Management of suspected drug-induced rash, kidney injury and liver injury in adult patients on DS-TB treatment and/or antiretroviral treatment

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This booklet has been compiled to improve the management of rash, renal injury and drug-induced liver injury in ADULT patients on TB treatment and/or antiretroviral therapy. If you need further assistance, please call the National HIV and TB HCW Hotline, 0800 212 506 / 021 406 6782 / "WhatsApp" or send an SMS or "Please call me" to 071 840 1572.

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Abbreviations: ALP= alkaline phosphatase; ALT=alanine transferase; ART=antiretroviral therapy; BPaL-L= bedaquiline, pretomanid, linezolid, levofloxacin; DILI= drug-induced liver injury; DRESS= drug rash with eosinophilia and systemic symptoms; DR-TB=drug-resistant tuberculosis; DS-TB=drug-sensitive tuberculosis; DTG=dolutegravir; E=ethambutol; GIT=gastrointestinal tract; H=isoniazid; IM=intramuscular; INR=international normalised ratio; IRIS=immune reconstitution inflammatory syndrome; IV=intravenous; LFTs=liver function tests; NSAIDs= non-steroidal anti-inflammatory drugs; R=rifampicin; SJS/TEN=Stevens-Johnson syndrome/toxic epidermal necrolysis; TAF-tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; ULN=upper limit of normal; Z=pyrazinamide.

WHEN USING THIS BOOKLET PLEASE NOTE:

1. The algorithms are intended for management of skin rashes, kidney injuries and drug-induced liver injuries in **adult, non-pregnant, non-lactating** patients only.
2. If a recommended laboratory test is not available at your facility, refer the patient.
3. Always attempt to get the contact details of the patient as part of the history. This is necessary if the patient needs to be recalled.

1.1 RASH IN A PATIENT ON ART AND / OR CO-TRIMOXAZOLE

Patient who is taking antiretroviral therapy (ART) and / or co-trimoxazole develops a rash

Did the rash appear while on ART and / or co-trimoxazole?

Yes

- Take an accurate drug **history**
- **Assess rash severity**. Does the patient have any of the following:
  - Unwell patient / GIT symptoms / respiratory symptoms
  - Fever
  - Hepatitis (check ALT)
  - Raised eosinophil count
  - Skin blistering or mucosal involvement (eyes, mouth, genitalia)
  - Malaise, achiness, fatigue

Yes

THIS IS A SEVERE SKIN REACTION

- STOP ALL drugs including ART and co-trimoxazole immediately
- Hospitalise
- If on ABACAVIR, see abacavir hypersensitivity reaction section
- Wait for rash and other symptoms/signs to settle

Have rash and other symptoms settled?

Yes

- **Do not rechallenge with the same ART**
- **For appropriate choice of ART and co-trimoxazole rechallenge, discuss the patient with an expert or call the hotline (0800 212 506)**

No

Discuss the patient with an expert or call the hotline (0800 212 506) for further assistance

No

THIS IS NOT A RASH DUE TO ART OR CO-TRIMOXAZOLE

Consider the differential diagnosis e.g. immune reconstitution inflammatory syndrome (IRIS), pruritic papular eruption (PPE), seborrheic dermatitis, folliculitis, Kaposi sarcoma, herpes zoster, eczema, scabies.

Discuss patient with an expert or call the hotline (0800 212 506) for further assistance.

No

Continue ART and treat rash symptomatically with oral antihistamines. Advise the patient to return if rash worsens, other symptoms develop, or no improvement in rash.

CO-TRIMOXAZOLE RECHALLENGE

see Section 1.5

RASH IN A PATIENT ON ANTIRETROVIRAL THERAPY AND / OR CO-TRIMOXAZOLE

Rash in a patient taking dolutegravir

Hypersensitivity reactions to dolutegravir have been reported in a small proportion of patients (< 1%). Presentation includes rash, systemic symptoms and organ dysfunction. Dolutegravir should be discontinued immediately and ALT should be monitored. Dolutegravir should not be rechallenged in these patients[1].

Rash in a patient taking protease inhibitors

Darunavir contains a sulphonamide moiety and has also been associated with severe rashes (e.g. Stevens-Johnson syndrome)[2]. Manage as for other severe skin reactions.

Rash in a patient taking NRTIs

Mild rashes have been reported with tenofovir and zidovudine and generally do not require treatment discontinuation[2]. For abacavir, see below.

ABACAVIR HYPERSENSITIVITY REACTION

Incidence and presentation of abacavir hypersensitivity reaction

The incidence of the abacavir hypersensitivity reaction is approximately 4.3%[3]. It usually occurs within the first six weeks of therapy[4]. However, it may occur at any time during abacavir therapy[5]. It is a multi-organ syndrome and consists of two or more of the following symptoms[6]:

- Rash (70%)
- Fever (70 to 80%)
- Respiratory symptoms: cough, dyspnoea, pharyngitis (18 to 30%)
- GIT symptoms: nausea, vomiting, diarrhoea, abdominal pain (50%)
- Constitutional symptoms: malaise, achiness, fatigue (40 to 60%)

Most patients (98%) have fever and/or rash as part of the hypersensitivity reaction[5,6]. The rash generally presents as maculopapular or urticarial, but erythema multiforme has also been reported[6]. The symptoms worsen with continued therapy and may be life-threatening[6]. Other less common features of abacavir hypersensitivity reaction include: lethargy, oedema, and paraesthesia[6].

Abacavir hypersensitivity reaction may progress to anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death[5].

Risk factors for abacavir hypersensitivity reaction

Risk factors for abacavir hypersensitivity include female sex, non-African ethnicity and the presence of the HLA-B*5701 gene[4]. Genetic testing may be used to confirm the risk of abacavir hypersensitivity.

Management of abacavir hypersensitivity reaction

It is a severe, life-threatening reaction that requires immediate cessation of abacavir. Abacavir should be discontinued even if other diagnoses (respiratory illness, flu-like illness, gastroenteritis or other drugs) are possible and a hypersensitivity reaction cannot be ruled out[5]. Where feasible, screening for the presence of the HLA-B*5701 gene may be done to confirm the diagnosis of abacavir hypersensitivity. The symptoms start resolving within 1-2 days upon cessation of the drug[4]. Once rash and other symptoms/signs have settled, substitute with an alternative antiretroviral drug, e.g. TDF or TAF (according to eGFR) or zidovudine (if Hb > 8).

Abacavir should never be rechallenged in a patient who has had a known or suspected hypersensitivity reaction as it may lead to anaphylaxis. If no improvement occurs after stopping abacavir, refer to an expert or call the HIV hotline (0800 212 506).

1.2 RASH IN A PATIENT ON DS-TB TREATMENT WITH / WITHOUT ART AND / OR CO-TRIMOXAZOLE

Patient presents with rash while taking DS-TB treatment, with / without ART and / or co-trimoxazole

Did the rash appear while on TB treatment, with / without ART and / or co-trimoxazole?

Yes

- Take an accurate drug **history**
- **Assess rash severity.** Does the patient have any one of the following:
  - Feeling unwell / GIT symptoms / respiratory symptoms
  - Fever
  - Hepatitis (check ALT)
  - Skin blistering or mucosal involvement (eyes, mouth, genitalia)
  - Raised eosinophil count
  - Malaise, achiness, fatigue

Yes

THIS IS A SEVERE SKIN REACTION

- Stop ALL drugs including TB treatment, ART, and co-trimoxazole
- Hospitalise
- Wait for rash and other symptoms/signs to settle

Have rash and other symptoms settled?

No → Discuss the patient with an expert or call the hotline (0800 212 506) for further assistance.

Yes

Start TB background regimen:

- levofloxacin (15-20mg/kg daily, max 1000mg) PLUS
- linezolid (600mg daily if weight ≥ 36 kg; 300mg daily if weight 30-35.9 kg) PLUS
- terizidone (10-15mg/kg, max 750mg)

Avoid linezolid if Hb<8. If linezolid or terizidone are contra-indicated/unavailable, substitute with clofazimine (100mg daily) or amikacin (15mg/kg daily, IV/IM). Avoid amikacin if eGFR < 60 mL/min. Avoid IM amikacin if INR raised. If levofloxacin is not available, moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a more significant effect on QT interval prolongation. If less than three background drugs are available, call the hotline. Monitor patient for at least 1 week.

Did the patient develop rash on TB background therapy?

Yes → **CO-TRIMOXAZOLE RECHALLENGE** see section 1.5

No

Consider rechallenge of TB treatment (see algorithm 1.3) after confirming TB diagnosis and checking available TB drug susceptibilities.

No

THIS IS NOT A RASH DUE TO TB TREATMENT, ART OR CO-TRIMOXAZOLE

Consider the differential diagnosis e.g. immune reconstitution inflammatory syndrome (IRIS), pruritic papular eruption (PPE), seborrheic dermatitis, folliculitis, Kaposi sarcoma, herpes zoster, eczema, scabies.

Discuss patient with an expert or call the hotline (0800 212 506) for further assistance.

No

Continue TB treatment and ART and treat rash symptomatically with oral antihistamines. Advise the patient to return if rash worsens, other symptoms develop or no improvement in rash.

Consider restarting ART once TB treatment has been successfully rechallenged. Call the hotline (0800 212 506) for further assistance.

RASH IN A PATIENT TAKING DS-TB TREATMENT

Prevalence of rash in patients taking first-line TB treatment

The prevalence of rash in patients taking TB treatment ranges between 4.7% and 23%[1-3]. All the first-line TB drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) are associated with rash.

Onset and presentation of TB treatment-induced rash

The onset of rash is typically within the first 2 months of TB treatment[3].

The types of rash that occur with TB treatment vary from less severe morbiliform/maculopapular skin eruptions to severe life-threatening reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS)[1]. Morbiliform/maculopapular skin reactions are the most common types of skin reactions that occur with TB drugs, accounting for 95% of cases[1].

Other less common skin reactions include fixed drug eruptions, lichenoid drug eruption, and cutaneous vasculitis[1].

General management of TB treatment-induced rash

The assessment of severity of the rash is vital as it influences the overall management, including treatment interruption and referral to higher levels of care.

Morbiliform/maculopapular skin reaction

Most morbiliform/maculopapular skin reaction cases are self-limiting and can be managed symptomatically with oral antihistamines. However, a small percentage may progress to DRESS or SJS/TEN. Thus, close monitoring of the patient for signs of worsening rash, systemic involvement, and mucosal involvement is recommended.

SJS/TEN/DRESS

Life-threatening skin reactions such as SJS/TEN or DRESS require admission to hospital for management. Stop all drugs including TB treatment, antiretroviral therapy, and co-trimoxazole. Only rechallenge TB treatment with close monitoring and as an inpatient[4].

Background TB therapy

Start TB background regimen: levofloxacin (15-20mg/kg daily, max 1000mg) + linezolid (600mg daily if weight ≥ 36 kg; 300mg daily if weight 30-35.9 kg) + terizidone (10-15mg/kg, max 750mg). Avoid linezolid if Hb<8 g/dL. If any of the above are contra-indicated/unavailable, substitute with clofazimine (100mg daily) or amikacin (15mg/kg daily, IV/IM). Avoid amikacin if eGFR < 60 mL/min. Avoid IM amikacin if INR raised. If less than three background drugs are available, call the hotline. Where levofloxacin is not available, moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a more significant effect on QT interval prolongation.

References

[1] Lehloenya, RJ, et al. Cutaneous adverse drug reactions to anti-tuberculosis drugs: state of the art into the future. Expert Review of Anti-infective Therapy. 2012. 10(4): 475-486.
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1.3 TB TREATMENT RECHALLENGE AFTER SKIN REACTION

Once the rash has settled and the patient is clinically well, consider rechallenge of the TB treatment. Has the TB diagnosis been confirmed by either microbiological tests or convincing clinical and/or radiological features?

Yes

Is the TB drug susceptible?

No

Do not rechallenge TB treatment. Discuss the patient with an expert or call the hotline (0800 212 506).

Yes

Is the patient on intensive phase of TB treatment?

Yes

Intensive phase
Continue TB background regimen for **at least 2 weeks** before rechallenging TB treatment:

Rechallenge TB treatment in hospital. During rechallenge, evaluate the patient for itching, rash, fever and symptoms and signs of anaphylaxis daily. Discontinue the drug immediately if the patient starts to develop a new rash, even if the rash is mild. Monitor ALT, eosinophils, and creatinine 3 times a week, or more frequently if baseline was abnormal.

Rechallenge Schedule
Day 1: Rifampicin 75 mg daily
Day 2: Rifampicin 300 mg daily
Day 3 and 4: Rifampicin 600 mg daily (if < 55 kg, rifampicin 450 mg daily)
Day 5: Add Isoniazid 50 mg daily
Day 6: Isoniazid 100 mg daily
Day 7 and 8: Isoniazid 300 mg daily
Day 9: Add Pyrazinamide 250 mg daily
Day 10: Pyrazinamide 1 g daily
Day 11: Pyrazinamide 25 mg/kg/day (max 2 g)
If patient tolerates these 3 TB drugs, stop TB background regimen and continue rifampicin, isoniazid and pyrazinamide to complete 2 months intensive phase in total, followed by 4 months continuation phase.

Rechallenge with ethambutol if intolerant to any of the above 3 drugs:
Day 12: Ethambutol 100 mg daily
Day 13: Ethambutol 400 mg daily
Day 14: Ethambutol 15 mg/kg/day (max 1200 mg)

No

Continuation phase
Continue TB background regimen for **at least 2 weeks** before rechallenging TB treatment:

Rechallenge TB treatment in hospital. During rechallenge, evaluate the patient for itching, rash, fever and symptoms and signs of anaphylaxis daily. Discontinue the drug immediately if the patient starts to develop a new rash, even if the rash is mild. Monitor ALT, eosinophils, and creatinine 3 times a week, or more frequently if baseline abnormal.

Rechallenge Schedule
Day 1: Rifampicin 75 mg daily
Day 2: Rifampicin 300 mg daily
Day 3 and 4: Rifampicin 600 mg daily (if < 55 kg, rifampicin 450 mg daily)
Day 5: Add Isoniazid 50 mg daily
Day 6: Isoniazid 100 mg daily
Day 7: Isoniazid 300 mg daily

If patient tolerates both drugs, stop the TB background regimen and the individual TB drugs. Start the patient on a fixed dose combination of rifampicin and isoniazid.
Continue for 4 months in total.

TB TREATMENT RECHALLENGE AFTER SKIN REACTION

Do not rechallenge pyrazinamide if the patient presented with a rash and life-threatening hepatitis (transaminitis with total bilirubin > 40 µmol/L and/or coagulopathy and/or encephalopathy).

Note: sometimes excipients (inactive ingredients in a drug formulation) may cause skin reactions. If the patient tolerates individual drugs during rechallenge, but does not tolerate the fixed dose combination of RHZE (rifampicin, isoniazid, pyrazinamide, ethambutol) or RH (rifampicin, isoniazid), discuss with an expert or call the HIV hotline (0800 212 506).

If successfully rechallenged, the length of TB treatment required after rechallenge can be calculated by subtracting the duration of treatment received prior to rash, from the total duration of TB treatment. Time spent on the background regimen and during rechallenge does not contribute to total duration of treatment.

If uncertain, discuss with an expert or call the HIV hotline (0800 212 506).

References (for section 1.1)

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1.4 MODIFYING TB TREATMENT REGIMEN AFTER SKIN REACTION

If one of the TB drugs are not tolerated during rechallenge in the INTENSIVE PHASE

RIFAMPICIN not tolerated

Substitute with rifabutin. Continue rifabutin, isoniazid, pyrazinamide, ethambutol for **2 months**, then rifabutin and isoniazid for **4 months**
Consider **BPaL-L** for 6 months as alternative if rifabutin not available (refer to 2023 RR-TB guidelines)

ISONIAZID not tolerated

Give rifampicin, pyrazinamide, ethambutol and levofloxacin (preferred)/ moxifloxacin for **6-9 months**

PYRAZINAMIDE not tolerated

Confirm isoniazid susceptibility

If susceptible, continue rifampicin, isoniazid and ethambutol for **9 months**

If not susceptible, refer to expert or call the hotline

Refer to an expert or call the hotline (0800 212 506) if more than one TB drug is not tolerated during rechallenge, or if patient is in the continuation phase, or if unsure about the duration of TB treatment after rechallenge.

References

Maartens, G. Meintjes, G. Mendelson, M. Cotton, M. Rabie, H. Aid for AIDS Clinical Guidelines. 11th edition. Cape Town: AFA; 2016.

Lehloenya, RJ et al. Therapeutic trial of rifabutin after rifampicin-associated DRESS syndrome in tuberculosis-human immunodeficiency virus co-infected patients. Open Forum Infectious Diseases. 2016. Jun 20:3(3): ofw130. (doi: 10.1093/ofid/ofw130.)

1.5 CO-TRIMOXAZOLE RECHALLENGE OR REPLACEMENT

Severe / life-threatening skin reactions

Do not desensitise/rechallenge co-trimoxazole or dapsone in patients with previous or current life-threatening skin reaction to co-trimoxazole (e.g. Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme). Discuss with an expert or call the HIV hotline (0800 212 506).

Skin reactions that were NOT severe / life-threatening

Primary prophylaxis

The aim of primary prophylaxis is to prevent opportunistic infections. If the skin reaction was not severe, patients receiving co-trimoxazole for primary prophylaxis with CD4 count < 200 cells/µL or WHO stage 2, 3 or 4 disease, should be switched to dapsone 100 mg po daily as an alternative[1]. Note that there is a risk of cross-reactivity between co-trimoxazole and dapsone[1].

Primary prophylaxis is not necessary if the CD4 count is > 200 cells/µL.

Secondary prophylaxis after treatment of pneumocystis pneumonia

The aim of secondary prophylaxis is to prevent recurrence of opportunistic infections. If the patient was taking co-trimoxazole as secondary prophylaxis after treatment of pneumocystis pneumonia, switch to dapsone.

Secondary prophylaxis after treatment of toxoplasmosis

If patient was taking co-trimoxazole as secondary prophylaxis after toxoplasmosis infection, dapsone cannot be used as it is not effective against toxoplasmosis. There are 2 options:

1. Clindamycin plus pyrimethamine plus folinic acid[2,3]
2. Co-trimoxazole desensitization

Acute treatment of pneumocystis pneumonia or toxoplasmosis

Patients who developed a skin reaction while taking co-trimoxazole for treatment of pneumocystis pneumonia or toxoplasmosis will require in-hospital rapid desensitization. See protocol below.

Rapid co-trimoxazole desensitization protocol

This should always be done as an in-patient **without steroid or antihistamine cover**[1,4]. Stop the desensitization if a rash, pruritus, fever or any other symptoms (e.g. burning of the skin) develop. Use diluted co-trimoxazole suspension for the desensitization.

Dilution is as follows:

Mixture A - Trimethoprim 0.04 mg / sulfamethoxazole 0.2 mg / 5 mL: Take 1 mL co-trimoxazole suspension (trimethoprim 40 mg/sulfamethoxazole 200 mg/5mL) and dilute to 1 litre with water and shake well[5].

Mixture B - Trimethoprim 0.004 mg /sulfamethoxazole 0.02 mg /5 mL: Take 1 mL of mixture A and dilute to 10 mL with water[5].

Rapid in-hospital desensitization protocol		
Time	**Dose of diluted co-trimoxazole suspension**	**Dose of co-trimoxazole being administered**
Time 0	Administer 5 mL orally of mixture B (discard balance of mixture B)	trimethoprim 0.004 mg/sulfamethoxazole 0.02 mg
Time 1 hour	Administer 5 mL orally of mixture A (after shaking well)	trimethoprim 0.04 mg/sulfamethoxazole 0.2 mg
Time 2 hours	Administer 50 mL orally of mixture A (after shaking well and discard balance of mixture A)	trimethoprim 0.4 mg/sulfamethoxazole 2 mg
Time 3 hours	Administer 0.5 mL orally of co-trimoxazole suspension diluted to 5 mL with distilled water	trimethoprim 4 mg/sulfamethoxazole 20 mg
Time 4 hours	Administer 5 mL orally of undiluted co-trimoxazole suspension	trimethoprim 40 mg/sulfamethoxazole 200 mg
Time 5 hours	Administer 2 single strength co-trimoxazole tablets orally	trimethoprim 160 mg/sulfamethoxazole 800 mg
Time 6 hours	Start full dose co-trimoxazole	

Note: If there is any uncertainty regarding co-trimoxazole rechallenge, discuss with an expert or call the HIV hotline (0800 212 506).

References

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2. 1 RENAL IMPAIRMENT IN A PATIENT TAKING TENOFOVIR DISOPROXIL FUMARATE (TDF)

If patient is on tenofovir alafenamide (TAF), discuss with expert or call the hotline (0800 212 506)

Patient presents with eGFR < 50 mL/min on TDF-based antiretroviral therapy (ART) regimen
[Note that dolutegravir is expected to cause a small initial rise in creatinine up to 30 micromol/L, but it is not nephrotoxic]

ACUTE KIDNEY INJURY SUSPECTED

STOP TDF immediately and switch to abacavir. If abacavir is contraindicated, use zidovudine, provided that haemoglobin is > 8 g/dL.

Check if any drugs need dose adjustment. See Renal Adjustment Table (2.2).

Stop all nephrotoxic drugs (e.g. amphotericin B, NSAIDs, aminoglycosides), if possible.

- **Identify and treat concomitant cause for the kidney injury e.g. acute/chronic gastroenteritis, dehydration, sepsis**
- **Continue abacavir**
- **Do a blood gas to check for acidosis and electrolyte abnormalities**
- **Rehydrate and monitor urine output**
- **Do urine dipstick. If proteinuria 1+ or more, discuss with an expert or call the hotline (0800 212 506) for further assistance**
- **Monitor renal function regularly according to clinical condition**

Was an underlying cause other than TDF identified?

Yes

Has underlying cause resolved and eGFR > 50 mL/min after 1 month?

Yes

Stop abacavir. Start TDF or TAF. Continue routine eGFR monitoring.

No

Continue abacavir.

No

Renal injury was potentially related to TDF. Continue abacavir or use TAF and don't rechallenge TDF.

CHRONIC KIDNEY DISEASE SUSPECTED

STOP TDF and switch to abacavir or tenofovir alafenamide (TAF).

Check if any drugs need dose adjustment. See Renal Adjustment Table (2.2).

Stop all nephrotoxic drugs (e.g. amphotericin B, NSAIDs, aminoglycosides), if possible.

- **Do regular eGFR monitoring and urine dipstick**
- **Consider other causes of kidney disease e.g. HIVAN, opportunistic infections, malignancies, hepatitis B, diabetes, hypertension**
- **Consider renal ultrasound if available**

Continue abacavir or TAF. Refer for appropriate management of chronic kidney disease.

TAF/FTC co-formulation suitable if eGFR > 30 mL/min.
TAF suitable if eGFR > 15 mL/min.
TAF is preferred to abacavir if patient is also HepBsAg positive.

RENAL IMPAIRMENT IN A PATIENT TAKING TENOFOVIR DISOPROXIL FUMARATE (TDF)

Note that dolutegravir is not nephrotoxic. It can cause a small increase in serum creatinine (< 30 micromol/L) due to interference with tubular secretion of creatinine. It occurs in the first month after initiation and does not progress.

Presentation of TDF-induced kidney injury

TDF may cause[1]:

- Acute kidney injury
- Chronic kidney disease with accelerated decline in eGFR (> 3 mL/min per 1.73m^2 per year)
- Subclinical renal tubular dysfunction, characterised by increased concentration of glucose and/or low molecular protein in the urine and reduced reabsorption of phosphate
- Fanconi syndrome — characterised by glycosuria, hypophosphataemia, proteinuria, hypouricaemia, hypokalemia and tubular acidosis
- Tubulointerstitial nephritis

Incidence of TDF-induced kidney injury

Treatment-limiting renal disease due to TDF is rare. Fanconi syndrome requiring treatment discontinuation occurred in 0.5-1% of patients in clinical trials and has been reported in 1 to 1.5% of patients in cohort studies[1].

The incidence of TDF-associated kidney injury, defined as a decline in renal function below 50 mL/min/1.73 m^2 in a South African adult cohort was 3% over 12 months[2]. In a Zambian cohort, the reported incidence of moderate (eGFR 30-59 mL/min) or severe (eGFR ≤ 29 mL/min) renal dysfunction associated with TDF was 1.84% over 12 months[3].

Risk factors for TDF-induced kidney injury[4]:

- Pre-existing renal impairment
- Older age
- Advanced HIV disease
- Low body weight
- Concomitant use of protease inhibitors
- Concomitant use of nephrotoxic drugs
- Diabetes mellitus
- Hypertension

Monitoring for TDF-induced kidney injury

Kidney injury can occur any time during TDF therapy. Therefore, monitoring of eGFR is recommended at baseline, 3 months, 10 months and yearly thereafter[5].
To minimise kidney injury, TDF should not be initiated in patients with an eGFR < 50 mL/min. Monitor eGFR weekly if concomitant use of other nephrotoxic drugs (e.g. amphotericin B, aminoglycosides) cannot be avoided.

Management of acute kidney injury in a patient taking TDF

If eGFR drops to below 50 mL/min, stop TDF and switch to abacavir[5,6,7] . If abacavir is contraindicated, use zidovudine, provided that haemoglobin is > 8 g/dL[5,6]. Renally excreted drugs e.g. lamivudine will require dose adjustment. If uncertain about dose adjustment of other renally excreted drugs, seek expert advice or call the HIV hotline. Stop all other nephrotoxic drugs. Rule out other causes of renal dysfunction, e.g. diarrhoea, opportunistic infections and sepsis. Patients should always be referred to a higher level of care if acute kidney injury does not improve or worsens despite stopping TDF.

TENOFOVIR ALAFENAMIDE (TAF)

Tenofovir is available orally in two prodrug forms: tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), which are converted intracellularly to the pharmacologically active form tenofovir di-phosphate (DP). TDF is generally recommended for most patients. TAF has fewer renal and bone adverse effects. TAF can be given at lower eGFRs depending on the formulation (see table 2.2). TAF has been associated with more weight gain, a less favourable lipid profile, and has some important drug-drug interactions. TAF 25 mg should not be given in combination with ritonavir-boosted PI regimens. TAF may be given with rifampicin: although serum TAF levels are reduced, intracellular concentrations of the active metabolite are higher than those obtained with TDF. TAF is recommended for patients who are co-infected with hepatitis B and who also have mild renal impairment or osteoporosis[8].

Note: If AKI develops in a patient on TAF, it should still be replaced with abacavir or zidovudine (If Hb > 8) and managed as for AKI on TDF[8].

References

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[2] Kamkuemah, M, et al. Renal impairment in HIV-infected patients initiating tenofovir-containing antiretroviral therapy regimens in a primary healthcare setting in South Africa. Tropical Medicine and International Health. 2015. 20(4):518-526.
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2.2 RENAL ADJUSTMENT OF ANTIRETROVIRALS / ANTITUBERCULOUS DRUGS / PROPHYLACTICS

Drug	Standard adult dose	eGFR 30-50 mL/min	eGFR 15-30 mL/min	eGFR < 15 mL/min
Abacavir	600 mg daily OR 300 mg 12 hourly	Unchanged	Unchanged	Unchanged
Atazanavir/ritonavir	300 mg/100 mg daily	Unchanged	Unchanged	Unchanged
Darunavir/ritonavir	600 mg/100 mg 12 hourly OR 800 mg/ 100 mg daily (depending on mutations)	Unchanged	Unchanged	Unchanged
Dolutegravir	50 mg daily	Unchanged	Unchanged	Unchanged
Efavirenz	600 mg nocte (or 400 mg if < 40 kg)	Unchanged	Unchanged	Unchanged
Etravirine	200 mg 12 hourly	Unchanged	Unchanged	Unchanged
Lamivudine	300 mg daily OR 150 mg 12 hourly	Unchanged	150 mg daily	50 mg daily[#]
Lopinavir/ritonavir	400 mg/100 mg 12 hourly	Unchanged	Unchanged	Unchanged
Raltegravir	400 mg 12 hourly	Unchanged	Unchanged	Unchanged
Rifabutin	300 – 450 mg daily	Unchanged	Unchanged, but consider dose reduction of 50% if toxicity suspected	Unchanged, but consider dose reduction of 50% if toxicity suspected
Rilpivirine	25 mg daily	Unchanged	Unchanged	Unchanged
Tenofovir alafenamide (TAF)	25 mg daily	Unchanged	Unchanged	Avoid*
Tenofovir disoproxil fumarate (TDF)	300 mg daily	Avoid	Avoid	Avoid*
Zidovudine	300 mg 12 hourly	Unchanged	Unchanged	300 mg daily
Ethambutol	15 – 25 mg/kg daily	Unchanged	Standard dose 3 times weekly	Standard dose 3x per week
Isoniazid	4 – 6 mg/kg daily	Unchanged	Unchanged	Unchanged
Pyrazinamide	20 – 30 mg/kg daily	Unchanged	25 – 35 mg/kg 3 times weekly	25 – 35 mg/kg 3 times weekly
Rifampicin	8 – 12 mg/kg daily	Unchanged	Unchanged	Unchanged
Co-trimoxazole	800/160 mg daily	400/80 mg daily	400/80 mg daily	400/80 mg 3 times weekly if eGFR < 10 mL/min
Dapsone	100 mg daily	No recommendation	No recommendation	No recommendation

(Doses obtained from SAHCS Guidelines: 2023 update, NDoH Management of rifampicin-resistant TB Guidelines Sep 2023, SAMF 14th edition)

[#] Some experts recommend that the lowest available tablet dose of 150 mg lamivudine daily be used in patients with advanced renal disease to avoid having to use the liquid formulation of lamivudine, and because of the favourable safety profile and lack of data to suggest lamivudine dose-related toxicity.

** May be used if patient is on haemodialysis*

3.1 PATTERNS OF LIVER INJURY

Hepatic adaptation

Exposure to drugs may induce a physiologic, adaptive response in the liver, known as hepatic adaptation[1]. Adaptation causes low-grade, transient, and asymptomatic transaminase elevation which does not require treatment cessation[1]. Hepatic adaptation must be distinguished from a symptomatic drug-induced liver injury (DILI) which frequently has more marked transaminitis and requires drug cessation.

Hepatocellular pattern of liver injury

- In hepatocellular liver injury, ALT is disproportionately elevated compared to the elevation of ALP
- Hepatocellular injury may either be asymptomatic or symptomatic. Symptoms and signs include fatigue, anorexia, nausea, vomiting, abdominal pain, or right upper quadrant tenderness
- Drugs that may cause hepatocellular-pattern liver injury: isoniazid, pyrazinamide, rifampicin, moxifloxacin, levofloxacin, nevirapine, efavirenz, paracetamol (with chronic use/overdose)
- Hepatocellular DILI usually occurs within 2 to 12 weeks of drug initiation but may occur at any time during treatment[2]
- Efavirenz-associated and INH-associated DILI may occur up to a year after drug initiation[2]
- Generally, hepatocellular DILI resolves within 2 to 4 weeks of stopping the causative drug[2]
- Other causes of hepatocellular-pattern liver injury include acute viral hepatitis, chronic hepatitis B and C

Cholestatic pattern of liver injury

- In cholestatic liver injury, ALP is disproportionately elevated compared to ALT
- Cholestatic liver injury may result in a conjugated hyperbilirubinemia
- Features of cholestatic liver injury include nausea, fatigue, pruritus, dark urine, right upper quadrant tenderness and jaundice
- Purely cholestatic liver injury is rarely caused by TB treatment or antiretrovirals
- Drugs that may cause cholestatic-pattern liver injury: rifampicin, amoxicillin-clavulanic acid, cephalosporins, sulfonylureas, fluconazole
- Cholestatic DILI generally occurs within 2 to 12 weeks of drug initiation but may sometimes occur a year or more after drug initiation
- Cholestatic DILI resolves more slowly than hepatocellular DILI. Elevated enzyme concentrations should drop by 50 % within 4 to 12 weeks of drug cessation
- Other causes of cholestatic liver injury include extra-hepatic biliary obstruction, TB or TB-IRIS

Mixed pattern liver injury

- In mixed pattern liver injury, there are both hepatocellular and cholestatic features with moderate to marked elevations in both ALT and ALP[2]
- The presenting symptoms and signs include fatigue, anorexia, and nausea, followed by jaundice and often pruritus[2]
- Drugs that may cause mixed-pattern liver injury (DILI): rifampicin, efavirenz, anticonvulsants (phenytoin, carbamazepine, and lamotrigine), non-steroidal anti-inflammatory drugs (NSAIDs), co-trimoxazole, amoxicillin-clavulanic acid, flucloxacillin, fluconazole
- Onset of mixed DILI is typically within 2 to 12 weeks of drug initiation but may occur at any time during drug exposure[2]
- Mixed DILI resolves more slowly than a hepatocellular DILI
- Elevated enzyme concentrations should drop by 50 % within 4 to 12 weeks[2]
- IRIS may present with mixed-pattern liver injury

Isolated hyperbilirubinemia

- Total bilirubin > 40 micromol/L whilst other liver function tests (LFTs) remain normal[3]
- Usually benign and temporary
- Rifampicin is known to cause this during the first few weeks of therapy. It is not considered a liver injury and is due to interference with the transport of bilirubin[3]
- If hyperbilirubinaemia persists or worsens then intervention may be required

Note that abnormal baseline liver function tests are NOT a contraindication to starting standard TB treatment or antiretroviral therapy

References

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3.2.1 LIVER INJURY IN A PATIENT ON DS-TB TREATMENT WITH / WITHOUT ART

Patient presents with symptoms/signs of liver injury (e.g. nausea, vomiting, abdominal pain, malaise, anorexia, right upper quadrant tenderness, jaundice) on first-line TB drugs (rifampicin, isoniazid, pyrazinamide, ethambutol) with or without ART

Do ALT and total bilirubin. If jaundiced and/or ALT and total bilirubin cannot be obtained within 24 hours, STOP ALL TREATMENT and refer

Does the patient have:
- **symptoms/signs of liver injury and ALT > 120 IU/L; OR**
- **ALT > 120 IU/L and total serum bilirubin > 40 µmol/L?**

Yes

THIS IS A LIVER INJURY THAT REQUIRES CESSATION OF DRUGS

- **Admit patient to hospital**
- **STOP TB treatment, ART, and other hepatotoxic drugs e.g. co-trimoxazole, fluconazole, amoxicillin-clavulanic acid**
- **Do INR and full liver function tests to identify liver enzyme pattern**
- **Monitor blood glucose**
- **Test for viral hepatitis. Do hepatitis A IgM, hepatitis B surface antigen and core IgM antibody, and hepatitis C antibody**
- **Exclude pregnancy**

Start TB background regimen: levofloxacin (15-20mg/kg daily, max 1000mg) + ethambutol (800-1200mg daily) + linezolid (600mg daily if weight ≥ 36 kg; 300mg daily if weight 30-35.9 kg). Avoid linezolid if Hb<8g/dL. Terizidone (10-15mg/kg daily, max 750mg), amikacin (15mg/kg daily, IV/IM) and clofazimine (100mg daily) are also options if ethambutol or linezolid are contra-indicated/unavailable. Avoid amikacin if eGFR < 60 mL/min and IM amikacin if INR > 1.5. If levofloxacin is not available, moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a more significant effect on QT interval prolongation.

If patient has TB meningitis, please call the hotline (0800 212 506) for advice on appropriate background regimen

CONSIDER OTHER CAUSES OF LIVER DYSFUNCTION

Hepatocellular pattern of injury:
1. Hepatitis A, hepatitis B, hepatitis C
2. Herpes simplex virus infection

Cholestatic and Mixed pattern of injury:
1. Obstructive causes e.g. lymphoma, disseminated TB with obstruction, extra-hepatic obstruction
2. Sepsis
3. HIV cholangiopathy
4. IRIS
5. Chronic alcohol abuse

Perform an abdominal ultrasound to exclude obstructive causes

If unsure about findings discuss with an expert or call the hotline (0800 212 506)

Follow-up monitoring: Repeat ALT, bilirubin and INR (if baseline > 1.5) every 3 days

Has ALT decreased to < 100 IU/L and is bilirubin on a downward trend?

Yes
- Consider rechallenge of TB drugs after excluding other causes of liver injury and confirmation of TB diagnosis (Algorithm 3.2.2)
- Consult expert regarding TB treatment rechallenge in patients with acute liver failure (jaundice with encephalopathy and/or INR > 1.5)

No

Discuss the patient with an expert or call the hotline (0800 212 506)

Asymptomatic patient presents with elevated ALT or isolated hyperbilirubinemia

Is ALT > 200?

Yes

No

THIS IS A POTENTIAL LIVER INJURY REQUIRING CLOSE MONITORING

- Monitor for jaundice and other symptoms/signs of suspected DILI
- If asymptomatic, ALT < 120 IU/L and total bilirubin <40 µmol/L: Continue ART and TB treatment
- If asymptomatic, ALT > 120 IU/L but < 200 IU/L: Continue ART and TB treatment, monitor weekly
- If symptomatic, ALT < 120 IU/L and total bilirubin <40 µmol/L: Continue ART and TB treatment, monitor ALT weekly
- If asymptomatic isolated hyperbilirubinemia (see 3.1) continue ART and TB treatment. Monitor weekly. Discuss with expert if serum bilirubin > 100 µmol/L or persistently elevated

Follow-up monitoring: Is ALT improving?

Yes
- Stop laboratory monitoring
- Review the patient in 1 month
- Advise the patient to return to the clinic if any symptoms/signs of liver injury develop

No

If ALT continues to increase or is unchanged: Monitor ALT and bilirubin weekly for 4 consecutive weeks

If ALT increases to > 200 IU/L or bilirubin increases to > 40 µmol/L or patient becomes symptomatic, manage as a DILI

LIVER INJURY IN PATIENT ON DS-TB TREATMENT WITH OR WITHOUT ANTIRETROVIRAL THERAPY (ART)

Drug-induced liver injury (DILI) complicates first-line TB treatment in 5–33 % of patients. This wide variation is due to differing study populations and regimens[1]. The first-line antituberculosis drugs isoniazid, rifampicin and pyrazinamide can cause DILI. Ethambutol does not cause DILI.

Efavirenz can cause DILI[2]. LPV/r, DRV/r, ATV/r and dolutegravir rarely cause DILI[3]. Abacavir, tenofovir, emtricitabine, and lamivudine do not cause DILI.

Risk factors for DILI in patients taking TB treatment and ART[2,4]:

- Age > 35 years
- Female sex
- Pregnancy
- Hepatitis B/C co-infection
- Slow acetylator status (isoniazid-induced DILI)
- Malnutrition
- Alcohol abuse
- Pre-existing chronic liver disease

Management of DILI in patients taking TB treatment and ART

Stop TB treatment, ART, and other hepatotoxic drugs (e.g. cotrimoxazole, fluconazole) immediately if[5]:

1. ALT > 120 IU/L and symptomatic OR
2. ALT > 120 IU/L and jaundiced OR
3. ALT > 120 IU/L and total bilirubin > 40 IU/L OR
4. ALT > 200 IU/L regardless of symptoms or bilirubin OR
5. ALT > 2x baseline ALT in patients with existing liver disease

Jaundice in a patient with hepatocellular injury indicates severe liver injury, with a 10% chance of developing fulminant liver failure (jaundice with encephalopathy and/or coagulopathy)[1].

Initiate a TB background regimen consisting of levofloxacin (15-20mg/kg daily, max 1000mg) + ethambutol (800-1200mg daily) + linezolid (600mg daily if weight ≥ 36 kg; 300mg daily if weight 30-35.9 kg) to prevent development of resistance during rechallenge. Avoid linezolid if Hb<8 g/dL. Terizidone (10-15mg/kg daily, max 750mg), amikacin (15mg/kg daily, IV/IM) and clofazimine (100mg daily) are options if ethambutol or linezolid are contra-indicated/unavailable. Avoid amikacin if eGFR < 60 mL/min or IM amikacin if INR > 1.5. If levofloxacin is not available, moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a more significant effect on QT interval prolongation.

IRIS

Tuberculosis-associated immune reconstitution inflammatory syndrome (IRIS) is part of the differential diagnosis in patients with a suspected DILI. It is often difficult to distinguish a DILI from IRIS. Suspect the possibility of IRIS in a patient where ART was started soon after the initiation of TB treatment and with clinical deterioration. Patients may present with jaundice and tender hepatosplenomegaly. Worsening granulomatous infiltration of the liver or lymph node enlargement secondary to IRIS typically presents with cholestatic or mixed pattern liver injury. Abdominal ultrasound is indicated in these cases. Exclude other causes of clinical deterioration – failure of TB treatment due to possible DR-TB; poor adherence to DS-TB treatment; presence of another opportunistic infection; drug toxicity or reaction.

References

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3.2.2 TB DRUG RECHALLENGE AFTER DRUG-INDUCED LIVER INJURY ON TB TREATMENT WITH / WITHOUT ART

Before rechallenge, consider the following clinical question: Has the TB diagnosis been confirmed by either microbiological tests or convincing clinical and/or radiological features? If patient has TB meningitis, please call the hotline (0800 212 506) for assistance.

Yes

Is the TB drug susceptible?

No

Do not rechallenge with first line TB treatment. Discuss the patient with an expert or call the hotline (0800 212 506).

Yes

Once the ALT is < 100 IU/L, bilirubin is on a downward trend, and patient is asymptomatic, consider rechallenge of TB drugs.
DO NOT rechallenge first-line TB treatment if the patient presented with acute liver failure (jaundice with encephalopathy and/or INR > 1.5) without discussing with an expert or the hotline.

Is the patient on intensive phase of TB treatment?

Yes

Intensive phase, rechallenge as follows:

Continue background regimen

Day 1-3: Rifampicin 10mg/kg/day (max 600mg daily)
Day 3: Check ALT. If > 100 IU/L, consider rifampicin as culprit drug. Go to section 3.2.3
If ALT < 100 IU/L proceed to next step.
Day 4-7: Add isoniazid 5mg/kg/day (max 300mg daily)
Day 7: Check ALT. If > 100 IU/L, consider isoniazid as culprit drug. Go to section 3.2.3
If ALT < 100 IU/l proceed to next step.
Day 8-10: Consider adding pyrazinamide 25 mg/kg/day (max 2000mg daily)
Note: Only consider pyrazinamide rechallenge in cases of severe forms of TB e.g. miliary TB or TB meningitis, or intolerance to isoniazid.
Day 10: Check ALT. If ALT > 100 IU/L, consider pyrazinamide as culprit drug or if pyrazinamide not rechallenged, go to section 3.2.3
If ALT < 100 IU/L and pyrazinamide successfully rechallenged, re-start TB fixed dose combination (RHZE).

Stop TB background regimen.

Monitor ALT weekly for 4 weeks after rechallenge.

No

Continuation phase, rechallenge as follows:

Continue background regimen

Day 1-3: Rifampicin 10mg/kg/day (max 600mg daily)
Day 3: Check ALT. If > 100 IU/L, consider rifampicin as culprit drug and call the hotline.
If ALT < 100 IU/L proceed to next step.
Day 4-7: Add isoniazid 5mg/kg/day (max 300mg daily)
Day 7: Check ALT. If > 100 IU/L, consider isoniazid as culprit drug and call the hotline.
If ALT < 100 IU/L proceed to next step.
Day 8: If ALT < 100 IU/L and isoniazid successfully rechallenged, re-start TB fixed dose combination (RH) to complete the continuation phase.

Stop TB background regimen.

Monitor ALT weekly for 4 weeks after rechallenge.

Restart ART once TB treatment has been successfully rechallenged – refer to ART algorithm
(Algorithm 3.2.4).

TB TREATMENT RECHALLENGE AFTER DRUG-INDUCED LIVER INJURY (DILI)

Rechallenge of TB drugs should only be attempted once ALT is < 100 IU/L and bilirubin is on a downward trend[1,2]. Do not rechallenge TB drugs if drug-induced liver injury (DILI) resulted in acute liver failure (jaundice with encephalopathy and/or INR > 1.5)[2]. These cases need discussion with an expert or call the HIV hotline (0800 212 506).

Rechallenge of TB drugs has been found to be safe and effective in 60-90% of patients[2]. Frequent ALT monitoring during rechallenge is essential. Monitor ALT at least 3 times weekly during rechallenge and weekly for 1 month following successful rechallenge[2].

Pyrazinamide rechallenge is associated with re-occurrence of DILI and should not be routinely attempted. Consider pyrazinamide rechallenge in patients who developed DILI during the intensive phase of TB treatment if:

1. TB meningitis OR
2. Miliary TB OR
3. Isoniazid rechallenge fails[2]

If uncertain whether to attempt rechallenge with pyrazinamide, discuss with an expert or call the HIV hotline (0800 212 506).

If successfully rechallenged, the length of TB treatment required after rechallenge can be calculated by subtracting the duration of treatment received prior to DILI, from the total duration of TB treatment. Time spent on the background regimen and during rechallenge does not contribute to total duration of treatment. If uncertain, discuss with an expert or call the HIV hotline (0800 212 506).

References

[1] National Department of Health. National tuberculosis management guidelines. 2014. Available from http://www.sahivsoc.org/upload/documents/NTCP_Adult_TB%20Guidelines%2027.5.2014.pdf Accessed 20 July 2016.
[2] Boyles T, Berhanu RH, Gogela N, et al. Management of drug-induced liver injury in people with HIV treated for tuberculosis: 2024 update. S Afr J HIV Med. 2024;25(1), a1558. https://doi.org/10.4102/sajhivmed.v25i1.1558.

3.2.3 MODIFYING TB TREATMENT REGIMEN

If one of the TB drugs are not tolerated during rechallenge in the INTENSIVE PHASE

RIFAMPICIN rechallenge not tolerated

Start shorter regimen for rifampicin resistant TB treatment i.e. **BPaL-L** (bedaquiline, pretomanid, linezolid, levofloxacin) for **6 months**

If uncertain discuss with an expert or call the hotline (0800 212 506)

ISONIAZID rechallenge not tolerated

If pyrazinamide rechallenged successfully:
Continue rifampicin, ethambutol, levofloxacin (preferred) / moxi-floxacin, and pyrazinamide for a total of **6-9 months***

OR

Pyrazinamide not rechallenged:
Continue rifampicin, ethambutol and levofloxacin (preferred) / moxifloxacin for a total of **9 - 12 months***

*Subtract duration of TB treatment received prior to DILI

PYRAZINAMIDE not rechallenged or not tolerated

Confirm isoniazid susceptibility

If susceptible, continue rifampicin, isoniazid and ethambutol for a total of **9 months***

If not susceptible, refer to expert or call the hotline (0800 212 506)

*Subtract duration of TB treatment received prior to DILI

Monitor ALT weekly for 4 weeks after rechallenge

Refer to an expert or call the hotline (0800 212 506) if patient is in the continuation phase of TB treatment, if more than one TB drug is not tolerated during rechallenge, or if unsure about the duration of TB treatment after rechallenge

3.2.4 RESTARTING ART AFTER DILI ON TB TREATMENT AND ART

Patient presents with DILI on TB treatment and ART.

DO NOT rechallenge first-line TB treatment or ART if patient presented with acute liver failure (jaundice with encephalopathy and/or INR > 1.5). Patients with acute liver failure should be discussed with an expert or the hotline (0800 212 506).

After successful rechallenge of TB treatment, restart ART (for patients on third line ART or on failing ART regimens, call the hotline).

DILI developed on efavirenz-based regimen

DO NOT rechallenge efavirenz, even with an asymptomatic DILI

Switch to dolutegravir

Remember to dose dolutegravir at 50 mg twice daily if rifampicin was successfully rechallenged

DILI developed on double dose dolutegravir

Restart dolutegravir

Remember to dose dolutegravir at 50 mg twice daily if rifampicin was successfully rechallenged

DILI developed with double dose lopinavir/ritonavir

Switch to dolutegravir*

Remember to dose dolutegravir at 50 mg twice daily if rifampicin was successfully rechallenged

* if there is a history of integrase inhibitor resistance, discuss with an expert

3.3 LIVER INJURY IN A PATIENT ON ART

Patient presents with symptoms/signs of liver injury (e.g. nausea, vomiting, abdominal pain, malaise, anorexia, right upper quadrant tenderness, jaundice) on ART

Do ALT and total bilirubin. If patient is on ATV/r, also measure unconjugated bilirubin
If jaundiced and/or ALT and total bilirubin cannot be obtained within 24 hours, STOP ALL TREATMENT and refer to higher level of care immediately

Does the patient have:
- **symptoms/signs of liver injury and ALT > 120 IU/L; OR**
- **ALT > 120 IU/L and total serum bilirubin > 40 µmol/L?**

Yes

THIS IS A LIVER INJURY THAT REQUIRES CESSATION OF DRUGS

- **Admit patient to hospital**
- **STOP ART and other hepatotoxic drugs e.g. co-trimoxazole, fluconazole, amoxicillin-clavulanic acid**
- **Do INR and full liver function tests to identify liver enzyme pattern**
- **Monitor blood glucose regularly**
- **Test for viral hepatitis. Do hepatitis A IgM, hepatitis B surface antigen and core IgM antibody, and hepatitis C antibody**
- **Exclude pregnancy**

CONSIDER OTHER CAUSES OF LIVER DYSFUNCTION

Hepatocellular pattern of injury:
1. Hepatitis A, hepatitis B, hepatitis C
2. Herpes simplex virus infection

If unsure about findings discuss with an expert or call the hotline (0800 212 506)

Cholestatic and Mixed pattern of injury:
1. Obstructive causes e.g. lymphoma, disseminated TB with obstruction, extra-hepatic biliary obstruction
2. Sepsis
3. HIV cholangiopathy
4. Immune reconstitution inflammatory syndrome (IRIS)
5. Chronic alcohol abuse

Perform an abdominal ultrasound to exclude obstructive causes

Follow-up monitoring: Repeat ALT and bilirubin every 3 days, monitor INR if baseline > 1.5

Has ALT decreased to < 100 IU/L and is bilirubin on a downward trend?

Yes

Start new ART regimen if previous ART was considered to be the cause of the DILI
1. Do not rechallenge with offending drug (i.e. EFV, DTG or LPV/r)
2. If on EFV, change to DTG
3. If on TLD1, change DTG to LPV/r or ATV/r
4. If on TLD2, discuss with hotline
5. If on LPV/r, ATV/r or DRV/r, discuss with hotline

No

Discuss the patient with an expert or call the hotline (0800 212 506).

Asymptomatic patient presents with elevated ALT or isolated unconjugated hyperbilirubinemia

Is ALT > 200?

Yes

No

THIS IS A POTENTIAL LIVER INJURY REQUIRING CLOSE MONITORING

- Monitor for jaundice and other symptoms/signs of suspected DILI
- If asymptomatic, ALT < 120 IU/L and total bilirubin <40 µmol/L: Continue ART
- If asymptomatic, ALT > 120 IU/L but < 200 IU/L: Continue ART, monitor weekly
- If symptomatic, ALT < 120 IU/L and total bilirubin <40 µmol/L: Continue ART, monitor ALT weekly
- If isolated unconjugated hyperbilirubinemia due to atazanavir, continue treatment

Follow-up monitoring: Is ALT improving?

Yes

- Stop laboratory monitoring
- Review the patient in 1 month
- Advise the patient to return to the clinic if any symptoms/signs of liver injury develop

No

If ALT continues to increase or is unchanged: Monitor ALT and bilirubin weekly for 4 consecutive weeks

If ALT increases to > 200 IU/L or bilirubin increases to > 40 µmol/L or patient becomes symptomatic, manage as a DILI

If on treatment for cryptococcal meningitis or TB, rechallenge fluconazole or TB treatment before rechallenging ART

LIVER INJURY IN A PATIENT ON ART

Frequency of DILI on ART

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) can cause DILI[1,2]. It is more common with efavirenz than rilpivirine[3]. LPV/r, ATV/r, DRV/r and dolutegravir can also rarely cause DILI[4].The nucleoside reverse transcriptase inhibitors (NRTIs) used in the South African public sector (abacavir, emtricitabine, lamivudine, tenofovir and zidovudine) do not cause DILI. Abacavir hypersensitivity may lead to deranged LFTs[4].

Onset of DILI

Efavirenz may cause DILI any time during the course of ART (usually 3-6 months after initiation) and is not typically associated with rash or other features of a hypersensitivity reaction. LFTs can take several months to normalise. Data on dolutegravir is scarce, but it seems to cause a hepatocellular DILI from 1-8 months after initiation without immunoallergic features[4]. Protease inhibitors can cause idiosyncratic DILI usually within 8 weeks of initiation with variable patterns of liver enzyme elevation. Atazanavir can cause reversible, benign unconjugated hyperbilirubinemia without affecting other LFTs; this is not of clinical significance[5].

Risk factors for DILI

Risk factors for DILI in patients on ART include female sex, hepatitis B or C co-infection, concomitant hepatotoxic drugs used to treat opportunistic infections (e.g. co-trimoxazole, fluconazole, TB drugs) and abnormal baseline liver function tests[1,2,4].

Prognosis of DILI

Jaundice in a patient with hepatocellular injury indicates severe liver injury, with a 10 % chance of developing fulminant liver failure (jaundice with encephalopathy and/or coagulopathy)[6].

References

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National HIV & TB Health Care Worker Hotline

This is a free service for all health care workers

What questions can you ask?

The National HIV & TB Health Care Worker Hotline provides information on queries relating to:

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- Management of HIV in pregnancy
- PMTCT
- Drug interactions
- Treatment/prophylaxis of opportunistic infections
- Drug availability
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- Management of DS and DR tuberculosis
- Antiretroviral Therapy (ART):
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