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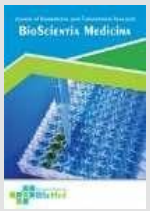

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# Tuberculosis with Drug-Induced Hepatitis: A Narrative Literature Review

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**A B S T R A C T**

Tuberculosis (TB) is an infectious disease that is a global health problem. The problem is that 5-28% of patients receiving tuberculosis treatment suffer from drug-induced hepatitis on antituberculosis drugs (OAT). The clinical picture should be differentiated from other liver diseases. The level of symptoms varies from asymptomatic to symptomatic, such as nausea, vomiting, abdominal pain, jaundice, hepatomegaly, and increased liver function. OAT use is stopped if clinical symptoms are found and ALT/AST increases ≥3 times, or if there are no symptoms but there is an increase in bilirubin ≥2 mg/dl or ALT/AST values ≥5 times without clinical symptoms. The use of OAT can be continued, but with supervision, if there are no clinical symptoms and the increase in ALT/AST is <2 times and the bilirubin value is <2 mg/dl. Treatment can be carried out again by reintroducing OATs one by one according to ATS recommendations.

## 1. Introduction

Tuberculosis (TB) is an infectious disease that is a global health problem. Tuberculosis is ranked as the 13th leading cause of death worldwide and the main cause of death due to infectious diseases. The World Health Organization (WHO) estimates that in 2022, TB will be ranked as the second leading cause of death due to infectious diseases after COVID-19. Data published by the 2021 Global Tuberculosis Report by the WHO shows that Indonesia has the third highest number of TB cases in the world after India and China. The Sustainable Development Goals include WHO's "End Tuberculosis" strategy, which has a 2035 target. The vision of the end-tuberculosis strategy is a TB-free world with zero deaths, illnesses, and suffering due to tuberculosis.[1,2]

The Global TB Report 2021 data states that a quarter of the world's population suffers from TB disease. In Indonesia, there are 824,000 cases of TB, and deaths due to TB are 93,000, or the equivalent of 11 deaths per hour. The incidence of multidrug-resistant (MDR) TB is 7900 cases, with the number of patients undergoing treatment being 5200. There were 293 cases of confirmed pre-Extended Detection and Response (XDR) or XDR TB, with 272 cases of patients undergoing treatment. TB sufferers are predominantly male rather than female. Data from the Ministry of Health of the Republic of Indonesia in 2020 shows that only 41.4% of TB patients received treatment, so around 58.6% of cases of TB patients have not received treatment and are at risk of infecting other people around them. One of the reasons for this decrease in treatment rates is the COVID-19 pandemic, so the TB problem is not a priority.[1,3,4]

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis. This disease can affect

the lungs and other organs. Tuberculosis can be prevented and cured. Compliance with taking medication is important for achieving recovery. Drug side effects often have a negative impact on compliance with medication, causing morbidity and even death. The Council for International Organizations of Medical Sciences (CIOMS) reports that hepatotoxicity accounts for more than 7% of all drug side effects, and 5-28% of patients receiving TB treatment suffer from drug-induced hepatitis (DIH) or anti-tuberculosis drug-induced hepatitis (OAT).[5,6] Drug-induced hepatitis is a health problem that has its own diagnostic challenges. The development of the world of medicine is characterized by many types of drugs that are used to increase the hope of healing from various diseases. This development also has its own impacts, such as increasing the risk of drug side effects. Hepatotoxicity due to OAT does not occur in every patient but can cause acute liver injury and even death if not detected early. This study aims to discuss the mechanisms and management of TB with drug-induced hepatitis.[5-7]

**Definition of drug-induced hepatitis**

Drug-induced hepatitis is an inflammation of the liver caused by a drug reaction. Side effects of drugs can occur in all organs of the body; the liver is the most vulnerable organ because most drugs are metabolized in the liver. The clinical picture of drug-induced hepatotoxicity is difficult to differentiate clinically from hepatitis, cholestasis, and other etiologies. A history of the use of other hepatotoxic drugs or substances should be known. The onset occurs rapidly, with symptoms ranging from malaise and jaundice to severe acute liver failure, especially in patients who are still taking the drug after the onset of hepatotoxicity. Clinical symptoms of drug-induced hepatitis appear within 5 days to 2 months after starting to take OAT.[7-12]

**Classification of drug-induced hepatitis**

The pathophysiological classification of drug hepatotoxicity is divided into two categories: intrinsic hepatotoxicity, direct toxic effect type or influenced by drug dose (predictable hepatotoxicity), and idiosyncratic hepatotoxicity (unpredictable hepatotoxicity). Predictable drugs are drugs that can be guaranteed to always cause liver cell damage if given to each patient at a high enough dose. This class of drugs can directly damage liver cells or indirectly by interfering with the liver's metabolic work. Unpredictable hepatotoxicity is liver damage that occurs not due to the intrinsic toxicity of the drug but due to idiosyncratic reactions that only occur in certain people and are difficult to predict. This only occurs in a small number of susceptible people.[13-20]

Classification of drug hepatotoxicity based on the pattern of liver damage or injury, namely hepatocellular, cholestatic, and mixed. This classification assesses the increase in levels of the liver enzymes ALT, AST, ALP, and bilirubin. Damage to hepatocyte cells is what causes the hepatocellular type. Cholestatic type due to damage to the bile and bile ducts. A mixed type is a combination of both. Assessment of the pattern of liver injury is very important because certain drugs tend to cause damage or injury with a characteristic pattern. This type of hepatocellular injury can cause fever, nausea, vomiting, anorexia, increased transaminase levels, and, if accompanied by jaundice, a poor prognosis. The cholestatic type is generally asymptomatic, and the increase in bilirubin is reversible (Table 1).[14,15,19,21]

Table 1. Pattern of liver damage or injury

| Damage pattern | Liver enzyme | Drugs example | Pathogenesis | Biochemical value |
|---|---|---|---|---|
| Hepatocellular | Increased ALT | Isoniazid, Pyrazinamide, Ketoconazole, Omeprazole, Statin, Risperidone | Hepatocyte damage | ALT/ULN / ~~ALP/ULN~~ = ≥5 |
| Cholestatic | Increased ALP and bilirubin | Amitriptyline, Captopril, Carbamazepine, Clindamycin, Phenobarbital, Phenytoin, Sulfonamides, Sulfamethoxazole | Bile damage and obstruction of bile flow | ALT/ULN / ~~ALP/ULN~~ = ≤2 |
| Mixed | Increased ALP and ALT | Rifampicin, Amoxicillin, Clavulanic acid, Steroid, Chlorpromazine, Clopidogrel, Erythromycin, Estrogen, Irbesartan | Hepatocyte cell damage and bile flow obstruction | ALT/ULN / ~~ALP/ULN~~ = 2-5 |

ULN: upper limit of normal

**Mechanisms of drug-induced hepatitis**

Drug-induced hepatitis occurs through three pathways. The first pathway is the initial mechanism of toxicity, namely drug metabolites and parent drugs, which cause direct cell stress, disrupt mitochondrial function, and trigger specific immune reactions. Cytochrome P450 (CYP450) is the most important drug metabolism enzyme for making hepatotoxic reactive metabolites. It does this by acting as a bridge for phase 1 oxidative drug metabolism. Conjugate metabolism in phase 2 can also produce hepatotoxic metabolites such as acyl glucuronides, which are known to cause drug-induced hepatitis.[14,15,22] Reactive metabolites can cause cell stress through the mechanism of decreasing glutathione and binding to enzymes, fats, nucleic acids, or other cell structures. Reactive metabolites or parent drugs can specifically inhibit hepatocellular function. Reactive metabolites inhibiting the mitochondrial metabolic chain can cause a decrease in adenosine triphosphate (ATP) and increase the concentration of reactive oxygen species (ROS), inhibit β-oxidation, which causes deoxyribonucleic acid (DNA) damage or disrupt replication, or directly disrupt mitochondrial permeability by forming pores. Pores are located on the inside of the membrane so that electron transport in the mitochondria is inhibited to a severe stage, accompanied by an increase in ROS and c-jun N-terminal kinase (JNK) in the cytosol, resulting in liver damage.[15,20,22]

In the second pathway, cell stress occurs, causing mitochondrial permeability disorders. If the initial

mechanism does not directly disrupt mitochondrial function, it can occur in two steps: through the direct pathway mediated by severe cell stress (intrinsic pathway) or through the indirect pathway of amplified death receptors, which is triggered by mild cellular stress (extrinsic pathway). Intrinsic pathway: severe cell stress activates the endoplasmic reticulum pathway, lysosomal permeabilization, and JNK, followed by activation of pro-apoptotic signals and inhibition of anti-apoptotic signals, thereby disrupting mitochondrial permeability.[14,15,21,22]

Extrinsic pathway occurs when mild cell stress can increase the inflammatory response associated with cell stress or other factors that can modulate the natural immune system. The major histicompatibility complex (MHC)-dependent antigen protein will release tumor necrosis factor alpha (TNFα), Fas ligand (FasL), and interferon gamma (IFγ) from Kupffer cells (macrophages in the liver) and cytotoxic T cells as an initial immune response. Reactive metabolites cause cell stress or inflammation, which occurs together with the release of cytokines, which will form a "danger signal," which increases MHC class II-dependent antigens so that hepatocytes are more easily injured (autoimmune hepatotoxicity).[14,15,16,22] This extrinsic pathway causes TNFα and FasL to When a cell's death receptors, TNF and Fas Receptor Associated Death Domain Proteins (FADD), bind to them, they turn on the initiator caspase 8. This sets off the apoptosis process by increasing the activity of proteins that help cells die. The third pathway is damage to mitochondrial function, causing apoptosis and cell damage. Disruption of mitochondrial permeability causes a massive influx of protons through the inner mitochondrial membrane that stops ATP synthesis. A decrease in ATP due to impaired mitochondrial permeability results in matrix expansion, mitochondrial outer membrane permeability, and rupture, accompanied by the release of cytokine C and pro-apoptotic mitochondrial proteins from the intermembrane space into the cytosol.[15,22,23]

**Drug-induced hepatitis due to OAT**

Hepatotoxicity associated with OAT is difficult to predict because most TB patients use a combination of drugs during the therapy period. The first line of OAT that is hepatotoxic is pyrazinamide, isoniazid, and rifampicin. 2nd-line OATs that can cause hepatotoxicity are Etionamide, Protionamide, Levofloxacin, Moxifloxacin, Bedaquiline, P-aminosalicylic acid, Clofazimine, and Delamanid. Hepatotoxicity can be characterized by increased levels of transaminase enzymes. Risk factors for drug-induced hepatitis due to OAT include drug factors, age, gender, nutritional status, alcohol intake, and comorbidities.[24-27]

Table 2. Hepatotoxic OAT

| | | |
|---|---|---|
| **OAT Line 1** | | Pyrazinamide (Z) |
| | | Isoniazid (H) |
| | | Rifampicin (R) |
| **OAT Line 2** | Group A | Levofloxacin/Moxifloxacin (Lfx/Mfx) |
| | | Bedaquiline (Bdq) |
| | Group B | Clofazimine (Cfz) |
| | Group C | Ethionamide (Eto) |
| | | Prothionamide (Pto) |
| | | P-aminosalicylic acid (PAS) |
| | | Delamanid (In) |

**Diagnosis of drug-induced hepatitis**

The diagnosis of drug-induced hepatitis can be confirmed through history-taking, physical examinations, and supporting examinations. The level

of symptoms varies from asymptomatic to symptomatic. Anamnesis obtained from TB patients who were undergoing OAT treatment for 5 days to 2 months gave symptoms such as decreased appetite, nausea, vomiting, dizziness, fever, and dark tea-colored urine. Physical examination revealed jaundice of the eyes and skin; hepatomegaly was also found. Liver function can return to normal if OAT is stopped, but drug reactions can reappear if used again.[27-33] This can be used as a basis for suspicion of the symptoms of drug-induced hepatitis due to OAT. Laboratory tests that can be carried out include examination of the liver enzymes ALT, AST, and bilirubin. The criteria for drug-induced hepatitis, based on the Indonesian Lung Doctors Association (PDPI), are liver function abnormalities due to the use of hepatotoxic OAT. The use of OAT is stopped if 1) clinical symptoms such as jaundice, nausea, and vomiting are found; 2) clinical symptoms and an increase in ALT or AST ≥3 times; 3) there are no symptoms but there is an increase in bilirubin ≥2 mg/dl or an ALT/AST value ≥5 times. Guidelines for cut-off values for drug-induced hepatitis are explained in Table 3.

Table 3. Cut-off points for drug-induced hepatitis

| **Guidelines** | **The cut-off value of drug-induced hepatitis and discontinuing treatment** |
|---|---|
| American Thoracic Society (ATS) | ALT >200 IU/l, or ALT >120 IU/l, symptoms. |
| British Thoracic Society (BTS) | ALT or AST >200 IU/l, increased bilirubin. |
| European Respiratory Society (ERS), World Health Organization (WHO), International Union Againts Tuberculosis and Lung (IUATLD) | ALT or AST >200 IU/l, icteric |
| IUATLD, Hongkong Tuberculosis Service (HKTBS) | ALT >200 IU/l, bilirubin >40 µmol/l |

**Laboratory evaluation**

Antinuclear antibodies test (ANA) can help rule out a diagnosis of autoimmune liver disease. Hepatitis A was excluded if anti-HAV was negative. Hepatitis B is excluded if a negative value is obtained on the hepatitis B surface antigen (HBsAg) or hepatitis B core antigen (anti-HBc) examination. Hepatitis C was excluded with anti-HCV negativity. This test may remain negative for several weeks after the onset of hepatitis C. Hepatitis E is excluded from anti-HEV negativity.[7,9,29] Abdominal ultrasonography (USG) is effective for evaluating gallbladder, biliary tract, and liver tumors. Computerized tomography (CT) scans can help detect liver lesions measuring one cm or more and several other conditions.[7,9,29] This examination can visualize other structures in the abdomen. Magnetic resonance imaging (MRI) can be used to detect cysts, hemangiomas, and primary and secondary tumors. The portal vein, hepatic vein, and biliary tract can be seen without contrast injection. Biopsy aims to detect the presence of abnormal cells in the liver, such as tumor tissue or cancer. A biopsy can be performed if laboratory and radiological examinations show liver problems. Histopathological evaluation is an important examination in diagnosis.[6,9,8]

Table 4. Supporting examinations

| Differential diagnosis | Supporting examination |
|---|---|
| Hepatitis A,B,C,E | IgM anti-HAV; HBsAg, IgM anti-HBc, anti-HCV, IgM & IgG anti-HEV. |
| Autoimmune hepatitis | ANA |
| Hepatis cirrhosis, liver cyst or tumor, gallbladder disease | USG, CT scan or MRI. |
| Detect the presence of abnormal cells in the liver, such as tumor tissue or cancer | Biopsy |

The severity scale for drug side effects consists of ratings from 1 to 5. Scale 4 is called serious adverse events (SAEs), and scale 5 is death. The term SAEs in Active Drug Safety Monitoring (aDSM) side effects is defined as side effects that result in one of the risks, including: 1) hospitalization or extended hospitalization to manage adverse events; 2) permanent disability; 3) congenital abnormalities; and 4) threatening soul or death. ADSM consists of the following three core activities: 1) Patients undergoing TB treatment must undergo systematic clinical and laboratory assessments during TB treatment to detect drug toxicity and drug side effects; 2) all detected side effects must be managed in a timely manner to provide the best treatment for patients; 3) all serious side effects (scale 3 and above) and SAEs must be systematically collected in the patient document. The severity rating scale for TB drug side effects is summarized in Table 5.

Table 5. Drug side effect severity rating scale

| | | |
|---|---|---|
| **Scale 1** | Mild | Symptoms cause no disturbance or minimal disturbance. Do not interfere with activities such as going to work, shopping, cooking, or using transportation. |
| **Scale 2** | Moderate | Symptoms cause greater disruption and interfere with activities such as going to work, shopping, cooking, using transportation |
| **Scale 3** | Severe | Symptoms cause the inability to carry out daily activities such as going to work, shopping, cooking, using transportation |
| **Scale 4** | Very severe | Symptoms result in the inability to perform basic activities such as bathing, dressing, going to the toilet, eating and walking or requiring medical intervention or surgery to prevent permanent impairment, disability or death. |
| **Scale 5** | Death | Death, regardless of cause or relationship to TB drugs. |

Medication supervisors (PMOs) also carry out daily supervision of patients and report to health workers about the side effects of medications experienced by patients. Health workers will carry out data collection in accordance with the recording and reporting that apply to the national TB program, and the overall data will be reported to the National Pharmacovigilance Center (NPC). This data collection is from all countries to assess the safety of TB regimens during treatment and create future policies. Health workers must

actively document and monitor drug side effects (MESO) and evaluate them based on the severity scale.[36]

**Management of TB with drug-induced hepatitis**

**Non-pharmacological**

Medication side effects often have a negative impact on medication adherence. Patients can decide unilaterally on treatment if they do not have good education about the side effects of drugs. This has a negative impact on healing. Education about the side effects of drugs and the treatment that will be carried out by doctors needs to be provided from the start of treatment to patients and PMOs, so that patients and PMOs can report if they feel side effects from drugs and can continue treatment so they don't drop out of the drug. Malnutrition in TB patients will result in decreased OAT metabolism, resulting in liver cell damage and, as a result, increasing the risk of hepatotoxicity. Therefore, it is necessary to provide education about nutritional intake from the start of treatment. Other risk factors that can be controlled, such as comorbidities and drug interactions, must also be considered.[9,14,21]

**Pharmacological**

Patients with hepatitis virus-carrier conditions, a history of acute hepatitis, and alcohol consumption can be given OAT as long as it is confirmed that there is no evidence of chronic liver disease. Prevention of the risk of hepatotoxicity in these conditions should be considered. TB treatment should be postponed if there is acute disease in the liver due to the virus. Treatment should be postponed until the situation improves. For patients with liver disorders, liver function tests should be performed before treatment begins. If SGPT levels increase more than three times, the regimen in Table 4 needs to be considered. The principle of managing TB with drug-induced hepatitis is to reduce the amount of hepatotoxic drugs used.[8,14,29]

**Drug-sensitive tuberculosis**

First step, stop OAT that is hepatotoxic (RHZ). For TB patients who experience hepatotoxicity, after it is resolved with liver function returning to normal (SGPT <2 times) and clinical symptoms disappearing, treatment can be restarted by reintroducing OAT one by one with serial liver function monitoring. OAT administration should be postponed for 2 weeks after clinical symptoms if it is not possible to carry out liver function tests. Drug administration begins with rifampicin, with or without ethambutol. Giving rifampicin 150 mg on the first day, 300 mg on the second day, and 450 mg on the third day until continued to the full dose (according to body weight), then isoniazid can be given. Isoniazid is given with an initial dose of 100 mg on the first day, 200 mg on the second day, and 300 mg on the second day. third, after rifampicin, can be tolerated. Patients receive a regimen of rifampicin, isoniazid, and ethambutol for 9 months if it is proven that after 3–7 days of reintroduction there is no improvement in liver function.[37,39]

Table 6. Combination of drug-sensitive TB with drug-induced hepatitis

| | | |
|---|---|---|
| **Two drugs** | **hepatotoxic** | Rifampicin, isoniazid, and ethambutol for 9 months. |
| **One drugs** | **hepatotoxic** | Rifampicin, ethambutol, fluoroquinolone for 2 months followed by rifampicin and ethambutol for 10 months. |
| **No drugs** | **hepatotoxic** | Ethambutol, aminoglycosides, fluoroquinolones, ethionamide, cycloserine and other new drugs. At least 3 OAT combinations. Duration of therapy 18-24 months. |

The process of reintroducing the medication might lead to a rise in SGPT levels. Therefore, it is imperative to discontinue the last medicine that was reintroduced, as it is the underlying cause of drug-induced hepatitis. Intensify the monitoring of liver function in cases of liver abnormalities and drug-induced hepatitis. Conduct tests specifically twice weekly for the first two weeks of treatment, then once weekly for the remaining two months of therapy. Afterward, maintain monthly monitoring until the treatment is finished. Individual OAT combinations may be administered upon re-initiation or rechallenge. It's crucial to be on the lookout for any potential OAT resistance that could arise from improper dosing and administration techniques. Patients with jaundice should avoid taking pyrazinamide as part of their medication regimen. Streptomycin is no longer employed as an initial choice for oral antibiotic therapy.[29,35] The British Thoracic Society (BTS) advises administering isoniazid at an initial dosage of 50 mg per day, gradually increasing it to 300 mg per day, in order to resume OAT treatment in patients experiencing hepatotoxicity. If there is no hepatotoxic reaction within 2–3 days, the medication will be continued. Administer Rifampicin initially at a dosage of 75 mg per day, then gradually increase to 300 mg after 2-3 days, and further adjust to 450 mg based on the patient's body weight (50 kg). Proceed with medication if there is no hepatotoxicity. Pyrazinamide can be administered initially at a dosage of 250 mg per day, which can be increased to 1 g after 2-3 days and then further increased to 1.5 g for a person weighing 50 kg.[33]

Table 7. The recommendations for reintroducing OAT in tuberculosis (TB) patients who have developed drug-induced hepatitis.

| **Source** | **Stop OAT** | **When to start OAT** | **Starting OAT** | **Liver function observation recommendation** | **When recurrent hepatitis drug induced occurs** |
|---|---|---|---|---|---|
| ATS | Yes | ALT ≤80 IU/L | • R +/- E full dose.<br>• After 3-7 days H (full dose)<br>• P only if mild hepatitis drugs induced. | Evaluate ALT after 3-7 days of H administration | Stop adding the last drugs. |
| BTS | Yes | ALT on normal limit | • H initial 50 mg/day<br>• Slow titration 2-3 days to 300 mg/days<br>• Add R 75 mg/days<br>• Slow titration 2-3 days to 300 mg/days<br>• Next, 450 mg to suit body weight<br>• Add Z 250mg/day<br>• Slow titration on 2-3 days until 1 gr<br>• Titration until 1,5 gr to suit body weight | Monitor liver function everyday | Stop suspected drugs, alternatif regiment referred to trained doctor. |
| ERS, WHO, IUATLD | Yes | ALT on normal limit | Start drugs with full dose. | Liver function monitoring (no frequency recommended) | Stop all drugs. |

Rifampicin is the most effective OAT against TB germs, and rifampicin should be used in combination with OAT. However, if drug-induced hepatitis occurs due to Rifampicin, then the OAT combination

recommended by the American Thoracic Society (ATS) is isoniazid, pyrazinamide, ethambutol, and ofloxacin for 2 months, followed by isoniazid, ethambutol, and ofloxacin for 10 months. Pyrazinamide is the most hepatotoxic OAT. Without following pyrazinamide in the OAT combination, it should consist of isoniazid, rifampicin, and ethambutol for 9 months. Without isoniazid, patients can be treated with a combination of rifampicin, ethambutol, and pyrazinamide for 6 to 9 months.[38,39]

**Drug-resistant tuberculosis**

Some drugs used in drug-resistant TB (TB-RO) treatment regimens can cause hepatotoxicity. Temporary increases in ALT values can be seen during TB RO treatment and are usually self-limiting. In some cases, more serious hepatotoxic problems may occur, and early identification and good management are essential to prevent more severe liver injury. Patients undergoing TB-RO treatment must have a liver function test carried out before treatment begins and repeated every month, or it can be repeated if they have hepatotoxic symptoms after taking the medication. The recommended monitoring criteria and cut-off points for drug-induced hepatitis in TB-RO patients are the same as explained in Table 4. The Department of Health of the Republic of South Africa recommends that reintroduction of RO TB drugs be sequential, every 5 to 7 days, with monitoring of liver function before reintroduction of the next drug. The drug with the lowest hepatotoxicity is given first, namely linezolid, delamanid, and fluoroquinolone, as the main drug in the regimen. Sequential reintroduction of potentially hepatotoxic drugs can be performed with one drug added every 5 to 7 days. The next order of reintroduction is clofazimine, bedaquilin, etionamid, and isoniazid. Monitor liver function after the addition of each drug to identify drugs that may be causing liver injury. Pyrazinamide should not be reused. Perform liver function checks every month. This is explained in table 8.[36]

Table 8. TB-RO combination in drug-induced hepatitis

| Regimen | Hepatotoxic drugs | Treatment strategies | Recommendation |
|---|---|---|---|
| **Short-term** | Bdq, Lfx,/Mfx, Cfz, Eto, $INH^{DT}$ | Move to long-term treatment. | Make sure there are at least three effective drugs in the continuation phase |
| **Long-term** | Bedaquilin | Use Linezolid; select from OAT line 2 group C, add delamanid | Make sure there are at least three effective drugs in the continuation phase |
| | Linezolid | Use bedaquilin; select from OAT line 2 group C, add delamanid | Make sure there are at least three effective drugs in the continuation phase |
| | Levofloxacin | Use bedaquilin; select from OAT line 2 group C, add delamanid | Make sure there are at least three effective drugs in the continuation phase |
| | Clofazimine | Use bedaquilin; select from OAT line 2 group C, add delamanid | Make sure there are at least three effective drugs in the continuation phase |

## 2. Conclusion

Drug-induced hepatitis is an important thing that needs to be considered in the treatment of tuberculosis because it is related to the success of TB treatment. Anamnesis, physical examination, and support, especially liver function, are needed to prove suspicions and understand the mechanism of drug-induced hepatitis due to OAT. The management of TB with drug-induced hepatitis is to stop OAT or continue according to the liver function cut-off value. Reintroduction of OAT and serial liver function evaluations were carried out to determine the appropriate regimen for TB patients with drug-induced hepatitis.

## 3. References


1. World Health Organization (WHO). Global tuberculosis report. Geneva. 2021.
2. Indonesian Ministry of Health. Pedoman Nasional Pengendalian Tuberkulosis. Jakarta: Direktorat Pengendalian Penyakit dan Penyehatan Lingkungan Departemen Kesehatan RI. 2020.
3. Burhan E, Isbaniah F, Aditama TY. Tuberculosis dan Covid 19. Jakarta: Departemen Pulmonologi dan Kedokteran Respirasi. Fakultas Kedokteran Universitas Indonesia. 2021.
4. Chang TE, Huang YS, Su WJ, Perng CL, Huang YH, et al. The role of regular liver function monitoring in antituberculosis drug-induced liver injury. J Chin Med Assoc. 2019;7:535-40.
5. Molla Y, Wubetu M, Dessie B. Anti-tuberculosis drug induced hepatotoxicity and associated factors among tuberculosis patients at selected hospitals, Ethiopia. Hepat Med. 2021;13:1-8
6. Drug-Induced Liver Injury (DILI). Current status and future directions for drug development and the post-market setting. A consensus by a CIOMS Working Group. CIOMS. 2020.
7. Jussi J, David L, Robert M, Steven S, Jhon AJ, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006;174:935–52.
8. Yu YC, Mao YM, Chen CW, Chen JJ, Chen J, , et al. CSH guidelines for the diagnosis and treatment of drug-induced liver injury. Hepatol Int. 2017;3:221-41.
9. Annisa R, Fauzi ZA, Fridayenti. Perbedaan kadar SGPT pada pasien tuberkulosis paru sebelum dan sesudah fase intensif di Poliklinik Paru RSUD Arifin Achmad Pekanbaru. JOM FK.2020;2:1-10
10. Jeong I, Park JS, Cho YJ, Yoon HI, Song J, et al. Drug-induced hepatotoxicity of anti-tuberculosis drugs and their serum levels. J Korean Med Sci. 2015;2:167-72.
11. Djabir YY, Arsyad A, Usmar U, Wahyudin E, Arwi H, et al. The stages of development of liver and renal injuries in rats induced by fixed dose combination of antituberculosis regimen. FABAD J Pharm Sci. 2020;1;29-35.
12. Chen M, Zhang J, Wang Y, Liu Z, Kelly R, et al. The liver toxicity knowledge base: a systems approach to a complex end point. Clin Pharmacol Ther. 2013;5:409-12.
13. Soedarsono S, Riadi ARW. Tuberculosis drug-induced liver injury. JR. 2020;6:49-54.
14. EASL clinical practice guidelines. Drug induced liver injury. J Hepatol. 2019;70: 1222-61.
15. Katzung BG, Trevor AJ, Susan BM. Basic and clinical pharmacology. EGC. 2012;12:53-68.
16. Kim JS, He L, Qian T, Lemasters JJ. Role of the mitochondrial permeability transition in apoptotic and necrotic death after ischemia/reperfusion injury to hepatocytes. Curr Mol Med. 2003;6:527-35.
17. Nakagawa H, Maeda S, Hikiba Y, Ohmae T, Shibata W, et al. Deletion of apoptosis signal-regulating kinase 1 attenuates acetaminophen-induced liver injury by inhibiting c-Jun N-terminal kinase activation.

Gastroenterol. 2008;4:1311-21.
18. Roth RA, Ganey PE. Role of inflammation in drug induced liver injury. San Diego Academic Press. 2015:157-73.
19. Chalasani N, Björnsson E. Risk factors for idiosyncratic drug-induced liver injury. Gastroenterol. 2010;7:2246-59.
20. Fontana RJ. Pathogenesis of idiosyncratic drug-induced liver injury and clinical perspectives. Gastroenterol. 2014;4:914-28.
21. Yew WW, Chang KC, Chan DP. Oxidative stress and first-line antituberculosis drug-induced hepatotoxicity. Antimicrob Agents Chemother.2018;8:2637-47.
22. Pessayre D, Fromenty B, Berson A, Robin MA, Lettéron P, et al. Central role of mitochondria in drug-induced liver injury. Drug Metab Rev. 2012;1:34-87.
23. Han D, Dara L, Win S, Than TA, Yuan L, et al. Regulation of drug-induced liver injury by signal transduction pathways: critical role of mitochondria. Trends Pharmacol Sci. 2013;34(4):243-53.
24. Bouazzi OE, Hammi S, Bourkadi JE. First line anti-tuberculosis induced hepatotoxicity: incidence and risk factors. Pan Afr Med J. 2016;25:167-86
25. Nicoletti P, Devarbhavi H, Goel A, Venkatesan R, Eapen CE, et al. Genetic risk factors in drug-induced liver injury due to isoniazid-containing antituberculosis drug regimens. Clin Pharmacol Ther. 2021;4:1125-35.
26. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. Eur Respir J. 1996;9(10):2026-30.
27. Indonesian Ministry of Health. Petunjuk teknis; Penatalaksanaan tuberkulosis resistensi obat di Indonesia. Jakarta: Kementrian Republik Indonesia. 2020.
28. Gezahegn LK, Argaw E, Assefa B, Geberesilassie A, Hagazi M. Magnitude, outcome, and associated factors of anti-tuberculosis drug-induced hepatitis among tuberculosis patients in a tertiary hospital in North Ethiopia: A cross-sectional study. PLoS One. 2020;11:243-56.
29. Indonesian Pulmonologist Association. Tuberkulosis: Pedoman diagnosis dan penatalaksanaan di Indonesia. Jakarta: PDPI. 2021.
30. Maiti S, Parua S, Nandi DK, Mondal KC. Hepatotoxic effect of rifampicin as an anti-tuberculosis drug on male albino rat. JDDT.2022;3:26-32.
31. Chang TE, Huang YS, Chang CH, Perng CL, Huang YH, et al. The susceptibility of anti-tuberculosis drug-induced liver injury and chronic hepatitis C infection: A systematic review and meta-analysis. J Chin Med Assoc. 2018;2:111-8.
32. Shih TY, Pai CY, Yang P, Chang WL, Wang NC, et al. A novel mechanism underlies the hepatotoxicity of pyrazinamide. Antimicrob Agents Chemother. 2013;4:1685-90.
33. Jong E, Condradie F, Berhanu R, Black A, Jhon MA, et al. Consensus statement: Management of Drug Induced Liver Injury in HIV-Positive Patient Treated for TB. Sajhiv med. 2013;14:113-9.
34. Costiniuk CT, Gosnell BI, Manzini TC, Du Plessis CN, Moosa MY. Tuberculous Drug-induced Liver Injury and Treatment Re-challenge in Human Immunodeficiency Virus Co-infection. J Glob Infect Dis. 2015;4:151-56.
35. Indonesian Ministry of Health. Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.07/MENKES/755/2019 Tentang Pedoman Nasional Pelayanan Kedokteran Tatalaksana Tuberkulosis. Jakarta. 2019.
36. Department of Health-Republic of South Africa. Management of rifampicin-resistant tuberculosis; a clinical reference guide. 2019: 95-100.

37. Made AD, Tutik K. Drug induced hepatitis pada tuberkulosis paru dengan multisite tuberkulosis ekstraparu. JR. 2019;5:41-6
38. Sonika U, Kar P. Tuberculosis and Liver disease: management issue. Tropical Gastroenterol India.2012:113-9
39. Indonesian Pulmonologist Association. Panduan praktik klinis penyakit paru dan pernapasan. Jakarta: PDPI. 2021:75-6.