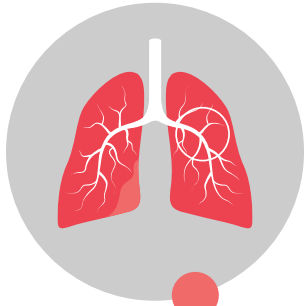
National Guidelines on
the Treatment of Tuberculosis Infection



New Developments in TB

Dr. Madeleine Muller
Family Physician CMH & Senior Lecturer WSU
SAAFP CONGRESS
8 September 2024

Overview

01

TB Testing

Xpert Ultra

02

Prevention

TPT guideliines

03

Children with TB

Treatment regimens

04

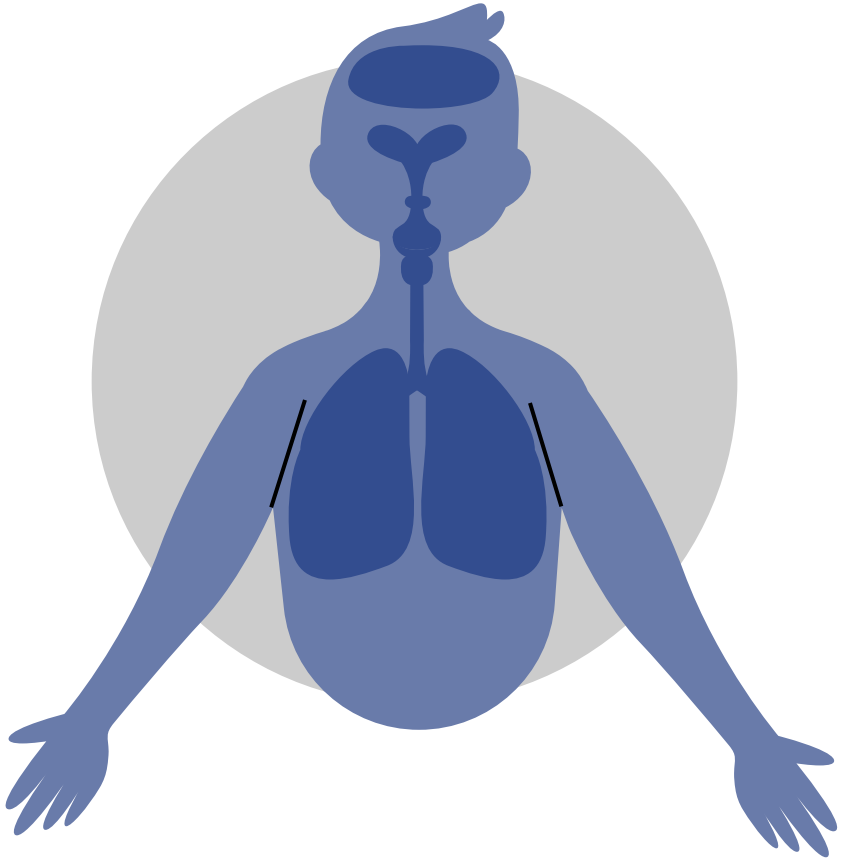
RRTB

BPaL-L

05

AT-DILI

New guildeine



TB related guidelines

CLINICAL MANAGEMENT OF RIFAMPICIN-RESISTANT TUBERCULOSIS Jan 2023

Updated Clinical Reference Guide

National Guidelines on the Treatment of Tuberculosis Infection Feb 2023

GUIDELINES FOR THE MANAGEMENT OF TUBERCULOSIS IN CHILDREN

2013

MEMORANDUM

REPLACEMENT OF THE FIRST- & SECOND-LINE PROBE ASSAYS WITH THE XPERT MTB/XDR ASSAY FOR DR-TB REFLEX TESTING ACROSS THE NHLS

26 July 2023

Paediatric STG & EML Update Nov 2023

CHAPTER 10

TUBERCULOSIS

GUIDANCE DOCUMENT

Guidance on the use of the Lateral flow urine lipoarabinomannan assay for the diagnosis of active tuberculosis in people living with HIV

POLICY UPDATE: FEBRUARY 2021

Document Name	TB Screening and Testing Standard Operating Procedure
Date of this Version	June 2022

Southern African Journal of HIV Medicine
ISSN: (Online) 2078-6751, (Print) 1608-9693

AOSIS

Page 1 of 7 Guideline

Management of drug-induced liver injury in people with HIV treated for tuberculosis: 2024 update

National TB Control and Management Programme TB Policies and Guidelines

To make it easier for you to get to all our TB policies, guidelines and SOPs, we've set up QR codes for each document. This way, you can quickly access the information you need without any hassle. Just use your smartphone to scan the code, and you'll instantly get the latest guidelines and policies right on your device. It's all about making sure you have the right info at your fingertips to help you do your job more effectively and provide the best care for your patients. **So, just open your camera or QR code scanner, point it at the code, and tap the link that pops up to see the document. Simple as that!**

Strategic and Operational Planning

- National Strategic Plan for HIV, TB and STIs (2023 - 2028)
- The National TB Strategic Plan (2023 - 2028)
- The TB Recovery Plan 3.0 (2024 - 2025)
- Department of Basic Education National Policy on HIV, STIs and TB for Learners, Educators, School Support Staff and Officials in all Primary and Secondary Schools in the Basic Education Sector (2017)
- Department of Basic Education National Policy on HIV, STIs and TB for Learners, Educators, School Support Staff and Officials in all Primary and Secondary Schools in the Basic Education Sector: Revised Field Guide on Tuberculosis (2021)

Policies, Guidelines and SOPs

TB Treatment

- National Tuberculosis Management Guidelines (2014)
- Guidelines for the Management of Tuberculosis in Children (2013)
- Clinical Management of Rifampicin-Resistant Tuberculosis (2023)
- ART Clinical Guidelines (2023)
- Standard Treatment Guidelines and Essential Medicines List for South Africa (2020) Primary Healthcare Level

TB Testing

- TB Screening and Testing SOP (2022)
- Guidance on the use of the Lateral Flow Urine lipoarabinomannan assay (LF-LAM) for the Diagnosis and Management of Active Tuberculosis in PLHIV (2021)

TB Prevention

- National Guidelines on the Treatment of the Tuberculosis Infection (2023)
- National Infection Prevention and Control Guidelines for TB, MDR-TB and XDR-TB (2015)

Data Management

- Integrated TB/HIV Data Management (2019) Standard Operating Procedure
- District Health Management and Information System (DHMIS 2016) Standard Operating Procedures, Facility Level
- District Health Management Information System Policy (DHMIS 2011)

Tuberculosis Statistics

Household contacts

Estimated contacts of people diagnosed with TB in 1 year

104400

TB Incidence

New infections in SA per year (360000)

615/10000

UN target for TPT

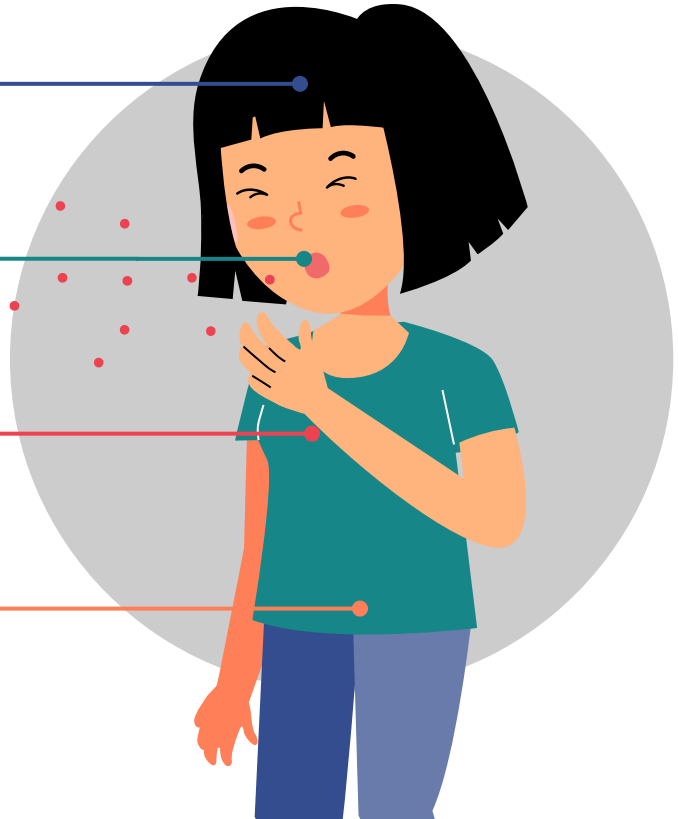
Number of people to give TPT between 2018 and 2022

30 million

SA target for TPT

Number of people to give TPT between 2018 and 2022

2 572100



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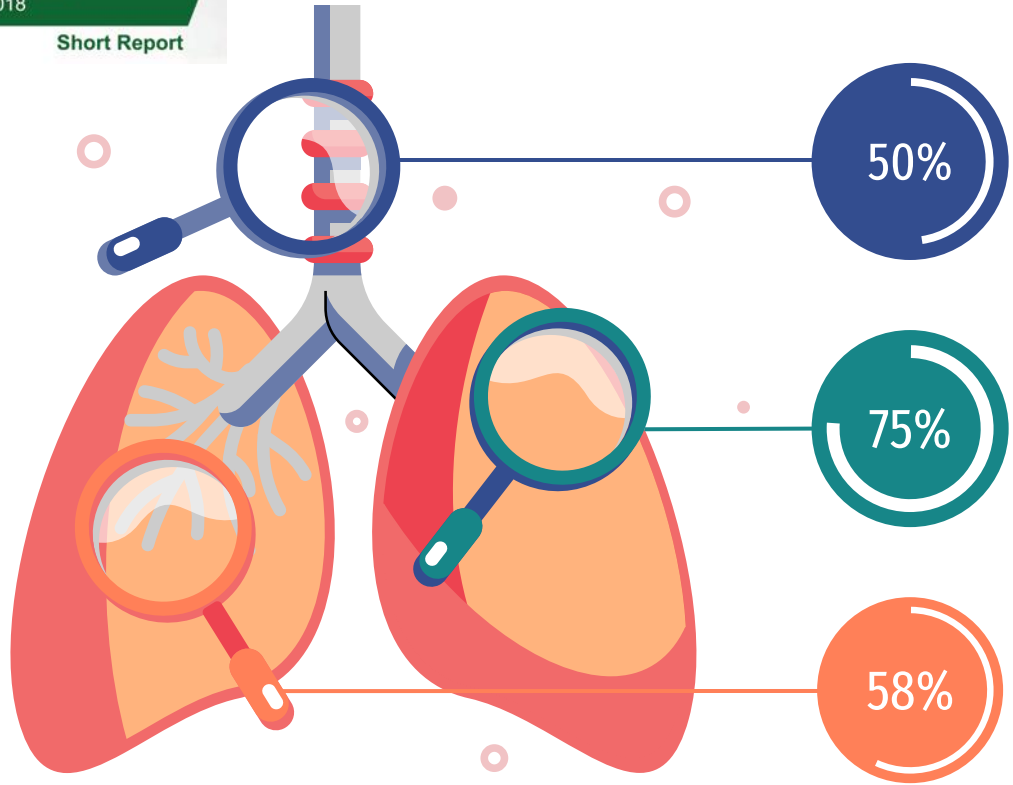
Cecilia Makiwane Hospital
Family Medicine Department

The First National TB Prevalence Survey
South Africa 2018
Short Report

END TB STRATEGY WHO by 2025



TB Incidence

Reduce by 50%

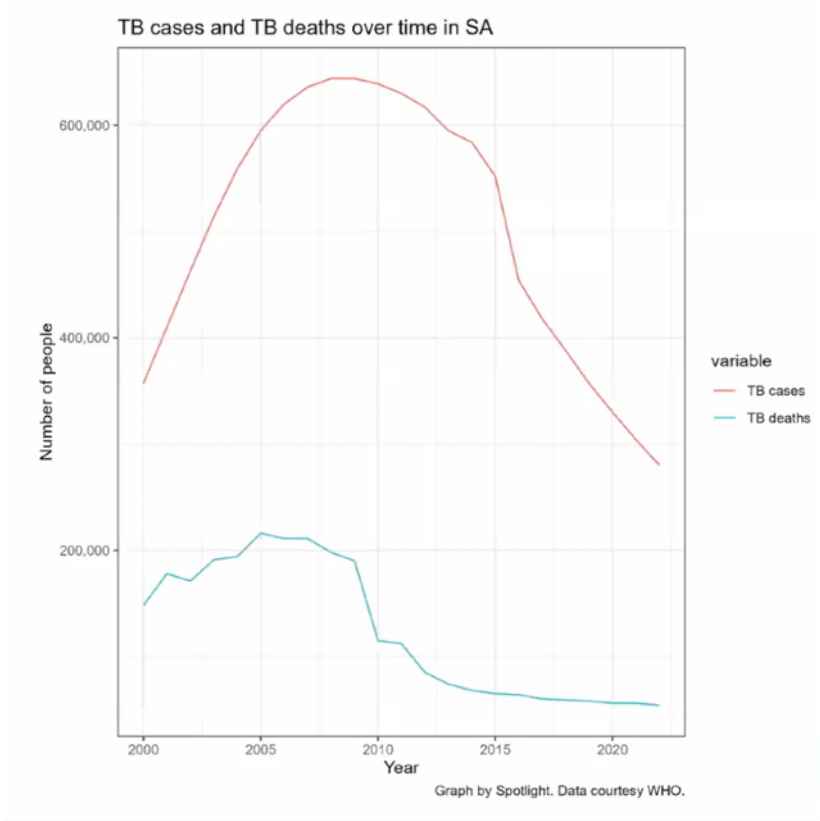
TB Mortality

Reduce by 75%

Sub-clinical TB

57,8% of patients did not report symptoms – but has a positive GXP
(TB prevalence study)

TB in South Africa



Tuberculosis profile: South Africa

Population 2022: 60 million

Estimates of TB burden*, 2022

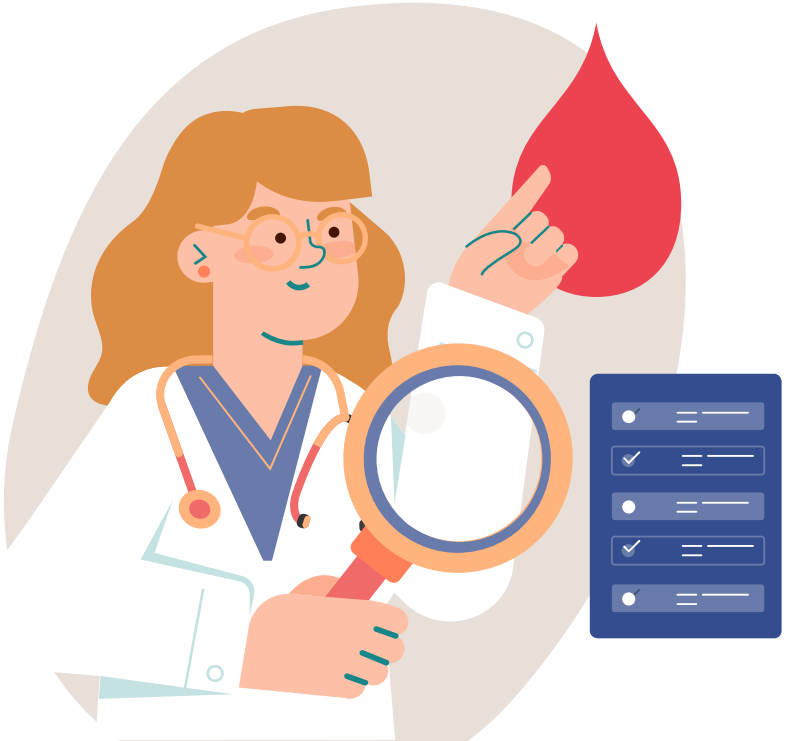
	Number	(Rate per 100 000 population)
Total TB incidence	280 000 (182 000-398 000)	468 (304-665)
HIV-positive TB incidence	152 000 (99 000-217 000)	255 (166-362)
MDR/RR-TB incidence**	11 000 (6 700-16 000)	19 (11-26)
HIV-negative TB mortality	23 000 (22 000-24 000)	39 (37-41)
HIV-positive TB mortality	31 000 (9 900-64 000)	52 (17-107)

54% of people falling ill with TB are living with HIV
57% of those dying with TB have HIV infection

NDOH Knowledgehub TB Presentation Aug 2024
Prof Graeme Meintjies

CMH
Cecilia Makiwane Hospital
Family Medicine Department

01



TB Testing Modalities

TB TESTS

NAAT: Nucleic Acid Amplification Tests

Xpert MTB

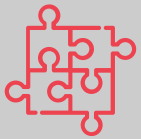
Ultra
XDRTB

TB-culture & pDST

- Xpert MTB Rif Ultra unsuccessful
- PLHIV - Xpert MTB Rif Ultra negative
- When a DST is required
- Previously treated patients

Line Probe Assays (LPA)

First-line LPA (FL-LPA) e.g. GenoType MTBDRplus
Second-line LPA (SL-LPA) e.g. GenoTypeDRs



Smear (AFB)

Baseline and in Smear positive: at 7w and 23w

Document Name	TB Screening and Testing Standard Operating Procedure
Date of this Version	June 2022

Xpert MTB Ultra

- Overall sensitivity: 87.6% on sputum in comparison to culture
  - Less sensitive in HIV positive patients and children
- But only 38-81% of patients produce sputum

- EPTB specimens: sensitivity compared to culture
  - 95% in smear positive
  - 69% in smear negative

Diagnostic accuracy of the Xpert MTB/RIF assay for extrapulmonary and pulmonary tuberculosis when testing non-respiratory samples: a systematic review

Laura Maynard-Smith[1], Natasha Larke[2], Jurgens A Peters[1] and Stephen D Lawn[1,3*]

Lympnodes (70- 96%)
- High yield
- FNA: rinse needle in 1 – 1.5ml saline: send for Xpert Ultra

Pleural fluid (34%-75%)
- Low to average yield
- Always send TB culture
- Rx any pleural exudate as TB In HIV positive patients

Non-pleural serious fluid (67%)
- Low yield – always send culture
- Ascites
- Joint fluid

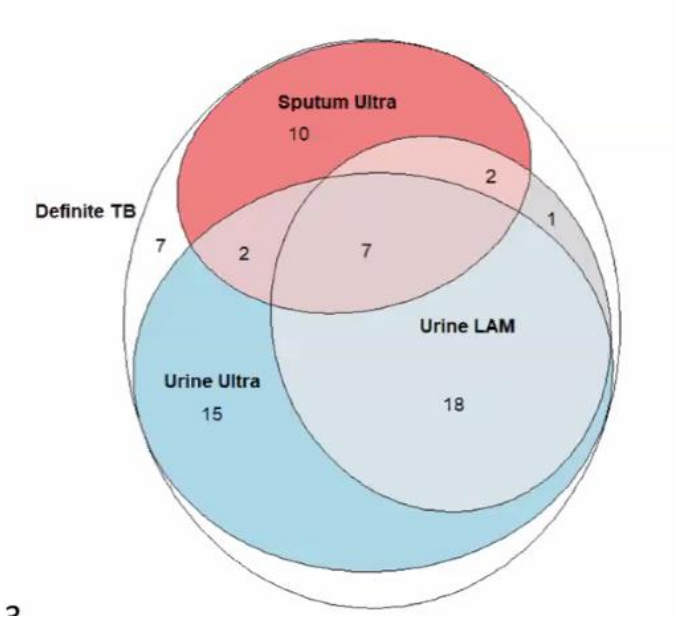
Xpert MTB Ultra

Xpert Ultra on CSF
- HIGH YIELD
- Sensitivity of 70%-89% vs 43% with culture
- Useful if LP delayed (picks up dead bacilli)
- Unlikely to get false positive

Bahr et.a. Diagnostic accuracy of Xpert MTB/Rif Ultra for TBM in HIV infected adults, The Lancet Infectious Diseases, 18 (1)

Urine
- Centrifuge 15-45ml of urine
- 68% Xpert Ultra positive in a cohort of patients with TB (only 37% of patients produced sputum)
- uLam: 45%
- Xpert Ultra on Sputum: 34%

Stead, Poster abstract 761, CROI 2023



Xpert Ultra Trace & Unsuccessful results

MTB complex detected Rif unsuccessful

- Definitely has TB
- Don't know if Rifampicin resistant
- Send another sample for culture and LPA
- Rx with DSTB treatment and FU culture results

MTB Trace detected, Rif Unsuccessful

- MTB detected at lowest trace possible: could be dead bacilli
- Consider in clinical context
- Less likely if TB treatment in last 2 years
- ALWAYS significant if on CSF

Unsuccessful

- Poor quality specimen or technical causes
- Repeat test

Xpert Ultra MTB trace detected

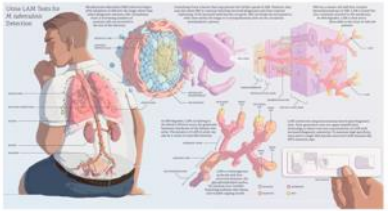
Client completed TB treatment within last 2 years

- Do TB culture and DST
- If asymptomatic – wait for result
- Clinical presentation consistent with TB: start DSTB treatment

Client has not been treated for TB in last 2 years

- Do CXR where available
- **Findings suggestive of TB**: Start DSTB treatment and send sputum for TB culture and DST
- **Patient is asx** and no clinical findings: Continue routine care

Urinary TB LAM



ALERE-LAM	Sensitivity	Specificity
HIV positive adults: symptomatic with CD4 >200 c/ml	16% (CI 8-31%)	95% (CI 81-97%)
HIV positive adults: symptomatic with CD4 <200 c/ml	45% (31-61%)	89% (77-94%)
HIV positive children	46,6% (33 – 61%)	76,45% (57-95%)
HIV negative children	32,33% (7,6 – 57%)	79% (62 – 95%)

Urinary TB Lam has a role to play in both our HIV negative and positive children

Seid, G., Alemu, A., Tsedalu, T. and Dagne, B., 2022. Value of urine-based lipoarabinomannan (LAM) antigen tests for diagnosing tuberculosis in children: systematic review and meta-analysis. *IJID regions*, *4*, pp.97-104.

Bulterys MA, Wagner B, Redard-Jacot M, Suresh A, Pollock NR, Moreau E, Denkinger CM, Drain PK, Broger T. Point-Of-Care Urine LAM Tests for Tuberculosis Diagnosis: A Status Update. J Clin Med. 2019 Dec 31;9(1):111

Indications for U-Lam

In-patients

- HIV positive pt
- Irrespective if TB suspected or not
- Irrespective of CD4
- Irrespective of AHD

Out patients

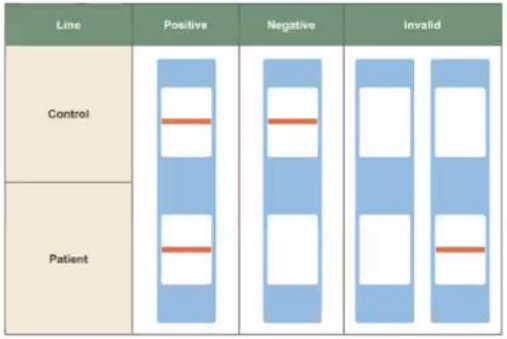
- HIV positive pt
- Signs and symptoms of TB
- CD4 <200cells/mm3
- AHD stage 4 or who are seriously ill

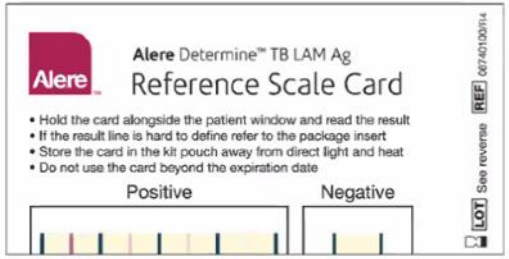
Guidance on the use of TB-Lam for diagnosis of active TB in patients with HIV. Policy update Feb 2021

Alere urine lipoarabinomannan (LAM) test

- Always use Reference Scale Card
  - Very faint bands are negative
  - Only read as + if patient band:
    = or > intensity of 1+ band

- Read and discard after 25 minutes
  - Maximum 35 minutes

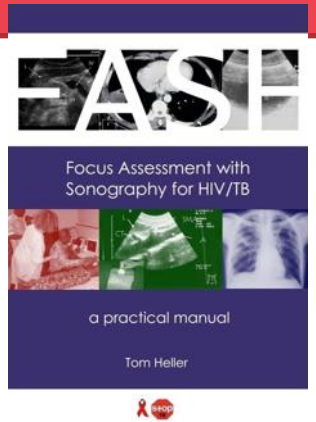


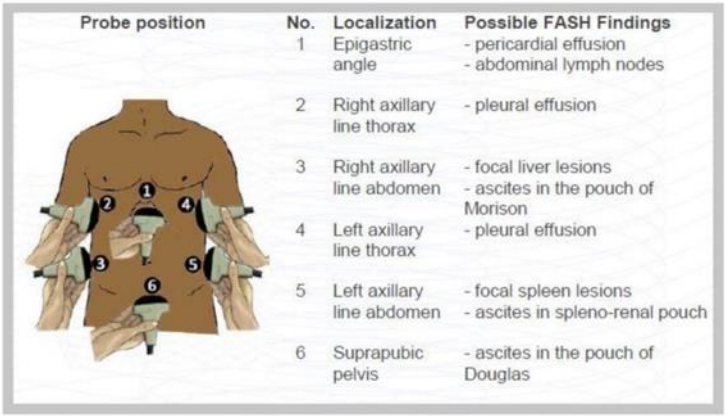


1+ band

FASH: Focused ultrasound for HIV/TB

- Supportive – not confirmatory
  - effusions (pleural / pericardial/ ascitic)
  - Intra-abdominal nodes >10mm
  - Splenic hypodensities
- An abdominal ultrasound with any abnormal finding
- Pooled sensitivity of 63% (43-79%)
- Pooled specificity of 68% (42%-87%





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02

Prevention

TPT

National Guidelines on
the Treatment of
Tuberculosis Infection
Feb
2023

TB Test and Treat Approach

At each new Immuno-compromise

01

ALL People living with HIV

All adults, children >14 weeks and all pregnant and breastfeeding women

At each new exposure

ALL TB CONTACTS

All people that have had a high risk exposure

02

03

CONSIDER HIGH RISK GROUPS

Silicosis, Health care workers, inmates and TB survivors need extra consideration

SIGNIFICANT TB EXPOSURE

:

Known exposure to a person with **lung** TB,

who shared the **same enclosed space**
(at work, socially or in the household)

for **one or more nights,**
OR for **frequent or extended daytime** periods

during the three months
before the index patient started TB treatment.

Do NOT use the term household contact

Recent TB exposure: exposed in last 12 months

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Available Medicines

Pyridoxine for all patients
≥5 years old: 25mg/ day
<5 years: 12.5mg/ day

3HP

INH &
Rifapentine
Weekly
3 months

3RH

Rifampicin &
INH
Daily
3 months

6H

INH
Daily
6 months

12H

INH
Daily
12 months

3HP Preferred: safe & effective/ higher completion rates / less DILI

6H and 12H - low rates of adverse events / no INH resistance

People Living with HIV

ALL PLHIV Screen using a GeneXpert (regardless of symptoms) on diagnosis and annually

- All require an initial TPT course, regardless of significant exposure
- **NEW:** All children living with HIV (older than 14 weeks) – require a course of TPT

AND after any new exposure – TB test and treat approach
AND after "new episode of immunosuppression": not clarified in guideline

PLHIV who complete TB treatment: Offer TPT To all PLHIV >25kg after successful completing treatment for TB disease.

- Bacteriological proof of cure: Give TPT IF
  - Significant Exposure
  - Or if they have not had a course of TPT before.
- No bacteriological proof of cure: Review for IPT 3 months after completing treatment

Pregnant and breast feeding women

TPT guideline

- TPT offered to all pregnant or breastfeeding women living with HIV – regardless of TB exposure.
  - Do NOT defer TPT to post partum period.
- Breastfeeding NOT a contra-indication

CONTRADICTION: NEW AHD Guidelines: Recommend defer TPT until after delivery.

Box 10 TPT in pregnancy

As of March 2024, all South African Guidelines have been harmonised with the results of NEMLC review and the following recommendations:

- Defer TPT in all pregnant women until after delivery
- In the absence of TPT initiation, continued active screening for TB throughout pregnancy must be prioritised

Standard Treatment Options for **PLHIV**

Children <25kg

14 weeks of age: **6H**

Newborn HIV Positive
NOT TB exposed
Give BCG vaccine
Start 6H and pyridoxine at the 14 week visit

For HIV-positive infants who have just had the BCG vaccine and are not TB-exposed
TPT should be deferred for 14 weeks
INH impairs the effect of live BCG (M.bovis BCG) vaccine.

Children & Adults ≥25kg

All adults & Children
Weight ≥25kg
& initiating on DTG
12 H

On DTG with VL <50c/ml
Or non DTG regimen
3HP
Start TPT 2 weeks after ART

Pregnant & Breast feeding

12H

Start TPT 2 weeks after ART

7.3.2.2 Recommended weekly dosages for the 3HP regimen amongst adults, adolescents, and children weighing 25 kilograms or more living with HIV not on Dolutegravir or with supressed viral load.

Body weight (kg)	Rifapentine	Isoniazid	Duration
	150mg tablets (weekly)	300mg tablets (weekly)	
25-29.9	4	2	12 weeks (3 months)
30 – 49.9	6	3	12 weeks (3 months)
>50	6	3	12 weeks (3 months)

Newborn exposed to TB (APC 2023)

Criteria

for a newborn to be considered TB exposed

- Mom dx TB in last 2 months (including being diagnosed at birth)
- OR mom on treatment but still culture/ smear positive
- Mom on treatment but not clinically responding to treatment

Workup

- If X-ray available – do AP and lateral CXR and refer
- Check for
  - RR>60 or a breathing problem
  - Feeding problem
  - Birthweight <2500g/ premature
  - Abdominal distention / enlarged liver / spleen
  - Jaundice
  - Weight loss >10%
  - Appears unwell / lethargic

TPT regimens for CONTACTS – small children

Newborns

HIV Negative / HIV unexposed :
3RH or 6H

HIV positive / HIV exposed baby on NVP / DTG /LPV/rit:
6H

HIV Neg <25kg

3RH

Emphasis on those with a weakened immune system
cancer, diabetes, autoimmune disease, transplant patients on, r dialysis, or inherited immunodeficiencies

5.3.2.1 Recommended daily dosages for 3RH in HIV-negative children <25kg

Child's Weight (kg)	RH (Daily) fixed dose combinations		Duration
	75/50	If dispersed in water	
2-2.9	½ tablet	5ml	3 months
3-3.9	¾ tablet	7.5ml	
4-5.9	1 tablet	10ml	
6-7.9	1 ½ tablet	15ml	
8-11.9	2 tablets	20ml	
12-15.9	3 tablets	30ml	
16-24.9	4 tablets	40ml	
≥25	Use adult formulations and doses		

HIV Pos <25kg

6H
(if on ART – to avoid drug interactions)

5.3.2.2 Recommended daily dosages for the 6H regimen amongst children living with HIV

Weight band (kg)	Daily INH 100mg tablet	Duration
2 – 3.4	¼ tablet	6 months
3.5 – 4.9	½ tablet	
5 – 7.4	¾ tablet	
7.5 – 9.9	1 tablet	
10 – 14.9	1 ½ tablet	
15 – 19.9	2 tablets	
20 -24.9	3 tablets (or one 300mg tablet)	
≥25	Use adult formulations (maximum dose 300 mg per day)	

TPT regimens for CONTACTS older children ≥ 25kg and adults

HIV Neg ≥ 25kg

3HP (preferred)
12H

HIV Pos ≥ 25kg

3HP (but only if VL <50c/ml on DTG)

12H

Pregnant / Breastfeeding women

12H (if on ARVs)
3RH or 6H (HIV Neg)

4.3.2.2 Recommended daily dosages for the 3RH regimen in adult, adolescent and child ≥25kg contacts who are not living with HIV

Pre-treatment body weight	RH (150,75)	RH (300,150)
25-37 kg	2 tabs	
38-54 kg	3 tabs	
55-70 kg		2 tabs
>70kg		2 tabs

4.3.2.1 Recommended weekly dosages for the 3HP regimen for adult, adolescent, and child ≥25kg contacts not living with HIV

Body weight (kg)	Rifapentine	Isoniazid	Duration
	150mg tablets (weekly)	300mg tablets (weekly)	
25-29.9	4	2	12 weeks (3 months)
30 – 49.9	6	3	12 weeks (3 months)
>50	6	3	12 weeks (3 months)

Note: If 3HP is not available, 3RH should be used in adults, adolescents and children ≥25kg without HIV. Alternatively, 6H can be used.

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Family Medicine Department

03

Children with TB

What's new

Paediatric STG & EML
Update Nov 2023

CHAPTER 10
TUBERCULOSIS

The TB treatment decision algorithm in children

- Assign a score to each of the child's symptoms:
  - ≥ **11: Rx for TB**
  - A clinician could still decide to treat for TB even if < 11, or consider other childhood illness if ≥ 11

- **Any child with signs and symptoms** is regarded as a child with TB if they also have a
  - a suspicious CXR
  - AND/OR history of exposure or positive TST

- Try to **confirm diagnosis by an Xpert Ultra or culture**
  - Gastric aspirates
  - Sputum induction

Clinical Features	
Cough >2 weeks	+5
Fever > 2 weeks	+10
Reduced playfulness / energy	+4
Weight loss	+5
Haemoptysis	+9
Night sweats	+6
Enlarged typical lymph nodes	+7
Tachycardia	+4
Tachypnoea/ fast breathing	+2

Xpert MTB Ultra - children

- Gastric Lavage: 66% (GXP) GXP Ultra in culture positive children
- Induced sputum in children: 74% sensitivity
  - There was no difference between HIV pos and HIV neg children
  - The bigger the sample - the better (its centrifuged down)

In culture positive patients (Xpert Ultra)

- Urine 100%
- Joint fluid 88%
- Stool 88%
- Pleural fluid 48%

Gastrc Aspirates (78%)

- High Yield

STOOL

- Can be sent for **Xpert MTB Rif Ultra** at selected NHLS labs (NOT FOR CULTURE)
  - Less sensitive than gastric aspirate or induced sputum

- 898 children: sensitivity of stool Xpert-Ultra against culture positive
  - Sensitivity 59.0% to 76.8%,
  - Specificity exceeding 98.8%

Diagnostic accuracy, feasibility, and acceptability of stool-based testing for childhood tuberculosis

Bazezew Yenew, Petra de Haas, Yohannes Babo, Getu Diriba, Bihil Sherefdin, Ahmed Bedru, Ben Tegegn, Tilaye Gudina, Tadesse Getahun, Saro Abdella, Degu Jerene, Eveline Klinkenberg, Edine Tiemersma, the ASTTIE study group

ERJ Open Research 2024; DOI: 10.1183/23120541.00710-2023

Bacteriological confirmation

Xpert MTB Ultra or TB culture

- Sputum (children > 8 years old)
- Induced sputum in younger children
- Early morning gastric aspirate (empty stomach, no oral food intake for 4 hours)
- Stool
- CSF
- Pleural and ascitic fluids
- Fine needle aspirate biopsies of lymph nodes: rinse needle in SALINE and send for GXP
- Ear swabs for TB culture in chronic otorrhoea

TREATMENT: first identify the child with complicated TB

- Malnourished
- HIV positive
- Children <3 years
- Enlarged hilar and mediastinal lymphadenopathy with
  - obstruction
  - or occlusion with secondary atelectasis
  - Or hyperinflation
- Local spread of infection e.g. TB bronchopneumonia, pleural effusion or cavitation
- Disseminated disease e.g. military TB. TB meningitis and metastatic extrapulmonary involvement

TREATMENT: first identify the child with complicated TB

Non-severe disease

<8 years old: RHZ (2m) and RH (2m)
>8 years old: RHZE (2m) and RH (2m)

Severe disease

RHZE (2m) and RH (4-7months)
consider extending to 7 months for slow responders and children with HIV

TBM & Miliary TB

< 8 years old: Rif/ INH/ PZA/ Ethionamide for 6-9m
>8 years old: treat like adults

Children < 8 yers old: Non-Severe Tuberculosis Disease

Children up to 8 years:

Dosing recommendations for dispersible combinations tablets:

Pre-treatment body weight	2 months intensive phase given daily	2 months continuation phase given daily
	RHZ	**RH**
	75/50/150 mg dispersible tablet (scored) **OR** 75/50/150 mg per 4 mL solution*	75/50 mg dispersible tablet (scored) **OR** 75/50 mg per 4 mL solution*
2–2.9 kg	½ tablet or 2 mL	½ tablet or 2 mL
3–3.9 kg	¾ tablet or 3 mL	¾ tablet or 3 mL
4–7.9 kg	1 tablet or 4 mL	1 tablet or 4 mL
8–11.9 kg	2 tablets or 8 mL	2 tablets or 8 mL
12–15.9 kg	3 tablets or 12 mL	3 tablets or 12 mL
16–24.9 kg	4 tablets or 16 mL	4 tablets or 16 mL

Pyridoxine, oral, daily for 6 months if HIV-infected, malnourished, or with existing neuropathy:
- Child < 5 years: 12.5 mg.
- Child ≥ 5 years: 25 mg.

If RHZ solution not available

Weight	Intensive phase 2 months			Continuation phase 2 months
	RH	**PZA**		**RH**
	60/60 mg	Give one of the following:		60/60 mg
		150 mg* **OR** 150 mg/3 mL	500 mg	
2–2.9 kg	½ tablet	1.5 mL	Expert advice on dose	½ tablet
3–3.9 kg	¾ tablet	2.5 mL	¼ tablet	¾ tablet
4–5.9 kg	1 tablet	3 mL	¼ tablet	1 tablet
6–7.9 kg	1½ tablets		½ tablet	1½ tablets
8–11.9 kg	2 tablets		½ tablet	2 tablets
12–14.9 kg	3 tablets		1 tablet	3 tablets
15–19.9 kg	3½ tablets		1 tablet	3½ tablets
20–24.9 kg	4½ tablets		1½ tablets	4½ tablets
25–29.9 kg	5 tablets		2 tablets	5 tablets

*For each dose, dissolve 150 mg dispersible (1 tablet) in 3 mL of water to prepare a concentration of 50 mg/mL (150 mg/3 mL).

Children >8 years old – Non-Severe Tuberculosis Disease

Children > 8 years of age and adolescent (and > 25 kg):

Pre-treatment body weight	2 months intensive phase given daily	2 months continuation phase given daily	
	RHZE (150, 75, 400, 275)	**RH** (150, 75)	**RH** (300, 150)
25–37.9 kg	2 tablets	2 tablets	
38–54.9 kg	3 tablets	3 tablets	
55–70.9 kg	4 tablets		2 tablets
> 71 kg	5 tablets		2 tablets

AND

Children: Severe Tuberculosis Disease

Excluded TB meningitis and military TB

Consider 7 months for slow responders and children with HIV

Dosing recommendations for dispersible combinations tablets:

Pre-treatment body weight	2 months intensive phase given daily		4–7*** months continuation phase given daily
	RHZ	E	RH
	75/50/150 mg dispersible tablet (scored) **OR** 75/50/150 mg per 4 mL solution*	400 mg tablet **OR** 400 mg/8 mL solution**	75/50 mg dispersible tablet (scored) **OR** 75/50 mg per 4 mL solution*
2–2.9 kg	½ tablet or 2 mL	1 mL	½ tablet or 2 mL
3–3.9 kg	¾ tablet or 3 mL	1.5 mL	¾ tablet or 3 mL
4–7.9 kg	1 tablet or 4 mL	2.5 mL	1 tablet or 4 mL
8–11.9 kg	2 tablets or 8 mL	½ tablet or 4 mL	2 tablets or 8 mL
12–15.9 kg	3 tablets or 12 mL	¾ tablet or 6 mL	3 tablets or 12 mL
16–24.9 kg	4 tablets or 16 mL	1 tablet or 8 mL	4 tablets or 16 mL

	Intensive phase 2 months				Contin-uation phase at least 4 months (up to 7 months ***)
Weight	RH	PZA Give one of the following:		EMB	RH
	60/60	150 mg* **OR** 150 mg/3 mL	500 mg	400 mg tablet **OR** 400 mg/8 mL** solution	60/60
2–2.9 kg	½ tablet	1.5 mL	Expert advice on dose	1 mL	½ tablet
3–3.9 kg	¾ tablet	2.5 mL	¼ tablet	1.5 mL	¾ tablet
4–5.9 kg	1 tablet	3 mL	¼ tablet	2 mL	1 tablet
6–7.9 kg	1½ tablets		½ tablet	3 mL	1½ tablets
8–11.9 kg	2 tablets		½ tablet	½ tablet	2 tablets
12–14.9 kg	3 tablets		1 tablet	¾ tablet	3 tablets
15–19.9 kg	3½ tablets		1 tablet	1 tablet	3½ tablets
20–24.9 kg	4½ tablets		1½ tablet	1 tablet	4½ tablets
25–29.9 kg	5 tablets		2 tablets	1½ tablets	5 tablets

Miliary TB and TBM

- Bacilli in lungs, brain and other organs: assumed to have CNS involvement (potentially fatal)
- The RH 75/50 and RHZ 75/50/150: not enough CNS penetration:
  - **Use the 60/60 RH**

Rx of TBM and Miliary TB children < 25 kg

Body weight (kg)	Single phase of treatment, 6–9 months Once daily; 7 days a week		
	Rifampicin/Isoniazid (RH)*	Pyrazinamide (Z)	Ethionamide (Eto)
	60/60 mg dispersible tablet (scored)	500 mg tablet (scored) **OR** 500 mg/8 mL suspension**	250 mg tablet (scored) **OR** 250 mg/8 mL suspension***
< 2	Obtain Expert Advice		
2–2.9	¾ tablet or 3 mL	1 mL	1.5 mL
3–3.9	1 tablet or 4 mL	2 mL	2 mL
4–4.9	1½ tablets or 6 mL	2.5 mL	2.5 mL
5–5.9	1¾ tablets or 7 mL	3 mL	3 mL
6–6.9	2 tablets or 8 mL	½ tablet or 4 mL	½ tablet or 4 mL
7–8.9	2½ tablets or 10 mL		
9–9.9	3 tablets or 12 mL	¾ tablet or 6 mL	¾ tablet or 6 mL
10–11.9	3½ tablets or 14 mL		
12–12.9	4 tablets or 16 mL	1 tablet or 8 mL	1 tablet or 8 mL
13–14.9	4½ tablets or 18 mL		
15–16.9	5 tablets or 20 mL		1¼ tablets or 10 mL
17–17.9	5½ tablets or 22 mL	1¼ tablets or 10 mL	
18–19.9			1½ tablets or 12 mL
20–24.9	6 tablets or 24 mL	1½ tablets or 12 mL	

- Give a full 6m regimen: consider prolonging for another 3m if needed
  - Rifampicin (20mg/kg) max 600mg
  - INH (20mg/kg) max 400mg
  - PZA (40mg/kg) max 2000mg
  - Ethionamide (20mg/kg) max 1000mg
- For CNS: steroid therapy: Prednisone 2mg/kg/ day 4 weeks (max 60mg)
  - Taper to stop over a further 2 weeks

Children ≥ 8 years: treat as per adult guidelines. Treatment duration 6-9 months

TB Meningitis Complications

The degree of involvement is classified into 3 stages. Prognosis relates to the stage of the disease.

- Stage 1: Non-specific signs, conscious, rational, no focal neurological signs, no hydrocephalus.

- Stage 2: Signs of meningeal irritation, confusion and/or focal neurological signs.

- Stage 3: Stupor, delirium, coma and/or neurological signs, i.e. hemiplegia.

- Raised ICP
- Hydrocephalus
- Cerebral oedema
- Brain infarcts
- Hemi/quadriplegia
- Convulsions
- Hypnatraemia due to
    - SIADH (syndrome of inappropriate antidiuretic hormone secretion – low uric acid and low urine output) – restrict fluids
    - or cerebral salt wasting (normal uric acid and high urine output)– fluid replacement

CMH
Cecilia Makiwane Hospital
Family Medicine Department

4

RRTB

What's New

CLINICAL MANAGEMENT OF RIFAMPICIN-RESISTANT TUBERCULOSIS

Jan 2023

Updated Clinical Reference Guide

Xpert MTB/XDR assay

- To replace FL LPA and SL LPA as confirmatory test for RR TB
- Implementation started March 2023 – and will lead to discontinuation of LPA testing
- Xpert MTB ultra: Rif Resistant
    - Request a DRTB reflex test
        - Smear, TB culture, genotypic testing for FLQ and phenotypic testing for BDQ

- Xpert MTB-XDR
    - INH-S & FLQ-S/R – phenotype DST INH, BDQ, LZD
    - INH-R & FLQ-S - phenotype DST BDQ, LZD
    - INH-R & FLQ-R- phenotype DST BDQ, LZD, Pa (pretomanid) (and Clofazimine)

    - Can also test for resistance to ethionamide and SL injectables

DRTB Classification

Mono-Resistant TB

Resistance to only one anti-TB drug

Rif-Resistant TB

Resistance to at least Rif, without without resistance to other drugs

Poly-drug resistant TB

Resistance to more than one anti-TB drug, other than both Rif and INH

MDRTB

Resistance to RIF and INH only

Pre-XDR TB

Resistant to Rif (with /without INH) and resistant to one FLQ (either LFX or MOX)

XDR-TB

Resistant to Rif (with/ without INH) AND resistant to a FLQ (either LFX or MOX) AND to either BDQ or LZD

RRTB Treatment Groups

A

- Levofloxacin or Moxifloxacin
- Bedaquiline
- Linezolid (not if HB<8g/dl or neut < 0,75 or platelets >50)

B

- Clofazamine (possible cross resistance to BDQ)
- Terizidone (always use in CNS disease)

C

- EMB / PZA
- Delamanid (CNS disease)
- Meropenem / Imipenem
- Amikacin / Ethionamide /PAS

RRTB Treatment

- Severe extrapulmonary TB: **LONG INDIVIDUALISED REGIMEN**
    - e.g. TBM, TB pericarditis, osteo-articular, abdominal or disseminated / military disease:

- All other patients with HB>8g/dl: start **Short regimen** (BPaL-L)

Adjust regimen when LPA back

- **Resistance to BDQ, LZD or Pretomanid (Pa**): long regimen
- **INH-R:** BPaL-L
- **FLQ-S**: (regardless of injectable resistance): BPaL-L
- **FLQ-R**: Stop LVX: continue BPaL

- Pregnancy: Pretomanid is contra-indicated in pregnancy
    - Bedaquiline, delamanid, linezolid and levofloxacin

SHORT REGIMEN: BPaL-L

6 months in adults >15 years and non-pregnant

BDQ + Protentomid (Pa) + LZD (min 2m) + LFX

Extend to 9 months
Extensive Pulmonary disease
(e,g, bilateral cavitory disease with significant scarring)

Try to give LZD for the full 6 months – interrupt and transfuse if HB <8g/dl

DRTB in children: classify disease severity

Severe TB disease in children <15 years

- CXR: bilateral disease (consolidation, infiltrates) or presence of cavities
- Mediastinal lymph nodes causing airways compression
- Extrapulmonary forms of disease other than peripheral LN's or simple pleural effusion

Non-severe TB disease in children <15 years

- Peripheral lymphadenopathy
- CXR: unilateral disease (consolidation, infiltrates in >1 lobe in total) without cavities
- Small/ simple pleural effusions
- Mediastinal lymphnodes without airway compression

DRTB in children:

- BPAL only apply to **non-pregnant persons aged 15 years** and older
- Most children with RRTB do not require 18 months to achieve cure
  - *A shorter regimen recommended based on expert opinion*
  - Children with non-severe RRTB can be treated for 6m with at least 4 effective drugs
    - Children with more severe disease: 9-12 months
  - Usually give all 4 drugs for the full 6 months
    - Treatment can be extended to 9 months if needed
    - BDQ / DLM usually for 6 months but can be extended
    - LZD sometimes only tolerated for 2m: use for full 6 months if possible

CHILD <15 year regimens

- **Non-severe disease**: Treat for 6 months
  - *FLQ-S*: BDQ/ LFX/ CFZ/TRD/ LZD (2m)
  - *FLQ-R*: BDQ/ CFZ/TRD/**DLM**/ LZD (2m+)

- **Severe disease**: Treat for 9 months
  - *FLQ-S*: BDQ/ LFX/ CFZ/TRD/ LZD (2m+)
  - *FLQ-R*: BDQ/ CFZ/TRD/**DLM**/ LZD

- **CNS/military / bone / pericardial**: treat for minimum 12 months
  - BDQ/ (LFX) /LZD/ CFZ/TRD/DLM/ LZD

Prevention Drug Resistant TB
Find the drug resistance profile of the contact

INH-monoresistance

Rifampicin 15mg/kg daily for 4 months

Rif-monoresistance

INH 10mg/kg for 6m

MDRTB

Levofloxacin 15-20mg/kg for 6m AND/ OR INH 15-20mg/kg daily for 6m (max dose 600mg)

XDRTB

Refer all cases – close follow up

Linezolid

- **Peripheral neuropathy** (peak onset around 16 weeks)
  - Week 1-8: Consider reduction of dose / or change to longer regimen without LZD
  - Week 8-16: Reduce dose. Consider stopping if culture conversion has happened
  - Week 16+: Stop LZD if culture conversion has happened

- **Anaemia:** Can start BPal-L if Hb>8g/dl. Baseline FBC and diff and then at 2 weeks and 4 weeks. Every 4 weeks after that.
  - If HB<8g/dl
    - Week 2-8: admit for transfusion with packed cells
    - > 8 weeks: LZD can be stopped if there has been a clinical response.

- **Optic neuritis**: do baseline Snellen Visual Acuity and at every visit
  - If more than a 2 line drop: refer to opthalmologist or stop treatment

ART and RRTB

- Initiation of ART in patients on RRTB treatment
  - CD4 <50 cells/mm: 2 weeks
  - CD4 >5 cells/mm3: 2-8 weeks
  - RRTB meningitis: 4-6 weeks

New developments: WHO circular of June 2024 based on BEAT Trial
bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) for 6 months

BDLLfx continued for FQ-sensitive TB; BDLC for FQ-resistant TB.
For pregnant women/ children/ adolescents

Cecilia Makiwane Hospital
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05

AT-DILI

Drug induced liver injury

Anti-tuberculosis treatment DILI

Southern African Journal of HIV Medicine
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AOSIS
Page 1 of 7 Guideline

Management of drug-induced liver injury in people with HIV treated for tuberculosis: 2024 update

Baseline and Monitoring of LFT

Baseline LFT not routinely recommended, unless known risk factors

- If ALT / Tot-bili abnormal at baseline: monitor weekly until stable or improved (during treatment)
- Ignore increased AST or ALP/ GGT

Any patient with

- **visible jaundice / symptoms of hepatitis** (N&V / fatigue / RUQ pain / LOA / pale stools)
- **OR with a new rash**:
    - AT-DILI can be part of a hypersensitivity reaction such as Steven-Johnson Syndrome or DRESS

Do **LFT and INR**

PRESUMPTIVE AT-DILI Diagnosis

Make a **PRESUMPTIVE diagnosis** of AT-DILI based on LFT and symptoms

- Investigate and exclude other competing diagnosis
- Check response to interrupting treatment

Criteria for AT-DILI

ALT > 3x ULN with **symptoms** OR **jaundice** OR **Total-bili > 40umol/l**

OR

ALT >5x ULN regardless of symptoms or bilirubin

OR

Patient with liver disease / or baseline ALT>120 IU/l: A**LT > 2x baseline**

Final Diagnosis of AT-DILI

EXCLUDE other causes

- Full history of all **prescribe, OTC, herbal or illicit drugs**
- Children most common cause of hepatitis is Hepatitis A
- In adults: check for **hepatitis A, B & E**
- No need to check for **HSV / CMV or Epstein-Barr**

Check for **pregnancy** in child-bearing women

Abdominal ultrasound: only if cholestatic picture on LFT

FINAL DIAGNOSIS

Other causes excluded

& Response to interrupting treatment

Consider IRIS

TB IRIS

- Tender hepatomegaly
- Preponderance of ALP/ GGT
- Absence of jaundice and maintaining of ALT
- TB IRIS features in other systems

Only route to a definitive diagnosis: **liver biopsy** (invasive & not readily available)

With a mixed picture
safer to manage as DILI and monitor response

Severity assessment criteria for admission

Mild

No symptoms of hepatitis with INR <1.5

Moderate

Symptoms of hepatitis with INR <1.5

Severe

INR> 1.5, regardless of symptoms: refer to higher level care

- Most patients with AT-DILI should be **admitted**
- **Outpatients only if**:
  - results are obtained with 24hrs
  - Can return regularly

Management AT-DILI

STEP 1: REVIEW THE DIAGNOSIS

Review and confirm **initial TB diagnosis** (e.g. uLAM can be positive in non-tuberculosis mycobacterial infections)

- Try to get a bacterial confirmation
- If no bacterial confirmation: consider the strength of diagnosis case-by-case:
  - What was the response to treatment
  - If TB is unlikely: stop TB treatment and do not re-challenge

Management of AT-DILI (mild/mod)

STEP 2: REVIEW MEDICATION

Stop ALL TB medications and CTX

ARVs

- **If on ART < 6m**: consider interruption
- If on **DTG based regimen >6m**: consider continuing art
- If on **LPV/rit or EFV**: switch to DTG
- **DRV/rit or ATV/rit**: Cannot give with Rifampicin. Stop ART. When re-challenged use Rifabutin instead of Rifampicin

Fluconazole for CM

- If **CD4 >200** cells/mm3 & maintenance dose: stop fluconazole
- If **CD4 <200** cells/mm3 or intensive / consolidation phase: discuss with ID

Review other potentially **hepatotoxic drugs**

Background regimens (holding)

Individualised decision

- Patients on intensive phase: can use a 'background regimen'
- Patient on continuation phase: do not need

Recommended regimen:

Levofloxacin, Ethambutol and linezolid

If HB <8/dl – use clofazimine (100mg) or terizidone (750mg >35kg) instead of LZD

LVX: < 45kg 750mg / >45kg 1000mg
LZD >30kg 600mg
EMB <45kg 800mg / >45kg 1200mg

Monitoring – recovery phase

Monitor ALT 2-3x/week

Expect a downward tend in ALT within a few days
Median time to ALT <100 IU/L: 8 days (5-13)
If not coming down: discuss with specialist

Re-challenge when ALT <100 IU/ml

Re-challenge when ALT <100 IU/ml and total bilirubin on 'downward trend'

20-90% safe rechallenge

20-90% of adults patients with AT-DILI c**an be re-challenged** without re-occurrence
Most common re-occurrence with PZA

Rechallenge with RIF & INH / PZA?

Mild / moderate: **re-challenge with INH & then RIF**.
Only re-challenge PZA in patients with TBM or if INH or RIF not tolerated

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Re-challenging Anti-TB therapy

DAY 1

1

Start **INH** 300mg/d
(stop LZD/ CFZ / TZD)
Patient is on INH /EMB & LFX

DAY 3

3

Check ALT

If ALT raised: Stop INH

DAY 4

4

IF ALT not increased:
add **RIF** 600mg / day
Patient is on Rifinah/EMB & LFX

Day 7

7

Check ALT

If ALT raised: Stop RIF

DAY 8

8

Add **PZA** if TBM or unsuccessful re-challenge of INH/RIF
Stop LFX
Patient now on Rifafour

DAY 10

10

CHECK ALT

If ALT raised: Stop PZA

CHECK ALT weekly for 4 weeks after rechallenge

Unsuccessful re-challenge

Drug not tolerated	Suggested regimen
PZA	**RIF + INH + EMB** for 2m and then **RIF + INH** for 7m **TBM:** RIF + INH + EMB + LFX for 12 months
INH	**RIF +INH + PZA + LFX** for 6 – 9m Same regimen in TBM
RIF	**MDR-TB regimen (as per latest guidelines** TBM: MDR-TB regimen nervous system

More than 1 core drug: contact an ID specialist

Questions

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