspecific reactivity or HBsAg mutant infection. Additional testing is critical to clarify patients' true HBV status. This means that there needs to be close collaboration between virology and clinical teams to ensure that all test results are interpreted accurately.

We acknowledge that this study is limited by its small number of patients, its retrospective nature and the lack of overall information on HBV and HCV DNA levels before at the onset of DILI. However, the results of this study highlight the importance of HBV and HCV DNA and liver function monitoring in DR-TB patients with chronic HBV and or HCV co-infection who plan to receive SL anti TB treatment.

Conclusion

In this study, we found that patients with DR-TB/HBV/HCV co-infection were more susceptible to developing drug induced liver injury and having poor outcomes during DR-TB treatment compared non co-infected patients.

HIV co-infection was associated with increase mortality however, we found no significant mortality among HBV/or HCV co-infected DR-TB patient, these findings highlights the importance of hepatitis testing and providing additional support to DR-TB patients with viral hepatitis infection.

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