NATIONAL HIV & TB HEALTH CARE WORKER HOTLINE

0800 212 506

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

July 2020

2nd Edition

MEDICINES INFORMATION CENTRE

DIVISION OF CLINICAL PHARMACOLOGY

UNIVERSITY OF CAPE TOWN

First edition 2018, Second edition 2020

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 / send an SMS or "Please call me" to 071 840 1572.

Produced by:
National HIV and TB HCW Hotline
The Medicines Information Centre
Division of Clinical Pharmacology
Faculty of Health Sciences
University of Cape Town
www.mic.uct.ac.za

Authored by:
Christine Njuguna
Dr Hannah Gunter

First edition edited by:
Annoesjka M Swart
Anri Uys
Associate Prof Karen Cohen

Second edition edited by:
Annoesjka M Swart
Jackie Jones

Comments and contributions (first edition):
Prof Wendy Spearman
Prof Gary Maartens
Prof Graeme Meintjes
Dr Rannakoe Lehloenya
Prof Marc Blockman
Dr Dean Solomons
Dr Ashraf Grimwood
Dr Dawn Rossiter

Comments and contributions (second edition)
Prof Gary Maartens
Associate Prof Karen Cohen
Dr Hannah Gunter
Briony Chisholm
Vivian Raath
Ewan Tommy
Anri Uys

This publication was supported under funding provided by the Global Fund to Fight AIDS, Tuberculosis and Malaria through the National Department of Health of South Africa and the NDoH Pharmacovigilance Centre for Public Health Programmes. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Global Fund or the National Department of Health of South Africa.

Table of Contents

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. If treatment is recommended in hospital, patients should be admitted to hospital urgently.
4. 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.
5. If uncertain about the management of any of the adverse drug reactions, kindly seek expert advice or call the HIV hotline on 0800 212 506.

1.1 RASH IN A PATIENT ON EFAVIRENZ OR NEVIRAPINE

Patient who is taking efavirenz or nevirapine develops a rash*

Did the rash appear after starting antiretroviral therapy (ART)?

Yes

- Take an accurate drug **history**
- **STOP** any other non-essential drugs
- **Assess rash severity**. Does the patient have any one of the following:
  - Systemic illness/feeling unwell
  - Fever
  - Hepatitis (check ALT if on nevirapine)
  - Skin blistering
  - Mucosal involvement (eyes, mouth, genitalia)

No

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

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, develops other symptoms or no improvement.

Yes

This is a severe skin reaction!

- STOP ALL drugs including ART and co-trimoxazole immediately
- If on nevirapine, do ALT
- Wait for rash and other symptoms/signs to settle

Has rash and other symptoms settled?

Yes

Restart the patient on ART as follows:

- **Do not rechallenge with efavirenz or nevirapine**
- **Switch the nevirapine/efavirenz to a protease inhibitor (lopinavir/ritonavir) or an integrase inhibitor (dolutegravir)**

No

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

CO-TRIMOXAZOLE RECHALLENGE

(see section 1.6)

NEVER rechallenge co-trimoxazole if patient had a life-threatening skin reaction. For such cases, discuss with an expert or call the hotline (0800 212 506).

If patient was on **co-trimoxazole**, consider co-trimoxazole rechallenge as follows:

For primary prophylaxis

Do not rechallenge co-trimoxazole. Dapsone may be used unless skin reaction was life-threatening [Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), erythema multiforme, drug reaction with eosinophilia and systemic symptoms (DRESS)].

For secondary prophylaxis

Once rash settles, consider co-trimoxazole desensitisation if:

1. Patient is being treated for pneumocystis pneumonia or toxoplasmosis
2. Patient has prior history of pneumocystis pneumonia (secondary prophylaxis) and current CD4 count < 200 cells/µL

Discuss with an expert or call the hotline if considering co-trimoxazole desensitisation.

***Please note: The above algorithm does not include guidance for patients who are also on abacavir or dolutegravir**. Patients on abacavir who present with a rash and other symptoms (e.g. fever, GIT symptoms, general malaise or respiratory symptoms) may have an abacavir hypersensitivity reaction. Hypersensitivity reactions have also been described in patients taking dolutegravir. Please consult with the hotline (0800 212 506) in these cases or see section on abacavir hypersensitivity (1.5) for diagnosis and management.

RASH IN PATIENT TAKING EFAVIRENZ OR NEVIRAPINE

Incidence and presentation of efavirenz/nevirapine drug-induced rash

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine are the most common drug cause of rashes in patients taking first-line antiretroviral therapy (ART). NNRTI-associated rash occurs in 10-17% of patients within 3 to 18 weeks of starting the NNRTI[1,2] and most are mild. Severe reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme occur more frequently with nevirapine (0.3-1%) than efavirenz (0.1%)[1].

The presentation of an NNRTI-induced rash ranges from a mild macular, maculopapular or erythematous rash to a severe rash with blistering, moist desquamation and ulceration[1]. Efavirenz-induced rash is often maculopapular, photo-distributed and has non-tender palmar erythema.

Nevirapine hypersensitivity reaction

Nevirapine-associated hypersensitivity reaction is an immune-mediated reaction with rash and hepatotoxicity. It typically occurs within the first six weeks of therapy. Approximately half of patients presenting with hepatitis on nevirapine have an accompanying rash[3]. Therefore, all patients presenting with a rash on nevirapine need to have their ALT checked.

RASH IN 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[4].

References

[1] Chaponda, M, et al. Hypersensitivity reactions to HIV therapy. British Journal of Clinical Pharmacology. 2011. 71(5): 659-671.
[2] Luther, J, et al. Dermatologic adverse effects of antiretroviral therapy. American Journal of Clinical Dermatology. 2007. 8(4): 221-233.
[3] Intracaso, CE, et al. Cutaneous toxicities of antiretroviral therapy for HIV. Journal of American Academy of Dermatology. 2010. 63(4):563-569.
[4] Cada, DJ et al. Formulary drug reviews: Dolutegravir. Hospital pharmacy. 2014; 49(2): 184-195.

1.2 RASH IN A PATIENT ON TB TREATMENT

Patient presents with rash while taking first-line TB treatment, with or without ART

Did the rash appear after starting TB treatment?

Yes

- Take an accurate drug **history**
- **STOP** any other non-essential drugs
- **Assess rash severity.** Does the patient have any one of the following:
  - Systemic illness/feeling unwell
  - Fever
  - Hepatitis
  - Skin blistering
  - Eosinophilia (raised eosinophil count)
  - Mucosal involvement (eyes, mouth, genitalia)

No

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

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 or no improvement.

Yes

This is a severe skin reaction!

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

Has rash and other symptoms settled?

Yes

Start TB background regimen:
Levofloxacin (15-20mg/kg daily, max 1000mg) + linezolid (600mg daily) + terizidone (10-15mg/kg, max 750mg). Avoid linezolid if Hb<8. If any of the above are contra-indicated/unavailable, substitute with amikacin (15mg/kg daily, IV/IM). Avoid amikacin if eGFR < 60 mL/min or INR raised. If levofloxacin not available moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a higher risk of QT interval prolongation. Monitor patient for at least 1 week.

No

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

Did the patient develop rash on TB background therapy?

Yes

No

Consider rechallenge of TB treatment (see algorithm 1.3) after confirming TB diagnosis and checking that TB is drug susceptible.

CO-TRIMOXAZOLE RECHALLENGE

(see section 1.6)

NEVER rechallenge co-trimoxazole if patient had a life-threatening skin reaction. For such cases, discuss with an expert or call the hotline (0800 212 506).

If patient was on **co-trimoxazole**, consider co-trimoxazole rechallenge as follows:

For primary prophylaxis

Do not rechallenge co-trimoxazole. Dapsone may be used unless skin reaction was life-threatening [Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), erythema multiforme, drug reaction with eosinophilia and systemic symptoms (DRESS)].

For secondary prophylaxis

Once rash settles, consider co-trimoxazole desensitisation if:

1. Patient is being treated for pneumocystis pneumonia or toxoplasmosis
2. Patient has prior history of pneumocystis pneumonia (secondary prophylaxis) and current CD4 count < 200 cells/µL

Discuss with an expert or call the hotline if considering co-trimoxazole desensitisation.

Consider restarting ART once TB treatment has been successfully rechallenged. See flowchart 1.1

RASH IN A PATIENT TAKING 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

Generally the majority of morbiliform/maculopapular skin reaction cases are self-limiting and can be managed symptomatically with oral antihistamines. However, a small percentage may progress into 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, DRESS or TEN require admission to hospital for management. Stop TB treatment and other drugs that may be implicated (e.g. antiretroviral therapy, co-trimoxazole). Always rechallenge TB treatment with close monitoring and as an inpatient.

Background TB therapy

Start TB background regimen to avoid development of resistance: Levofloxacin (15-20mg/kg daily, max 1000mg) + linezolid (600mg daily) + terizidone (10-15mg/kg, max 750mg). Avoid linezolid if Hb<8. If any of the above are contra-indicated/unavailable, substitute with amikacin (15mg/kg daily, IV/IM). Avoid amikacin if eGFR < 60 mL/min or INR raised. If levofloxacin not available moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a higher risk of 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.
[2] Kuaban, C, et al. HIV seroprevalence rate and incidence of adverse skin reactions in adults with pulmonary tuberculosis receiving thiacetazone free anti-tuberculosis treatment in Yaounde, Cameroon. East African Medical Journal. 1997. 74(8): 474-477.
[3] Tan, WC, et al. Two years review of cutaneous adverse drug reaction from first-line anti-tuberculosis drugs. Medical Journal of Malaysia. 2007. 62(2): 143-146.
[4] Lehloenya, RJ, et al. Multiple drug hypersensitivity reactions to anti-tuberculosis drugs: five cases in HIV-infected patients. The International Journal of Tuberculosis and Lung Diseases. 2012. 16(9): 1260-1264.

1.3 TB DRUG 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 means 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:
Levofloxacin (15-20mg/kg daily, max 1000mg) + linezolid (600mg daily) + terizidone (10-15mg/kg, max 750mg). Avoid linezolid if Hb<8. If any of the above are contra-indicated/unavailable, substitute with amikacin (15mg/kg daily, IV/IM). Avoid amikacin if eGFR < 60 mL/min or INR raised. If levofloxacin not available moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a higher risk of QT interval prolongation.

Rechallenge TB treatment in hospital. During rechallenge, evaluate the patient for rash, fever and symptoms and signs of anaphylaxis daily. Discontinue the drug(s) immediately if the patient starts to develop a new rash, even if the rash is mild. Monitor ALT and creatinine 3 times a week. If baseline creatinine abnormal, monitor creatinine more frequently. Monitor eosinophil count frequently if raised.

Rechallenge Schedule
Day 1: Rifampicin 75 mg daily
Day 2: Rifampicin 300 mg daily
Day 3: Rifampicin 600 mg daily, if < 60 kg, rifampicin 450 mg daily
Day 5: Isoniazid 50 mg daily
Day 6: Isoniazid 100 mg daily
Day 7: Isoniazid 300 mg daily
Day 9: 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:
Levofloxacin (15-20mg/kg daily, max 1000mg) + linezolid (600mg daily) + terizidone (10-15mg/kg, max 750mg). Avoid linezolid if Hb<8. If any of the above are contra-indicated/unavailable, substitute with amikacin (15mg/kg daily, IV/IM). Avoid amikacin if eGFR < 60 mL/min or INR raised. If levofloxacin not available moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a higher risk of QT interval prolongation.

Rechallenge TB treatment in hospital. During rechallenge, evaluate the patient for rash, fever and symptoms and signs of anaphylaxis daily. Discontinue the drug(s) immediately if the patient starts to develop a new rash, even if the rash is mild. Monitor ALT and creatinine 3 times a week. If baseline creatinine is abnormal, monitor creatinine more frequently. Monitor eosinophil count frequently if raised.

Rechallenge Schedule
Day 1: Rifampicin 75 mg daily
Day 2: Rifampicin 300 mg daily
Day 3: Rifampicin 600 mg daily. If < 60 kg, rifampicin 450 mg daily
Day 5: 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 (Rifinah®). **Continue for 4 months in total**.

TB TREATMENT-INDUCED RASH RECHALLENGE

Do not rechallenge pyrazinamide if the patient presented with a rash with life-threatening hepatitis (transaminitis with total bilirubin > 34 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.

If TB drug rechallenge is tolerated, complete TB therapy with duration as per standard treatment guidelines. In determining the length of treatment required, **take into account the period completed before the reaction occurred.**

If rechallenge is not tolerated, discuss with an expert or call the HIV/ TB hotline (0800 212 506).

1.4 MODIFYING TB TREATMENT REGIMEN

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

RIFAMPICIN not tolerated

↓

STOP rifampicin and substitute with rifabutin

Continue rifabutin, isoniazid, pyrazinamide, ethambutol for **2 months**, then rifabutin and isoniazid for **4 months**

ISONIAZID not tolerated

↓

STOP isoniazid

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

PYRAZINAMIDE not tolerated

↓

STOP pyrazinamide

Continue rifampicin, isoniazid* and ethambutol for **9 months**

*Try to confirm isoniazid susceptibility. 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 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 ABACAVIR HYPERSENSITIVITY REACTION

Incidence and presentation of abacavir hypersensitivity reaction

The incidence of the abacavir hypersensitivity reaction is approximately 4.3%[1]. It usually occurs within the first six weeks of therapy[2]. However, it may also occur at any time during abacavir therapy[3]. It is a multi-organ syndrome and consists of two or more of the following symptoms[4]:

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

The majority (98%) of patients have fever and/or rash as part of the hypersensitivity reaction[3,4]. The rash generally presents as maculopapular or urticarial, but erythema multiforme has also been reported[4]. The symptoms worsen with continued therapy and may be life-threatening[4].

Other less common symptoms and signs of abacavir hypersensitivity reaction include: lethargy, oedema, abnormal chest x-ray, and paraesthesia[4].

Outcomes associated with abacavir hypersensitivity reaction include: anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death[4].

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[2]. 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[3]. 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[2]. Once rash and other symptoms/signs have settled, substitute with an alternative antiretroviral drug, e.g. tenofovir or zidovudine.

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.

References

[1] Hetherington,S, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. Clinical Therapeutics. 2002. 24 (4): 565-573.
[2] Luther, J, et al. Dermatologic adverse effects of antiretroviral therapy. American Journal of Clinical Dermatology. 2007. 8(4):221-233.
[3] Kivexa® [package insert]. GlaxoSmithKline. Bryanston, South Africa; 2005.
[4] Abacavir. In: DRUGDEX® System (electronic version 2017). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/ (cited: *06/*02/2017).

1.6 CO-TRIMOXAZOLE RECHALLENGE OR REPLACEMENT

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, should be switched to dapsone 100 mg po daily as an alternative[1].

Do not start dapsone for primary prophylaxis if the CD4 count is > 200 cells/µL.

If the skin reaction was life-threatening (e.g. Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms), do not substitute with dapsone. There is a risk of cross-reactivity between co-trimoxazole and dapsone[1].

Secondary prophylaxis/maintenance treatment after pneumocystis pneumonia

If the patient was taking co-trimoxazole as secondary prophylaxis (maintenance therapy) after pneumocystis pneumonia, commence dapsone in place of co-trimoxazole.

Consider co-trimoxazole rechallenge for the following indications:

1. Previous history of pneumocystis pneumonia with current CD4 count < 200 cells/µL[1],
2. Use of co-trimoxazole to treat severe acute infections such as pneumocystis pneumonia or toxoplasmosis[1].

If the reaction was life-threatening, discuss with an expert or call the HIV hotline.

Secondary prophylaxis/maintenance treatment after toxoplasmosis

If patient was taking co-trimoxazole as secondary prophylaxis (maintenance therapy) 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 using the slow desensitization protocol

If the reaction was life-threatening, discuss with an expert or call the HIV hotline.

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.

If the reaction was life-threatening, discuss with an expert or call the HIV hotline.

Rapid co-trimoxazole desensitisation 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 desensitisation.

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 distilled 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 distilled water[5].

Time	Dose of diluted co-trimoxazole suspension	Dose in mLs of undiluted co-trimoxazole suspension
Time 0	Administer 5 mL orally of mixture B. (Discard balance of mixture B)	0.0005 (trimethoprim 0.004 mg/sulfamethoxazole 0.02 mg)
Time 1 hour	Administer 5 mL orally of mixture A (after shaking well)	0.005 (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)	0.05 (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	0.5 (trimethoprim 4 mg/sulfamethoxazole 20 mg)
Time 4 hours	Administer 5 mL orally of undiluted co-trimoxazole suspension	5 (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.

References

[1] Maartens, G, Meintjes, G, Mendelson, M, Cotton, M, Rabie, H. Aid For AIDS Clinical Guidelines. 11th edition. Cape Town: AFA; 2016.
[2] Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available online: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf Accessed 9 June 2017.
[3] Katlama C, et al. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. Clinical Infectious Diseases 1996; 22:268.
[4] National Department of Health. Essential drugs programme. Hospital level (Adults) standard treatment guidelines and essential medicines list. 4th edition. Republic of South Africa: National Department of Health;
[5] National Health Laboratory Service. Western Cape academic hospitals antimicrobial recommendations and wound Care. 2012.

2. 1 KIDNEY INJURY IN A PATIENT TAKING TENOFOVIR

Patient presents with eGFR < 50 mL/min on tenofovir-based antiretroviral therapy (ART) regimen.

STOP TENOFOVIR immediately and switch to abacavir. If abacavir is contraindicated, then switch to zidovudine if haemoglobin > 8 g/dL.

Check if any drugs need renal dose adjustment. For dose adjustment of ART see Renal Adjustment of Antiretroviral Doses Table (2.2).
If unsure about dose adjustment of other drugs, discuss with an expert or call the hotline at 0800 212 506.

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

Is there a concomitant cause for the kidney injury e.g. acute/chronic gastroenteritis, dehydration, sepsis?

Yes

- **Continue abacavir/zidovudine**
- **Do a blood gas to check for acidosis and electrolyte abnormalities**
- **Rehydrate (obtain IV access, if required) and monitor urine output**
- **Do urine dipstick to check for proteinuria. If proteinuria 1+ or more, discuss with an expert or call the hotline (0800 212 506) for further assistance**
- **Treat the underlying condition**
- **Monitor renal function regularly according to clinical condition**

Has underlying condition resolved and eGFR > 50 mL/min?

Yes

Stop abacavir/zidovudine. Recommence tenofovir. Repeat eGFR at 1 month. If eGFR at 1 month > 50mL/min, continue routine eGFR monitoring.

No

Continue abacavir/zidovudine. Discuss with an expert or call 0800 212 506 for further assistance.

No

- **Continue abacavir/zidovudine**
- **Do monthly eGFR monitoring and urine dipstick**
- **Do urine protein:creatinine ratio**
- **If 1+ proteinuria or urine protein:creatinine ratio > 0.1, discuss with an expert or call the hotline (0800 212 506) for further assistance**
- **Consider other causes of kidney injury e.g. HIVAN, opportunistic infections, malignancies, Hepatitis B**
- **Consider non-HIV related causes e.g. diabetes, hypertension, atherosclerosis**

Has renal function improved?

Yes

Continue abacavir/zidovudine.

No

Continue abacavir/zidovudine. Discuss with an expert or call 0800 212 506 for further assistance.

KIDNEY INJURY ON TENOFOVIR

Presentation of tenofovir-induced kidney injury

Tenofovir may cause[1]:

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

Incidence of tenofovir-induced kidney injury

Treatment-limiting renal disease due to tenofovir 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 tenofovir-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 tenofovir was 1.84% over 12 months[3].

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

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

Monitoring for tenofovir-induced kidney injury

Kidney injury can occur any time during tenofovir therapy. Therefore, monitoring of eGFR is recommended at baseline, 3 months, 6 months, 12 months and yearly thereafter[5].
To minimise kidney injury, tenofovir 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 tenofovir

If eGFR drops to below 50 mL/min, stop tenofovir 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, HIV-associated nephropathy (HIVAN), opportunistic infections and sepsis. Patients should always be referred to a higher level of care if renal function does not improve within 1 month or worsens despite stopping tenofovir.

References

[1] Yombi, JC, et al. Antiretrovirals and the kidney in current clinical practice: renal pharmacokinetics, alterations of renal function and renal toxicity. AIDS. 2014. 28:621-632.
[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.
[3] Mulenga, L, et al. Effect of baseline renal function on tenofovir-containing antiretroviral therapy outcomes in Zambia. Clinical Infectious Diseases. 2014. 58(10):1473-1480.
[4] Fernandez, B, et al. Tenofovir nephrotoxicity: 2011 Update. AIDS Research and Treatment. 2011. 354908. doi:10.1155/2011/354908.
[5] National Department of Health. 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates. Available from: https://www.knowledgehub.org.za/elibrary/2019-art-clinical-guidelines-management-hiv-adults-pregnancy-adolescents-children-infants. Accessed 23 July 2019.
[6] Word Health Organization. Consolidated ARV guidelines. 2nd Edition. June 2016. Available from http://www.who.int/hiv/pub/arv/arv-2016/en/ Accessed 23 August 2016.
[7] Black, J, et al. Adult anti-retroviral therapy guidelines 2014. South African Journal of HIV Medicine. 2014. 15(4):121-143

2.2 RENAL ADJUSTMENT OF ANTIRETROVIRAL DOSES

Drug	Standard adult dose	eGFR 10-49 mL/min	eGFR < 10 mL/min
Abacavir	600 mg daily OR 300 mg 12 hourly	Unchanged	Unchanged
Atazanavir/ritonavir	300 mg/100 mg daily	Unchanged	Unchanged
Darunavir/ritonavir	600 mg/100 mg 12 hourly OR 800 mg/ 100 mg daily (depending on mutations)	Unchanged	Unchanged
Dolutegravir	50 mg daily	Unchanged	Unchanged
Efavirenz	600 mg nocte (or 400 mg if < 40 kg)	Unchanged	Unchanged
Etravirine	200 mg 12 hourly	Unchanged	Unchanged
Lamivudine	300 mg daily OR 150 mg 12 hourly	150 mg daily	50 mg daily
Lopinavir/ritonavir	400 mg/100 mg 12 hourly	Unchanged	Unchanged
Nevirapine	200 mg 12 hourly	Unchanged	Unchanged
Raltegravir	400 mg 12 hourly	Unchanged	Unchanged
Rilpivirine	25 mg daily	Unchanged	Unchanged
Stavudine	30 mg 12 hourly	15 mg 12 hourly	15 mg daily
Tenofovir	300 mg daily	Avoid	Avoid
Zidovudine	300 mg 12 hourly	Unchanged	300 mg daily

Table: ART dose adjustment in renal impairment (Doses obtained from Aid for AIDS Clinical Guideline. 2016. 11th ed. p.99)

3.1 PATTERNS OF DRUG-INDUCED LIVER INJURY (DILI)

Hepatic adaptation

Exposure to drugs may induce a physiologic, adaptive response in the liver, known as hepatic adaptation[1]. Adaptation causes low-grade, transient, asymptomatic transaminase elevation[1]. Hepatic adaptation should be distinguished from a symptomatic drug-induced liver injury (DILI) which frequently has more marked transaminitis and requires drug cessation.

To determine the pattern of DILI, calculate the following ratio:

$$Ratio = \frac{(\frac{ALT}{ULN})}{(\frac{ALP}{ULN})}$$

ALT = serum alanine aminotransferase
ALP = serum alkaline phosphatase
ULN = upper limit of normal

Hepatocellular DILI

- In hepatocellular DILI, ALT is disproportionately elevated compared to the elevation of ALP:
    - ALT ≥ 3 times ULN with Ratio ≥ 5
    - Hepatocellular DILI may either be asymptomatic or symptomatic. Symptoms and signs may include fatigue, anorexia, nausea, vomiting, abdominal pain or sign of right upper quadrant tenderness
- Examples of drugs that may cause hepatocellular-pattern liver injury: isoniazid, pyrazinamide, nevirapine, efavirenz, paracetamol (chronic use/overdose)
- Other causes of hepatocellular-pattern liver injury include acute viral hepatitis, chronic hepatitis B and C, IRIS (immune reconstitution inflammatory syndrome)
- Hepatocellular DILI usually occurs within the first 2 to 12 weeks of drug exposure but may occur at any time of drug exposure[2]
- Efavirenz-associated and INH-associated DILI may occur up to a year after drug initiation
- Generally, hepatocellular DILI resolves within 2 to 4 weeks of stopping the causative drug[2]

Cholestatic DILI

- In cholestatic DILI, ALP is disproportionately elevated compared to ALT:
    - ALP ≥ 2 times ULN with Ratio ≤ 2
- Cholestatic DILI may result in a conjugated hyperbilirubinemia
- Typical symptoms and signs of cholestatic DILI include nausea, fatigue, pruritus, dark urine and jaundice
- Examples of drugs that may cause cholestatic-pattern liver injury: rifampicin, amoxicillin-clavulanic acid, cephalosporins, sulfonylureas

- 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
- Purely cholestatic DILI is rarely caused by TB treatment or antiretrovirals

Mixed DILI

- Moderate to marked elevations in both ALT and ALP[2]:
    - ALT ≥ 3 times ULN and ALP ≥ 2 times ULN with Ratio > 2 to < 5
- In mixed DILI, there are features of both hepatocellular and cholestatic DILI
- Onset of mixed DILI is typically within 2 to 12 weeks of drug initiation but may occur at any time during drug exposure[2]
- The presenting symptoms and signs may include fatigue, anorexia and nausea followed by jaundice and often pruritus[2]
- Examples of drugs that cause mixed-pattern liver injury: rifampicin, efavirenz, anti-convulsants (phenytoin, carbamazepine, and lamotrigine), non-steroidal anti-inflammatory drugs (NSAIDs), co-trimoxazole, amoxicillin-clavulanic acid, flucloxacillin, fluconazole
- Mixed DILI resolves more slowly than a purely hepatocellular DILI
- Elevated enzyme concentrations should drop by 50 % within 4 to 12 weeks[2]
- IRIS may present with mixed-pattern liver injury

References

[1] Saukkonen, JJ, et al. An Official ATS Statement: Hepatotoxicity of anti-tuberculosis therapy. American journal of respiratory and critical care medicine. 2006. 174: 935-952.
[2] United States. National Library of Medicine. Livertox. Clinical and research information on drug-induced liver injury. Available from: http://www.livertox.nih.gov/Phenotypes_intro.html. Accessed: 31 Aug 2016.

3.2.1 LIVER INJURY IN A PATIENT ON TB TREATMENT AND ART

Patient presents with symptoms/signs of hepatitis (e.g. nausea, vomiting, abdominal pain, malaise, anorexia, right upper quadrant tenderness, jaundice) on antiretroviral therapy (ART) and first-line TB drugs (rifampicin, isoniazid, pyrazinamide, ethambutol)

Asymptomatic patient with ALT > 200 IU/L

Yes

Do ALT and total 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 any of the following in addition to symptoms/signs of hepatitis: ALT > 100 IU/L OR total serum bilirubin > 34 µmol/L?

Yes

No

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 full liver function test to identify liver enzyme pattern**
- **Calculate ratio (R): ALT/upper limit of normal (ULN) divided by ALP/ULN**

Hepatocellular liver enzyme pattern: ALT ≥ 3 times ULN, R ≥ 5

Cholestatic liver enzyme pattern: ALP ≥ 2 times ULN, R ≤ 2

Mixed liver enzyme pattern: ALT ≥ 3 times ULN, ALP ≥2 times ULN, R > 2 but < 5

IN HOSPITAL

Do INR and blood glucose and start **TB background regimen** as follows: Levofloxacin (15-20mg/kg daily, max 1000mg) + ethambutol (800-1200mg daily) + linezolid (600mg daily). Avoid linezolid if Hb<8. Terizidone (10-15mg/kg daily, max 750mg) and amikacin (15mg/kg daily, IV/IM) are also options if any of the above are contra-indicated/unavailable. Avoid amikacin if eGFR < 60 mL/min or INR raised. If levofloxacin not available moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a higher risk of QT interval prolongation.

If patient has TB meningitis, please call the hotline (0800 212 506) for assistance

EXCLUDE OTHER CAUSES OF LIVER DYSFUNCTION

Hepatocellular:

1. Hepatitis A IgM, hepatitis B surface antigen, hepatitis B core IgM antibody, hepatitis C antibody
2. Herpes simplex virus PCR
3. Immune reconstitution inflammatory syndrome (IRIS)

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

Cholestatic and Mixed:

1. Perform an abdominal ultrasound to exclude obstructive causes of liver dysfunction e.g. lymphoma, disseminated TB with obstruction, extra-hepatic obstruction
2. Sepsis as a contributing factor
3. HIV cholangiopathy
4. IRIS

For mixed pattern also exclude alcohol abuse

Follow-up monitoring: Repeat ALT and bilirubin every 2-3 days, monitor INR if baseline > 1.5

Has ALT decreased to < 100 IU/L, bilirubin and INR normalised?

Yes

- Consider rechallenge of TB drugs after excluding other causes of liver dysfunction and confirmation of TB diagnosis (Algorithm 3.2.2)
- DO NOT rechallenge TB treatment if patient had acute liver failure (jaundice with encephalopathy and/or coagulopathy); consult expert

No

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

THIS IS A POTENTIAL DILI REQUIRING CLOSE MONITORING

- If patient is asymptomatic, ALT < 100 IU/L but > 40 IU/L and total bilirubin < 34 µmol/L: Continue ART and TB treatment (if TB confirmed)
- If ALT is > 100 IU/L but < 200 IU/L, monitor weekly
- Monitor for jaundice and other symptoms/signs of DILI

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 hepatitis 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 > 34 µmol/L or patient becomes symptomatic, manage as a DILI

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

LIVER INJURY IN PATIENT ON TB TREATMENT AND ANTIRETROVIRAL THERAPY (ART)

DILI complicates first-line TB treatment in 1% of patients. The first-line antituberculosis drugs isoniazid, rifampicin and pyrazinamide can cause drug-induced liver injury (DILI). Ethambutol does not cause DILI.

DILI occurs more commonly with nevirapine than efavirenz[1]. Lopinavir/ritonavir and dolutegravir can also rarely cause DILI[6]. Abacavir, tenofovir, emtricitabine and lamivudine do not cause DILI.

Risk factors for DILI in patients taking TB treatment and ART[1,2]:

- Age > 35 years
- Female sex
- Pregnancy
- Hepatitis B/C co-infection
- Slow acetylator status (isoniazid-induced DILI)
- Malnutrition

Management of DILI in patients taking TB treatment and ART

Stop TB treatment and other hepatotoxic drugs immediately if[3]:

1. ALT > 100 IU/L and patient symptomatic OR
2. ALT > 200 IU/L OR
3. Total bilirubin > 34 µmol/L

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)[4].

Initiate a TB background regimen consisting of levofloxacin (15-20mg/kg daily, max 1000mg) + ethambutol (800-1200mg daily) + linezolid (600mg daily) to prevent development of resistance. Avoid linezolid if Hb<8. Terizidone (10-15mg/kg daily, max 750mg) and amikacin (15mg/kg daily, IV/IM) are also options if any of the above are contra-indicated/unavailable. Avoid amikacin if eGFR < 60 mL/min or INR raised. If levofloxacin not available moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a higher risk of QT interval prolongation.

Take note: Complete TB drug rechallenge before restarting ART.

References

[1] Jain, MK. Drug-induced liver injury associated with HIV medications. Clinics in liver disease. 2007. 11 (3): 615-639.
[2] 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
[3] Jong, E, et al. Consensus statement: Management of drug-induced liver injury in HIV-positive patients treated for TB. Southern African Journal of HIV Medicine. 2013. 14(3): 113-119.
[4] Saukkonen, JJ, et al. An Official ATS Statement: Hepatotoxicity of anti-tuberculosis therapy. American journal of respiratory and critical care medicine. 2006. 174: 935-952.
[5] Maartens, G, Meintjes, G, Mendelson, M, Cotton, M, Rabie, H. Aid for AIDS Clinical Guidelines. 11th edition. Cape Town: AFA; 2016.
[6] Livertox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Available from https://www.ncbi.nlm.nih.gov/books/NBK547852/ Accessed 26 May 2020

3.2.2 TB DRUG RECHALLENGE AFTER DRUG-INDUCED LIVER INJURY ON TB TREATMENT AND ART

Before rechallenge, consider the following clinical question: Has the TB diagnosis been confirmed by either microbiological means 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 normal 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 coagulopathy). Patients with acute liver failure should be discussed with an expert or the hotline.

Is the patient on intensive phase of TB treatment?

Yes

Intensive phase, rechallenge as follows:

Continue background regimen: Levofloxacin (15-20mg/kg daily, max 1000mg) + ethambutol (800-1200mg daily) + linezolid (600mg daily). Avoid linezolid if Hb<8. Terizidone (10-15mg/kg daily, max 750mg) and amikacin (15mg/kg daily, IV/IM) are also options if any of the above are contra-indicated/unavailable. Avoid amikacin if eGFR < 60 mL/min or INR raised. If levofloxacin not available moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a higher risk of QT interval prolongation.

Day 1: Rifampicin 10mg/kg/day (max 600 mg daily)
Day 3: Check ALT
Day 4-6: If ALT < 100 IU/l, add isoniazid 5mg/kg/day (max 300 mg daily)
Day 7: Check ALT
Day 8: If ALT < 100 IU/l, consider pyrazinamide 25 mg/kg/day
Note: Consider pyrazinamide rechallenge in cases of severe forms of TB e.g. miliary TB or TB meningitis, resistance or intolerance to rifampicin and isoniazid.
Day 10: Check ALT. If ALT < 100 IU/l and pyrazinamide successfully rechallenged, re-start TB fixed dose combination (RHZE). If pyrazinamide not rechallenged, continue RHE

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).

No

Continuation phase, rechallenge as follows:

Continue background regimen: Levofloxacin (15-20mg/kg daily, max 1000mg) + ethambutol (800-1200mg daily) + linezolid (600mg daily). Avoid linezolid if Hb<8. Terizidone (10-15mg/kg daily, max 750mg) and amikacin (15mg/kg daily, IV/IM) are also options if any of the above are contra-indicated/unavailable. Avoid amikacin if eGFR < 60 mL/min or INR raised. If levofloxacin not available moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a higher risk of QT interval prolongation.

Day 1: Rifampicin 10mg/kg/day (max 600 mg daily)
Day 3: Check ALT
Day 4-6: If ALT < 100 IU/l, add isoniazid 5mg/kg/day (max 300 mg daily)
Day 7: Check ALT
Day 8: If ALT < 100 IU/l, continue rifampicin and isoniazid to complete the continuation phase

Stop TB background regimen.

Monitor ALT weekly for 4 weeks after rechallenge.

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

Rechallenge of TB drugs should only be attempted once ALT is < 100 IU/L and jaundice has resolved[1-3]. Do not rechallenge TB drugs if drug-induced liver injury (DILI) resulted in acute liver failure (jaundice with encephalopathy and/or coagulopathy)[2,3]. 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, provided frequent ALT monitoring is conducted[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 can cause severe DILI on rechallenge and should not be routinely rechallenged. 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. Rifampicin or isoniazid rechallenge fails[2]

If uncertain whether or not to attempt rechallenge with pyrazinamide, discuss with an expert or call the HIV hotline.

The length of TB treatment required after rechallenge, depends on how far into TB therapy the DILI occurred and on the outcome of rechallenge. 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] Jong, E, et al. Consensus statement: Management of drug-induced liver injury in HIV-positive patients treated for TB. Southern African Journal of HIV medicine. 2013. 14(3): 113-119.
[3] Maartens, G, Meintjes, G, Mendelson, M, Cotton, M, Rabie, H. Aid for AIDS Clinical Guidelines. 11th edition. Cape Town: AFA; 2016.

3.2.3 MODIFYING TB TREATMENT REGIMEN

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

RIFAMPICIN not tolerated

STOP rifampicin

Start shorter regimen for rifampicin resistant TB treatment with normal dose INH (total duration **9 months**).

Monitor ALT weekly for 4 weeks after rechallenge.

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

ISONIAZID not tolerated

STOP isoniazid

Pyrazinamide rechallenged successfully (if required for severe forms of TB):
Continue rifampicin, ethambutol, levofloxacin (preferred) / moxifloxacin and pyrazinamide for **6 -9 months.**
OR
Pyrazinamide not rechallenged:
Continue rifampicin, ethambutol and levofloxacin (preferred) / moxifloxacin for **9 - 12 months.**

Monitor ALT weekly for 4 weeks after rechallenge.

PYRAZINAMIDE not tolerated

STOP pyrazinamide

Continue rifampicin, isoniazid* and ethambutol for **9 months.**

Monitor ALT weekly for 4 weeks after rechallenge.

*Try to confirm isoniazid susceptibility.
If not susceptible, refer to expert or call the hotline.

PYRAZINAMIDE not rechallenged

Continue rifampicin, isoniazid* and ethambutol for **9 months**.

Monitor ALT weekly for 4 weeks after rechallenge.

*Try to confirm isoniazid susceptibility.
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 in the continuation phase, 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 coagulopathy). 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.

DILI developed on a nevirapine-based regimen

DO NOT rechallenge the patient with nevirapine.

If previously on nevirapine and life-threatening DILI (transaminitis with bilirubin > 34 µmol/L with encephalopathy and/or coagulopathy) commence a protease inhibitor or integrase inhibitor.

In less severe cases that were previously on nevirapine, commence efavirenz.

Monitor ALT every 2 weeks for 2 months.

DILI developed on efavirenz-based regimen

DO NOT rechallenge efavirenz, even with an asymptomatic DILI.

If previously on efavirenz, switch to a protease inhibitor or an integrase inhibitor.

Monitor ALT every 2 weeks for 2 months.

DILI developed with double dose lopinavir/ritonavir or double dose dolutegravir

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

3.3.1 LIVER INJURY IN A PATIENT ON TB TREATMENT

Asymptomatic patient with ALT > 200 IU/L

Yes

Patient presents with symptoms/signs of hepatitis (e.g. nausea, vomiting, abdominal pain, malaise, anorexia, right upper quadrant tenderness, jaundice) on first-line TB drugs

Do ALT and total 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 any of the following in addition to symptoms/signs of hepatitis: ALT > 100 IU/L OR total serum bilirubin > 34 µmol/L?

Yes

No

THIS IS A LIVER INJURY THAT REQUIRES CESSATION OF DRUGS

- **Admit patient to hospital**
- **STOP TB treatment and other hepatotoxic drugs e.g. co-trimoxazole, fluconazole, amoxicillin-clavulanic acid**
- **Do full liver function test to identify liver enzyme pattern**
- **Calculate ratio (R): ALT/upper limit of normal (ULN) divided by ALP/ULN**

Hepatocellular liver enzyme pattern: ALT ≥ 3 times ULN, R ≥ 5

Cholestatic liver enzyme pattern: ALP ≥ 2 times ULN, R ≤ 2

Mixed liver enzyme pattern: ALT ≥ 3 times ULN, ALP ≥2 times ULN. R > 2 but < 5

IN HOSPITAL

Do INR and blood glucose and start **TB background regimen** as follows: Levofloxacin (15-20mg/kg daily, max 1000mg) + ethambutol (800-1200mg daily) + linezolid (600mg daily). Avoid linezolid if Hb<8. Terizidone (10-15mg/kg daily, max 750mg) and amikacin (15mg/kg daily, IV/IM) are also options if any of the above are contra-indicated/unavailable. Avoid amikacin if eGFR < 60 mL/min or INR raised. If levofloxacin not available, moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a higher risk of QT interval prolongation.

If patient has TB meningitis, please call the hotline (0800 212 506) for assistance

EXCLUDE OTHER CAUSES OF LIVER DYSFUNCTION

Hepatocellular:

1. Hepatitis A IgM, hepatitis B surface antigen, hepatitis B core IgM antibody, hepatitis C antibody
2. Herpes simplex virus PCR
3. Immune reconstitution inflammatory syndrome (IRIS)

Cholestatic and Mixed:

1. Perform an abdominal ultrasound to exclude obstructive causes of liver dysfunction e.g. lymphoma, disseminated TB with obstruction, extra-hepatic obstruction
2. Sepsis as a contributing factor
3. HIV cholangiopathy
4. IRIS

For mixed pattern also exclude alcohol abuse

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

Follow-up monitoring: Repeat ALT and bilirubin every 2-3 days, monitor INR if baseline > 1.5

Has ALT decreased to < 100 IU/L, bilirubin and INR normalised?

Yes

- Consider rechallenge of TB drugs after excluding other causes of liver dysfunction and confirmation of TB diagnosis (Algorithm 3.3.2)
- DON'T rechallenge TB drugs if patient had acute liver failure (jaundice with encephalopathy and/or coagulopathy); consult expert

No

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

THIS IS A POTENTIAL DILI REQUIRING CLOSE MONITORING

- If patient is asymptomatic, ALT < 100 IU/L but > 40 IU/L and total bilirubin < 34 µmol/L: Continue TB treatment (if TB confirmed)
- If ALT is > 100 IU/L but < 200 IU/L, monitor weekly
- Monitor for jaundice and other symptoms/signs of DILI

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 hepatitis 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 > 34 µmol/L or patient becomes symptomatic, manage as a DILI

TB DRUG-INDUCED LIVER INJURY (DILI)

The first-line anti-tuberculosis drugs isoniazid, rifampicin and pyrazinamide can cause drug-induced liver injury (DILI). Ethambutol does not cause DILI. DILI complicates first-line TB treatment in 1 % of patients.

Risk factors for TB DILI[1,2]*:*

- Age > 35 years
- Female sex
- Pregnancy
- Hepatitis B/C co-infection
- Slow acetylator status (isoniazid-induced DILI)
- Malnutrition
- HIV co-Infection

Management of TB DILI

Stop TB treatment and other hepatotoxic drugs immediately if[3]:

1. ALT > 100 and patient symptomatic OR
2. ALT > 200 OR
3. Total bilirubin > 34 µmol/L

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)[4].

Initiate a TB background regimen consisting of levofloxacin (15-20mg/kg daily, max 1000mg) + ethambutol (800-1200mg daily) + linezolid (600mg daily) to prevent development of resistance. Avoid linezolid if Hb<8. Terizidone (10-15mg/kg daily, max 750mg) and amikacin (15mg/kg daily, IV/IM) are also options if any of the above are contra-indicated/unavailable. Avoid amikacin if eGFR < 60 mL/min or INR raised. If levofloxacin not available moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a higher risk of QT interval prolongation.

References

[1] Jain, MK. Drug-induced liver injury associated with HIV Medications. Clinics in liver disease. 2007. 11 (3): 615-639.
[2] 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.
[3] Jong, E, et al. Consensus statement: Management of drug-induced liver injury in HIV-positive patients treated for TB. Southern African Journal of HIV medicine. 2013. 14 (3): 113-119.
[4] Maartens, G, Meintjes, G, Mendelson, M, Cotton, M, Rabie, H. Aid for AIDS Clinical Guidelines. 11th edition. Cape Town: AFA; 2016.
[5] Saukkonen, JJ, et al. An Official ATS Statement: Hepatotoxicity of anti-tuberculosis therapy. American Journal of respiratory and critical care medicine. 2006. 174 (8): 935-952.

3.3.2 TB DRUG RECHALLENGE AFTER DRUG-INDUCED LIVER INJURY ON TB TREATMENT

Before rechallenge, consider the following clinical question: Has the TB diagnosis been confirmed by either microbiological means 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 normal 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 coagulopathy). Patients with acute liver failure should be discussed with an expert or the hotline.

Is the patient on intensive phase of TB treatment?

Yes

Intensive phase, rechallenge as follows:

Continue background regimen: Levofloxacin (15-20mg/kg daily, max 1000mg) + ethambutol (800-1200mg daily) + linezolid (600mg daily). Avoid linezolid if Hb<8. Terizidone (10-15mg/kg daily, max 750mg) and amikacin (15mg/kg daily, IV/IM) are also options if any of the above are contra-indicated/ unavailable. Avoid amikacin if eGFR < 60 mL/min or INR raised. If levofloxacin not available, moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a higher risk of QT interval prolongation

Day 1: Rifampicin 10mg/kg/day (max 600 mg daily)
Day 3: Check ALT
Day 4-6: If ALT < 100 IU/L, add isoniazid 5mg/kg/day (max 300 mg daily)
Day 7: Check ALT
Day 8: If ALT < 100 IU/L, consider pyrazinamide 25 mg/kg/day
Note: Consider pyrazinamide rechallenge in cases of severe forms of TB e.g. miliary TB or TB meningitis, resistance or intolerance to rifampicin and isoniazid.
Day 10: Check ALT. If ALT < 100 IU/L and pyrazinamide successfully rechallenged, re-start TB fixed dose combination (RHZE). If pyrazinamide not rechallenged, continue RHE

Stop TB background regimen. Monitor ALT weekly for 4 weeks after rechallenge.

No

Continuation phase, rechallenge as follows:

Continue background regimen: Levofloxacin (15-20mg/kg daily, max 1000mg) + ethambutol (800-1200mg daily) + linezolid (600mg daily). Avoid linezolid if Hb<8. Terizidone (10-15mg/kg daily, max 750mg) and amikacin (15mg/kg daily, IV/IM) are also options if any of the above are contra-indicated/unavailable. Avoid amikacin if eGFR < 60 mL/min or INR raised. If levofloxacin not available, moxifloxacin (400mg daily) can be used, but its concentrations are reduced by rifampicin and it has a higher risk of QT interval prolongation

Day 1: Rifampicin 10mg/kg/day (max 600 mg daily)
Day 3: Check ALT
Day 4-6: If ALT < 100 IU/L, add isoniazid 5mg/kg/day (max 300 mg daily)
Day 7: Check ALT
Day 8: If ALT < 100 IU/L, continue rifampicin and isoniazid to complete the continuation phase

Stop TB background regimen. Monitor ALT weekly for 4 weeks after rechallenge.

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

Rechallenge of TB drugs should only be attempted once ALT is < 100 IU/L and jaundice has resolved[1-3]. Do not rechallenge TB drugs if drug-induced liver injury (DILI) resulted in acute liver failure (jaundice with either encephalopathy and/or coagulopathy)[2,3]. These cases need discussion with an expert or call the HIV hotline.

Rechallenge of TB drugs has been found to be safe and effective in 60-90% of patients provided frequent ALT monitoring is conducted[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 can cause severe DILI on rechallenge and should not be routinely rechallenged. Consider pyrazinamide rechallenge in patients who developed a DILI during the intensive phase of TB treatment if:

1. TB meningitis OR
2. Miliary TB OR
3. Rifampicin or isoniazid rechallenge fails[2].

If uncertain whether or not to attempt rechallenge with pyrazinamide, discuss with an expert or call the HIV hotline.

The length of TB treatment required after rechallenge, depends on how far into TB therapy the DILI occurred and on the outcome of rechallenge. If uncertain, discuss with an expert or call the HIV hotline.

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] Jong, E, et al. Consensus statement: Management of drug-induced liver injury in HIV-positive patients treated for TB. Southern African Journal of HIV medicine. 2013. 14(3): 113-119.
[3] Maartens, G, Meintjes, G, Mendelson, M, Cotton, M, Rabie, H. Aid for AIDS Clinical Guidelines. 11th edition. Cape Town: AFA; 2016.

3.3.3 MODIFYING TB TREATMENT REGIMEN

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

RIFAMPICIN not tolerated

STOP rifampicin

Start shorter regimen for rifampicin resistant TB treatment with normal dose INH (total duration **9 months**).

Monitor ALT weekly for 4 weeks after rechallenge.

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

ISONIAZID not tolerated

STOP isoniazid

Pyrazinamide rechallenged successfully (if required for severe forms of TB):
Continue rifampicin, ethambutol, levofloxacin (preferred) / moxifloxacin and pyrazinamide for **6 -9 months.**
OR
Pyrazinamide not rechallenged:
Continue rifampicin, ethambutol and levofloxacin (preferred) / moxifloxacin for **9 - 12 months.**

Monitor ALT weekly for 4 weeks after rechallenge.

PYRAZINAMIDE not tolerated

STOP pyrazinamide

Continue rifampicin, isoniazid* and ethambutol for **9 months.**

Monitor ALT weekly for 4 weeks after rechallenge.

*Try to confirm isoniazid susceptibility.
If not susceptible, refer to expert or call the hotline.

PYRAZINAMIDE not rechallenged

Continue rifampicin, isoniazid* and ethambutol for **9 months**.

Monitor ALT weekly for 4 weeks after rechallenge.

*Try to confirm isoniazid susceptibility.
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 in the continuation phase, or if unsure about the duration of TB treatment after rechallenge.

3.4 LIVER INJURY IN A PATIENT ON EFAVIRENZ/NEVIRAPINE

Asymptomatic patient with ALT > 200 IU/L

Yes

Patient presents with symptoms/signs of hepatitis (e.g. nausea, vomiting, abdominal pain, malaise, anorexia, right upper quadrant tenderness, jaundice) on first-line 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 to higher level of care immediately

Does the patient have any of the following in addition to symptoms/signs of hepatitis: ALT > 100 IU/L OR total serum bilirubin > 34 µmol/L?

Yes

No

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 full liver function tests to identify liver enzyme pattern**
- **Calculate ratio (R): ALT/upper limit of normal (ULN) divided by ALP/ULN**

Hepatocellular liver enzyme pattern: ALT ≥ 3 times ULN, R ≥ 5

Cholestatic liver enzyme pattern: ALP ≥ 2 times ULN, R ≤ 2

Mixed liver enzyme pattern: ALT ≥ 3 times ULN, ALP ≥ 2 times ULN, R > 2 but < 5

IN HOSPITAL

Do INR and blood glucose.

EXCLUDE OTHER CAUSES OF LIVER DYSFUNCTION

Hepatocellular:

1. Hepatitis A IgM, hepatitis B surface antigen, hepatitis B core IgM antibody, hepatitis C antibody
2. Herpes simplex virus PCR
3. Immune reconstitution inflammatory syndrome (IRIS)

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

Cholestatic and Mixed:

1. Perform an abdominal ultrasound to exclude obstructive causes of liver dysfunction e.g. lymphoma, disseminated TB with obstruction, extra-hepatic obstruction
2. Sepsis as a contributing factor
3. HIV cholangiopathy
4. IRIS

For mixed pattern also exclude alcohol abuse

Follow-up monitoring: Repeat ALT and bilirubin every 2-3 days, monitor INR if baseline > 1.5

Has ALT decreased to < 100 IU/L, bilirubin and INR normalised?

Yes

Start new ART regimen

1. If previously on nevirapine and life-threatening DILI (transaminitis with bilirubin > 34 µmol/L with encephalopathy and/or coagulopathy) commence a protease inhibitor or integrase inhibitor. In less severe cases that were previously on nevirapine, commence efavirenz
2. If previously on efavirenz, switch to a protease inhibitor or an integrase inhibitor

No

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

Note: Patients who presented with acute liver failure (jaundice with encephalopathy and/or coagulopathy) should be discussed with an expert or HIV hotline (0800 212 506) before re-starting ART

THIS IS A POTENTIAL DILI REQUIRING CLOSE MONITORING

- If patient is asymptomatic, ALT < 100IU/L but > 40 IU/L and total bilirubin < 34 µmol/L – Continue ART
- If ALT is > 100 IU/L but < 200 IU/L, monitor weekly
- Monitor for jaundice and other symptoms/signs of DILI

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 hepatitis 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 > 34 µmol/L or patient becomes symptomatic, manage as a DILI

If on treatment for opportunistic infections e.g. fluconazole for cryptococcus or TB treatment, 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) efavirenz and nevirapine, can both cause DILI[1,2]. DILI occurs more commonly with nevirapine than efavirenz[1,2]. Lopinavir/ritonavir and dolutegravir can also rarely cause DILI[7].The nucleoside reverse transcriptase inhibitors (NRTIs) used in the South African public sector's 1st line ART regimen (abacavir, emtricitabine, lamivudine, tenofovir) do not cause DILI.

Onset of efavirenz/nevirapine DILI

Most cases of DILI due to nevirapine, occur within the first 6-8 weeks of therapy[3]. DILI due to nevirapine may present as part of a hypersensitivity reaction characterised by rash, fever and raised liver enzymes[3]. Nevirapine-related DILI cases present with associated rash 50 % of the time[4]. In patients with a rash due to nevirapine, DILI may develop up to 2 weeks after onset of the rash[5].

Efavirenz may cause DILI any time during the course of ART and is not associated with rash.

Risk factors for efavirenz/nevirapine DILI

Risk factors for DILI in patients on ART include female sex, hepatitis B and hepatitis C co-infection, concomitant hepatotoxic drugs used to treat opportunistic infections (e.g. co-trimoxazole, fluconazole, TB drugs) and abnormal baseline liver function tests[1-3].

In addition, higher CD4 counts (CD4 count > 250 cells/µL in females and CD4 > 400 cells/µL in males) are associated with an increased risk of nevirapine hypersensitivity reaction[2]. Therefore, nevirapine should not be started in patients with baseline CD4 counts above these thresholds.

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

[1] Jain, MK. Drug-induced liver injury associated with HIV medications. Clinics in liver disease. 2007. 11 (3):615-639.
[2] Rivero, A, et al. Liver toxicity induced by non-nucleoside reverse transcriptase inhibitors. The Journal of antimicrobial chemotherapy. 2007. 59(3):342-346.
[3] United States. National Library of Medicine. Livertox. Clinical and research information on drug-induced liver injury. Available from: https://livertox.nlm.nih.gov/php/searchchem.php Accessed: 14 Feb 2017.
[4] Intracaso, CE, et al. Cutaneous toxicities of antiretroviral therapy for HIV. Journal of American academy of dermatology. 2010. 63(4):563-569.[5] Sanne, I, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. The Journal of infectious diseases. 2005. 191(6):825-829.
[5] Sanne, I, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. The Journal of infectious diseases. 2005. 191(6):825-829.
[6] Saukkonen, JJ, et al. An Official ATS Statement: Hepatotoxicity of anti-tuberculosis therapy. American Journal of respiratory and critical care medicine. 2006. 174(8):935-952.
[7] Livertox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Available from https://www.ncbi.nlm.nih.gov/books/NBK547852/ Accessed 26 May 2020

NATIONAL HIV & TB HEALTH CARE WORKER HOTLINE

	0800 212 506 **021 406 6782**		E-MAIL **pha-mic@uct.ac.za**
	SMS/PLEASE CALL ME/WHATSAPP **071 840 1572**		WEBSITE **www.mic.uct.ac.za**
	FACEBOOK **HIV & TB Health Care Worker Hotline, South Africa**		FREE APP ON GOOGLE PLAY **SA HIV/TB Hotline**

Contact us - we will gladly assist you! This service is free

What questions can you ask?

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

- Pre-exposure prophylaxis (PrEP)
- Post exposure prophylaxis (PEP)
- HIV testing
- Management of HIV in pregnancy & PMTCT
- Drug interactions
- Treatment/prophylaxis of opportunistic infections
- Drug availability
- Adherence support
- Management of tuberculosis
- Antiretroviral Therapy (ART)
  - ~ When to initiate
  - ~ Treatment selection
  - ~ Recommendations for laboratory and clinical monitoring
  - ~ How to interpret and respond to laboratory results
  - ~ Management of adverse events

Who answers the questions?

The centre is staffed by specially-trained pharmacists. They have direct access to the latest information databases, reference sources and a team of clinical consultants.

When is this service available?

The hotline operates from Mondays to Fridays 8:30am - 4:30pm.

UNIVERSITY OF CAPE TOWN MIC CLINICAL PHARMACOLOGY

MEDICINES INFORMATION CENTRE

NATIONAL HIV & TB HEALTH CARE WORKER HOTLINE 0800 212 506