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FOR ATTENTION: **FACILITY MANAGERS, PHARMACISTS, PHARMACIST ASSISTANTS, AUTHORIZED PRESCRIBERS**

CIRCULAR **H08/2024**

ADOPTION OF UPDATED NDOH GUIDELINES ON TB PREVENTIVE TREATMENT (TPT)
TREATMENT OF TUBERCULOSIS INFECTION, 2023

BACKGROUND

In 2023, the National Department of Health (NDoH) released the "National Guidelines on the Treatment of Tuberculosis Infection," expanding eligibility for Tuberculosis Prevention Treatment (TPT) to include HIV-negative adults and children at risk of developing Tuberculosis (TB) disease. This expansion also includes shortened TPT regimens such as the 3-month weekly course of Isoniazid and Rifapentine (3HP) or a 3-month daily course of Rifampicin and Isoniazid (3RH).

RATIONALE FOR EXPANDED ELIGIBILITY FOR TPT: A TB TEST AND TREAT APPROACH

In order to work towards the goal of achieving Tuberculosis (TB) elimination in South Africa, TPT needs to be implemented more comprehensively for people with significant TB exposure and for individuals at high risk of developing TB. The core principle of a TB test and treat approach is: **Offer TB testing to all individuals with significant TB exposure or at high risk of TB disease progression as recommended by the Targeted Universal TB Testing (TUTT) policy. Initiate TB treatment in all individuals diagnosed with TB and offer TPT in individuals in whom TB has been excluded.**

CURRENT TPT IMPLEMENTATION

TPT is currently offered to people living with HIV as a once-off course of 12 months, and to close TB contacts who are HIV positive and children under 5 years old, regardless of HIV status.

The 3HP regimen was introduced in the Western Cape in December 2022 for implementation in a phased in approach per circular: **H171 of 2022**

ADOPTION OF NDoH TPT GUIDELINES

The NDoH Guidelines on the Treatment of Tuberculosis Infection 2023 will now be adopted in Western Cape with the following deviations:

1. **TPT should not be offered routinely to HIV positive individuals post TB treatment.** Only offer TPT again if the patient has a new exposure to a close contact with TB. Ensure that TB disease is excluded before commencing TPT.
2. Universal TPT for diabetics is not recommended. **TPT should be offered to individuals with diabetes only if they have had a close TB contact, after TB has been excluded.**
3. While we acknowledge the option of a 3RH regimen in **patients above 25kg**, the province has sufficient donated rifapentine for the short course option in these patients. We advise preferential use of 3HP if it is a regimen option.

1. TPT REGIMEN OPTIONS

Treatment option	Definition
3HP	three months of weekly isoniazid plus rifapentine
3RH	three months of daily rifampicin plus isoniazid
6H	six months of daily isoniazid monotherapy
12H	12 months of daily isoniazid monotherapy

2. SUMMARY OF TPT REGIMEN OPTIONS BY PATIENT TYPE

PATIENT CATEGORY		WHAT TO DO	REGIMEN
Adults and adolescents including children ≥25kg	HIV-positive	**PLHIV**: Test for TB regardless of ART status and give TPT once TB disease is excluded. If newly diagnosed with HIV, start ART immediately and TPT within the next two weeks.	**3HP* or 12H**
		Previously treated with TPT*:** If re-exposed to any close contact with TB, retest for TB and give TPT once TB disease has been excluded.	
		Evaluate all **HIV-positive pregnant women** regardless of CD4 count and give TPT once TB disease has been excluded.	**12H**
	HIV-negative	**Contacts:** Evaluate all HIV-negative adults, adolescents and children ≥25kg in close contact with people diagnosed with TB and start TPT once TB disease has been excluded.	**3HP, 3RH or 6H**
		Evaluate all HIV-negative **at-risk groups** (on anti-TNF treatment, on dialysis, preparing for organ or haematological transplant, or with silicosis). Once TB disease is excluded, start TPT.	
		Evaluate HIV-negative adults and adolescents who **previously received TPT**, if re-exposed to a close contact with TB and start TPT once active TB has been excluded.	
		Evaluate all TB exposed **HIV-negative pregnant women** and give TPT once TB disease has been excluded.	**3RH or 6H**
Infants and children <25kg	HIV -positive	**Children living with HIV (CLHIV):** Evaluate all children older than 14 weeks of age living with HIV for TB and start TPT once active TB has been excluded. ART should be started immediately if newly diagnosed with HIV. TPT should be started within two weeks of ART initiation.	**6H****
		Contacts: Evaluate all TB-exposed CLHIV and start TPT after TB disease has been excluded, regardless of previous treatment or TPT.	
	HIV-negative	**Contacts:** Evaluate HIV-negative children in close contact with a TB patient and start TPT after active TB disease has been excluded.	**3RH**
		Test other **HIV-negative at-risk children** (weakened immune system e.g., cancer, autoimmune diseases, transplant patients on immunosuppressive drugs, receiving dialysis, or inherited immunodeficiencies) for TB and start TPT once TB disease has been excluded	

* For adults, adolescents and children ≥25kg *initiating* a dolutegravir-containing ART regimen, 12H is preferred. For PLHIV who are virally suppressed (VL<50 copies/mL) on a dolutegravir-containing regimen, 3HP is preferred.,

** In children <25kg initiating a dolutegravir-containing ART regimen, 6H is preferred. Once the dolutegravir levels from the DOLPHIN-2, DOLPHIN-kids and TBTC Study 35 trials are available, 3HP will likely be the preferred option in all PLHIV. If 3HP is not available, use either 6H (children<25kg) or 12H (adults, adolescents and children ≥25kg)

***Previously treated with TPT**:** If re-exposed to any close contact with TB, retest for TB and give TPT once TB disease has been excluded. 12H is a once off course. 6H or 3HP is recommended for subsequent exposures depending on eligibility of the regimen.

3. RIFAPENTINE USE IN TPT REGIMEN

Utilizing shorter duration TPT regimens, whenever feasible, will reduce the burden of treatment on individuals, households and healthcare services. The 3HP regimen is as safe and effective, achieves significantly higher treatment completion rates and has lower risk of hepatotoxicity compared to the 6H regimen. It is the preferred option if there are no contraindications.

The Western Cape Government Health & Wellness (WCGHW) has received donated rifapentine stock from the Global Fund. The Provincial Pharmaceutics and Therapeutics Committee (PPTC) has granted approval for utilizing the donated rifapentine for eligible TPT patients as per this circular. The coding of rifapentine will be reviewed once the donated stock has been depleted.

3.1 PROGRAMMATIC IMPLEMENTATION FOR A 3HP REGIMEN

Rifapentine is not provincially coded and thus province does not procure rifapentine. The stock levels of rifapentine will be closely monitored at the Cape Medical Depot (CMD). While province has donated rifapentine in excess, it is essential to ensure that patients who begin a course of 3HP can complete their treatment regimen. This should be considered when implementing 3HP.

The following options are proposed:

1. **Dispense one month of treatment initially, followed by the remaining two months at the subsequent visit.**
2. **Supply patients with the full three-month course at the time of dispensing.**

Both options aim to ensure that patients prescribed the 3HP regimen can complete their treatment without interruption.

4. GUIDANCE ON DRUG INTERACTIONS

The *Interim National Clinical Guidance on the Use of 3HP* provided information on drug-drug interactions and the effect on isoniazid and rifapentine but did not provide detailed management strategies. In collaboration with the Medicine Information Centre, we have developed a table (annexure 1) to aid clinicians in selecting the most appropriate TPT regimen for their patients considering any concurrent treatment that they may be on.

5. ORDERING OF RIFAPENTINE

Rifapentine can be ordered via the pharmacy ordering system from the Cape Medical Depot (CMD).

DEPOT CODE	DESCRIPTION	ICN
7300011	RIFAPENTINE 150 MG; TABLET;24'S	3767663

6. TRAINING

People Development Centre (PDC) hosted a Provincial HAST Policy Update session on 12 July 2023 in the Metro district and on 26 July 2023 in the Rural district, the updated TPT guidelines where covered in the training. Video recordings are available on the PDC online resource library.

National Department of Health conducted TPT training on 11 October 2023. Training was attended by Metro Health Services (NDoH), Rural Health Services (RHS) and City of Cape Town supported by PDC. Training covered expanded eligibility criteria, clinical guidelines, management of adverse events and recording and reporting. All in-person attendees were given National Guidelines on the Management of Tuberculosis Infection booklets, additional booklets were distributed to RHS districts for online attendees.

PDC also has TPT included in the Prevention and management of HIV as well as Prevention and management of TB. Both programmes are currently online on the PDC online school. https://wcgh-pdc-online-school.thinkific.com/

7. ADVERSE EVENTS

Reporting of Adverse Drug Reactions (ADRs) provides important information that enables improvement in the quality of patient care. Rifapentine will be introduced to a wider population, hence the need for enhanced pharmacovigilance. The Western Cape Department of Health and Wellness (WCDHW) has appointed the Medicines Information Centre (MIC) to manage ADR reporting in the province. The MIC performs causality assessments on the ADRs. Healthcare workers are advised to complete the information as accurately and with as much detail as possible.

Official WCDHW ADR reporting can be done in the following ways:

1. Email the completed ADR form (annexure 2) to the Medicine Information Centre (MIC), who captures the information into Sinjani (pha-mic@uct.ac.za)
2. Local facility capture on Sinjani

**** Note: it is recommended that only clinicians/pharmacists capture reports on Sinjani. If there is insufficient capacity for this, please send the completed form to MIC who will capture the information on behalf of the reporter****

8. IEC MATERIAL

Service Priorities Coordination (SPC) in collaboration with NPO partner TB proof produced IEC material on TPT and TUTT as part of the basket of services available to users, in both poster and pamphlet formats. Material will be printed and distributed to all districts in due course.

9. DATA MANAGEMENT FOR MONITORING AND EVALUATION

TPT will continue to be reported as per current indicators:

- Eligible for TPT
- Initiated on TPT
- Completed TPT

There are no additional recording and reporting requirements

Yours sincerely,

Dr JO ARENDSE
CHIEF DIRECTOR: ECSS
DATE: 9 Feb 2024

Annexure 1

Western Cape Government FOR YOU

GUIDANCE FOR DRUG INTERACTIONS WITH
INH (isoniazid) daily or 3HP [isoniazid + rifapentine (RFP)] once weekly

MEDICINES INFORMATION CENTRE

INTERACTING DRUG	INTERACTION WITH:		COMMENT
	ISONIAZID (INH)	ISONIAZID AND RIFAPENTINE (3HP)	
ANTICOAGULANTS			
Warfarin	Rare cases of increased INR.	Potential reduced effects of warfarin.	Both INH & 3HP: Monitor INR & adjust warfarin dose accordingly.
ANTIDIABETICS			
Insulin	↓ Blood glucose lowering effect of insulin. Monitor blood glucose & adjust insulin dose accordingly.	No clinically significant interaction expected.	3HP recommended.
Glimepiride	↑ Glimepiride Hypoglycaemia risk > in elderly & chronic renal failure. Monitor blood glucose & adjust glimepiride dose accordingly.	No interaction reported.	3HP recommended.
Metformin	No interaction expected.	No interaction expected.	
ANTIEPILEPTICS			
Carbamazepine	↑ Carbamazepine	↑ Carbamazepine	Therapeutic drug monitoring required for carbamazepine, phenytoin & valproic acid, & dose adjustments required where necessary. Alternatively, lamotrigine or levetiracetam may be used.
Phenytoin	↑ Phenytoin	↓ OR ↑ Phenytoin	
Valproic acid	↑ Valproic Acid and possible ↑ INH	↓ Valproic Acid	
ANTIHYPERTENSIVES			
Amlodipine	No interaction reported.	↓ Amlodipine Monitor blood pressure & adjust dose of amlodipine accordingly.	INH recommended.
ANTIPSYCHOTICS			
Clozapine	No interaction reported.	↓ Clozapine Monitor response & adjust Clozapine dose accordingly.	INH recommended.
Haloperidol	↑ Haloperidol Monitor & adjust dose of haloperidol accordingly.	No clinically significant interaction expected.	3HP recommended.
Olanzapine/Quetiapine/ Risperidone	No interaction reported.	No interactions reported, but rifapentine is predicted to ↓ antipsychotics.	INH recommended.
ANTIRETROVIRALS			
Dolutegravir	No interaction reported.	↓ Dolutegravir	INH recommended to ART naïve people living with HIV. 3HP recommended if VL <50/LDL on a DTG regimen.
Protease Inhibitors (Atazanavir/ritonavir (r); Darunavir/r Lopinavir/r)	No interaction reported.	Do not co-administer.	INH recommended.
CARDIAC GLYCOSIDE			
Digoxin	No interaction reported.	Potential ↓ digoxin concentrations. Monitor serum digoxin concentra- tions & adjust dose accordingly.	INH recommended.
CONTRACEPTIVES			
Combined Oral Contraceptive (COC), Progestogen only oral contraceptive, Emergency contraception, Etonogestrel subdermal Implant.	No clinically significant interaction.	Potential ↓ contraceptive efficacy. Additional non-hormonal/barrier contraception must be used during & for 2 weeks after 3HP treatment cessation.	Injectable contraceptives (Medroxyprogesterone acetate or Norethisterone enan- thate) may be used for patients on 3HP.
GLUCOCORTICOIDS			
Prednisone, prednisolone	Possible ↓ INH, depending on acetylator status.	↓ Prednisone, prednisolone	Monitor for efficacy and increase dose of prednisone/prednisolone if needed if on 3HP.

Note: Rifampicin and rifapentine are both potent enzyme inducers, the drug interaction effect of rifampicin will however be more pronounced due to the daily dose of administration.

Please note inducing effect of RFP is expected to last for up to 2 weeks after stopping RFP. Remember to reduce increased doses of interacting medicine 2 weeks after discontinuing RFP.

NEED HELP?

Contact the TOLL-FREE National HIV & TB Health Care Worker Hotline

0800 212 506 /021 406 6782

Alternatively "WhatsApp" or send an SMS or "Please Call Me" to 071 840 1572

www.mic.uct.ac.za

February 2024, Version 1

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5. PUBMED
6. World Health Organization. WHO Family Planning, A Global Handbook for Providers, Updated 4th Edition 2022, United States Agency for International Development.
7. Faculty of Sexual & Reproductive Healthcare May 2022. FSRH Clinical Guidance: Drug Interactions with Hormonal Contraception
8. National Department of Health (RSA). National Tuberculosis Management Guidelines 2014

Annexure 2

Western Cape Government Health
BETTER TOGETHER.

SAHPRA South African Health Products Regulatory Authority

MEDICINES INFORMATION CENTRE

ADVERSE DRUG REACTION (ADR)/PRODUCT QUALITY PROBLEM REPORT FORM (WESTERN CAPE PUBLIC SECTOR) (Including Herbal Products)

Reporting Health Care Facility/Practice					
Tel: (021) 406 6829 **Fax:** (021) 448 0503 **E-mail:** pha-mic@uct.ac.za	Facility/Practice				
	District		Tel		
	Province		Fax		

Patient Details									
Patient Initials		File/Reference Number		Date of Birth/Age					
Sex	☐ M ☐ F ☐ Unk	Race		Weight (kg)		Height (cm)		Pregnant?	☐ N ☐ Y
Allergies				Estimated Gestational Age at time of reaction					
RVD positive: ☐ N ☐ Y ☐ Unk		Baseline CD4:	Current CD4:	TB: ☐ N ☐ Y ☐ Unk		Type of TB: ☐ DS-TB ☐ DR-TB			

Suspect Medicine(s) including all other medicines patient was taking at time of reaction [Including over-the-counter and herbal products]

Trade Name [Generic Name if Trade Name is unknown]	Route	Dose (mg) and Interval	Date Started/Given	Date Stopped	Reason for use	Batch Number	Expiry Date

Adverse Drug Reaction/Product Quality Problem			
Date and time of onset of reaction		Date reaction resolved/duration	

Please describe Adverse Reaction/Product Quality Problem: (kindly add as much clinical information as possible)

Intervention(tick all that apply)	**Patient Outcomes (tick all that apply)**
☐ No intervention	☐ ADR recovered/resolved ☐ recovering/resolving
☐ Intervention unknown	☐ Not recovered/not resolved
☐ Patient Counselled/non-medical treatment	☐ Patient Died: Date of death: _____
☐ Discontinued Suspect Drug; **Replaced with**: _____	☐ Impairment/Disability ☐ Congenital Anomaly
☐ Decreased Suspect Drug Dosage; **New Dose**: _____	☐ Patient Hospitalised or Hospitalisation prolonged
☐ Treated ADR - with: _____	☐ Life Threatening ☐ Other: _____
☐ Referred to Hospital: **Hospital Name**_____	☐ ADR reappeared after restarting suspect drug/similar drug
☐ Other Intervention (e.g., dialysis): _____	(rechallenge)? ☐ N ☐ Y ☐ Not done ☐ Unknown

Laboratory Results			**Additional Laboratory Results**		
Lab Test	**Test Result**	**Test Date**	**Lab Test**	**Test Result**	**Test Date**

Co-morbidities/Other Medical Condition(s)

Reported by:			
Name		E-mail	
Designation	☐ Nurse ☐ Pharmacist ☐ Doctor ☐ Other:	Telephone	
Date reported		Signature	

THIS ADR REPORT IS NOT A CONFIRMATION THAT THE REPORTER OR THE SUSPECT MEDICINE(S) CAUSED THE ADR **V1.0 03/21**

National Guidelines on the Treatment of Tuberculosis Infection

February 2023

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

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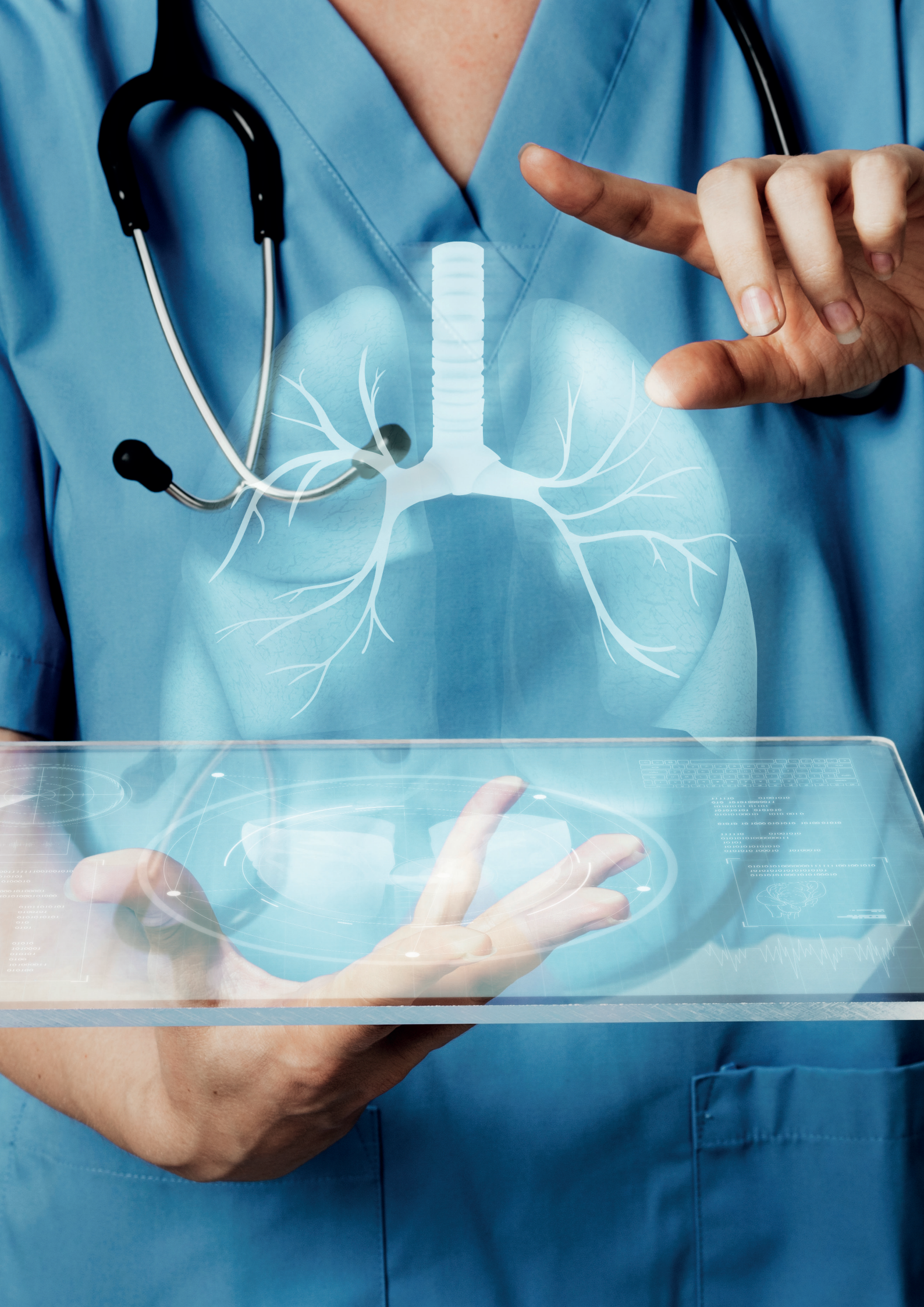


PREFACE

Dr. S. S. S. Buthelezi
Director General: Health

Tuberculosis (TB), HIV and AIDS are the major causes of morbidity and mortality in the country. Modelling work conducted showed that a combination of interventions implemented at scale is required to reach the 2025 End TB Strategy targets of reducing the TB incidence by 50 per cent and the TB mortality by 75 per cent. It is for this reason that the following interventions were implemented:

1. prevention of new infections and TB disease
2. early identification of people with TB through intensified and active TB detection strategies
3. reduction in loss to follow-up
4. improvement of treatment outcomes

Despite the increased uptake of Isoniazid Preventive Treatment (IPT) among people living with HIV and child contacts under five years of age, many eligible populations have still not received IPT, especially among people living with HIV.

The COVID-19 pandemic has reversed the gains made in TB control due to severe disruption of TB screening, testing, and treatment services. More effort is therefore required to ensure that we mitigate the losses incurred and catch up on progress against our targets.

This guideline has been revised based on the guidance provided by the World Health Organization (WHO), local evidence and experience with TB preventive treatment (TPT) implementation. The purpose is to guide implementation, the management of patients started on TPT and the monitoring and evaluation requirements. It is intended for clinicians, pharmacists and healthcare managers in the public and private sector.

I urge all healthcare workers to familiarise themselves with the content of this guideline and effectively implement the recommendations thereof to prevent TB disease in identified high risk groups. This intervention will reduce the burden of TB which continues to kill many people in the country and ensure that South Africans live long and healthy lives.

DR S S S BUTHELEZI
DIRECTOR GENERAL: HEALTH

ACKNOWLEDGEMENTS

The development of these guidelines for TB preventive treatment took hard work by officials of the Department of Health, and representatives from partner organisations. Amongst many, we wish to acknowledge the contributions of the following:

- Members of the National TB Think Tank, especially the TB Prevention Task Team
- World Health Organization (WHO)
- United States (US) President's Emergency Plan for AIDS Relief (PEPFAR)
- The Global Fund to Fight AIDS, TB and Malaria

LIST OF ABBREVIATIONS

ART	Antiretroviral treatment
BCG	Bacillus Calmette-Guérin
CCMDD	Central chronic medicine dispensing and distribution
CHW	Community health worker
CLHIV	Children living with HIV
CXR	Chest x-ray
DHMIS	District Health Management Information System
DTG	Dolutegravir
DSD	Differentiated service delivery
DS-TB	Drug-susceptible TB
FDC	Fixed-dose combinations
HIV	Human immunodeficiency virus
HLM	High level meeting
IGRA	Interferon-gamma release assay
IPT	Isoniazid preventive treatment
IRIS	Immune reconstitution inflammatory syndrome
LF-LAM	Lateral flow urine lipoarabinomannan assay
LFT	Liver function test
LTBI	Latent tuberculosis infection
MDR-TB	Multidrug-resistant TB
MMD	Multi-month dispensing
PEPFAR	President's Emergency Plan for AIDS Relief
PLHIV	People living with HIV
PMTCT	Prevention of mother-to-child transmission
PHC	Primary healthcare
RPC	Repeated prescription collection
SDGs	Sustainable development goals
TB	Tuberculosis
TBTC	Tuberculosis Trials Consortium
TIER	Three interlinked electronic registers
TLD	Tenofovir / Lamivudine / Dolutegravir
TPT	TB preventive treatment
TST	Tuberculin skin test
UN	United Nations
WHO	World Health Organization
Xpert	GeneXpert MTB/RIF (Ultra, or latest recommended version)
3HP	3 months of weekly isoniazid plus rifapentine
3RH	3 months of daily rifampicin plus isoniazid
6H	6 months of daily isoniazid monotherapy
12H	12 months of daily isoniazid monotherapy

LIST OF DEFINITIONS

Adherence	The extent to which a person's behaviour corresponds with agreed recommendations from a healthcare worker for taking medication, following a diet and/or making lifestyle changes
Adolescent	A person aged 15 to 19 years
Child	For practical purposes, children weighing >25kg (typically eight to ten years of age) can be treated with adult doses of TB medications including for TB preventive treatment (TPT). Children weighing >25kg can also usually produce sputum for TB testing. For reporting purposes, children are defined as 0 to 14 years of age by WHO.
Evaluation	The periodic assessment of the change in targeted results that can be attributed to the programme intervention, or the analysis of inputs and activities to determine their contribution to results
Infant	A child under one year of age
Index patient	A person (adult or adolescent) with infectious pulmonary TB
Latent TB infection	A state of immune response to stimulation by *Mycobacterium tuberculosis* antigens, indicated by a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA) test, with no evidence of active TB disease
Monitoring	The tracking of key elements of programme performance (inputs, activities and results) on a regular basis to provide continuous information on progress towards achieving goals, and alert staff and managers to problems, providing an opportunity for these to be resolved early
Recent TB exposure	Contact with a person diagnosed with pulmonary TB in the last 12 months. The person may be from the same household, or be a close contact outside of the household setting, e.g., a care provider, colleague, teacher, family member or friend
Significant TB exposure	Known exposure to a person (adult or adolescent) with pulmonary TB who shared the same enclosed space for one or more nights or for frequent or extended daytime periods during the three months before the index patient starting their TB treatment. Significant TB exposure can occur in *any setting*, e.g., the household, workplace, place of learning or care. Therefore, the term "household contact" is confusing since it is limited in scope and should no longer be used. "TB contact" will therefore be used throughout this document.
TB contact	All people (family members and other individuals; regardless of age and HIV status) who have had a 'significant TB exposure' – that is: shared the same enclosed space or shared living arrangement with a TB index patient for one or more nights or for frequent or extended daytime periods during three months before the start of current treatment in the TB index patient with pulmonary TB
TB disease	Disease caused by Mycobacterium tuberculosis. TB can either be bacteriologically confirmed or clinically diagnosed
TB exposed infants	Infants born to mothers who were diagnosed with TB before or after the baby was born, or other documented close TB exposure in the infant (e.g. another caregiver, family member, day care provider)
Silicosis	Lung fibrosis caused by the inhaling silica-containing
3HP	three months of weekly isoniazid plus rifapentine
3RH	three months of daily rifampicin plus isoniazid
6H	six months of daily isoniazid monotherapy
12H	12 months of daily isoniazid monotherapy

EXECUTIVE SUMMARY

Rationale for expanded eligibility for TPT: A TB test and treat approach

It is essential that TB preventive treatment (TPT) is scaled up to reduce the burden of TB in South Africa. Previously, TPT was offered only to people who were at the highest risk of progressing to TB disease after exposure (i.e., children younger than five years of age, and all people living with HIV, regardless of age). However, to achieve TB elimination, it is imperative to **implement TPT more comprehensively for *everyone* with significant TB exposure and all other individuals at high risk of TB**. Diagnostic evaluation processes, TPT initiation processes, TPT regimens, and clinical evaluation at follow-up will vary by age, HIV status, and pregnancy status. However, TB testing and TPT should be offered to *all* people with significant TB exposure or who have a high risk of TB disease progression – i.e. a TB test and treat (offering either TPT or active TB treatment) approach. The use of shorter duration TPT regimens, where possible, will reduce the burden of TPT treatment on individuals, households and on health services.

In most instances, people who should be offered TPT will share a household with at least one person who is concurrently on TB treatment. Therefore, where possible, **a *'family-centred'* approach to TPT initiation and adherence support should be adopted** by integrated healthcare worker teams or health services where possible. It is also important to consider the context of the household, and to offer similar regimens to affected household members, where possible.

TB test and treat approach: It is essential to rule out TB disease before initiating TPT. Therefore, all individuals (adults, adolescents, children and infants) should always be evaluated for TB disease before initiating TPT, including testing for active TB disease. Thereafter, the next decision, in the presence of significant TB exposure or TB risk, is to either offer TB treatment (in the presence of disease) or to offer TPT. In the past, uncertainty over diagnostic requirements and the limited availability of diagnostic tools were significant barriers to TPT access. The guiding principle for these revised guidelines is to help overcome several of these barriers.

All people considered for TPT should undergo clinical evaluation (symptom check and physical examination) **and be tested with GeneXpert (Xpert), even if asymptomatic**. TB testing strategies will vary by age as younger children cannot spontaneously expectorate sputum. Other clinically relevant samples should be considered in children (gastric aspirates, fine needle aspirates, stool). In children without symptoms, neither sputum testing nor chest x-ray (CXR) are therefore requirements to start TPT. Sputum testing should be attempted in children who can expectorate spontaneously (typically >=25kg), but if they are well (without symptoms) and unable to expectorate, they should start TPT, even if no CXR or sputum testing is available.

If unable to produce sputum, people considered for TPT should undergo clinical evaluation as a minimum, and a CXR where available. Other samples should be considered as clinically relevant. CXR is a valuable tool to rule out TB disease in adults and in children, but its absence should not pose a barrier to starting TPT in anyone – especially in children, if they are well and have no symptoms.

If test availability varies by setting, TB testing deficiencies should be urgently addressed in parallel to excluding active TB disease and encouraging TPT access. The National TB Prevalence Survey1 has highlighted the high burden of asymptomatic TB amongst adults and adolescents, reflecting the importance of having a low threshold for testing people for active TB, especially before offering TPT, including in people not historically considered to be at high risk of TB disease.

It is important to recognise the difference between testing for TB infection (e.g., TST, IGRA) and testing for TB disease (Xpert/culture, chest x-ray, LF-LAM). Tests for TB infection are useful to detect TB infection, and to predict who is at the highest risk of developing TB disease, but are not a requirement to starting TPT. If tests of infection are not available, this should not pose a barrier to TPT initiation. A positive test of TB infection means that the person is (or was previously) infected with *M.tb*, but does not indicate (or exclude) TB disease. Also, a negative test of TB infection does not mean that the person is not actually infected with *M.tb* or is not at risk for developing TB disease in the near future. Therefore, tests of TB infection are no longer listed in these algorithms and not are not requirement to initiate TPT. Any lack of availability of tests of TB infection should not impact whether somebody is offered TPT or not. In individual clinical scenarios, tests of TB infection may be used by clinicians as available as useful tests to determine TB infection status and the risk future disease progression.

In contrast, testing (clinical evaluation and other test) for TB disease is required before disease can be ruled out and should be made available to all people before being offered TPT (refer to the section on children for exceptions as clinically relevant).

People who require TPT

TB contacts: All adults, adolescents and children (including newborns or infants) exposed to TB require TPT once TB disease has been excluded through evaluation – irrespective of HIV status, pregnancy, or previous TB disease or treatment status. Significant TB exposure can occur in any setting, e.g. in the household, workplace, place of learning or care, or other. Therefore, the term "household contact" is confusing (the definition is too narrow) and should no longer be used. Going forward, the term "TB contacts" should therefore be used. After each TB exposure, the exposed person must be evaluated for TB again and either TB treatment or TPT should offered (e.g., repeat TB test and treat approach after each significant TB exposure). TPT is only effective while it is being given, so previous TPT does not protect against a new TB exposure.

All pregnant women with significant TB exposure (irrespective of age or HIV status) should be offered TPT once TB disease has been excluded through testing. TPT should therefore not be deferred to the post-partum period. TB disease should be ruled out repeatedly during pregnancy, through initial evaluation as described above, and by using symptom screening during subsequent antenatal visits. Further evaluation should be based on symptoms, the clinical picture and any new information on TB exposure.

People living with HIV (PLHIV): All adults, adolescents and children including infants living with HIV (irrespective of a known significant TB exposure) should receive a course of TPT once TB disease has been excluded through testing. People newly diagnosed with HIV should always be tested for TB prior to initiating antiretroviral treatment (ART). PLHIV who are already on ART, but who have not taken TPT before, should also be tested for TB. TPT should then be offered if no evidence of TB disease is found in PLHIV. Initiating ART should be prioritised and TPT should be started within the next two weeks. If PLHIV interrupted their ART, ART counselling should be undertaken and ART re-initiated.

Other high-risk groups:

Inmates in correctional facilities remain a priority group for treatment of TB infection because the confined indoor spaces they share with other people often practically mean they that meet the criteria of 'significant TB exposure'.

Healthcare workers have a very high risk of TB and should be considered for treatment of TB infection within TB and HIV occupational health services. At the minimum, setting-appropriate annual or bi-annual testing is recommended and additional evaluation, based on clinical indications (e.g. symptoms, new TB exposure) should be undertaken.

People who have previously had TB (TB survivors) are at higher risk of getting TB again and should be considered for treatment of infection after another significant TB exposure.

Silicosis: People with silicosis have a significant risk of developing TB disease and should be considered for treatment of infection regardless of significant TB exposure.

Choice of regimen

In South Africa, the current TPT options include isoniazid and rifapentine given once weekly for three months (3HP), daily rifampicin and isoniazid for three months (3RH), daily isoniazid for six months (6H) or daily isoniazid for 12 months (12H). As a rule, **shorter treatment options should be offered where feasible and available**. If 3HP is not available (or contra-indicated), 3RH or 6H should be offered for people who tested negative for HIV, and 12H for PLHIV (6H for children with HIV) and 3RH for children <25 kg. 3HP is not yet available in children < 25 kg in South Africa, 3RH should therefore be used, unless contra-indicated. Fixed-dose combinations (FDCs) for 3RH that are dispersible, scored and child-friendly, are routinely available in the country.

Options for TPT regimens will be revised immediately once new evidence regarding safety, efficacy, appropriate dosing and the required patient-friendly formulations become available. The TPT regimen chosen will depend on the patient's weight (in the case of children); HIV status; unique individual, household or family considerations; assessment of potential drug interactions with other medications (including ART); availability of TPT formulations and the current evidence. A child-friendly fixed-dose dispersible formulation of rifampicin and isoniazid (3RH) is already widely available, while a child-friendly rifapentine (P) formulation is not available yet. Therefore, 3RH is the preferred regimen for HIV-negative children <25 kg, who are not yet eligible for the 3HP regimen.

Children ≥25kg, adolescents and adults:

Older children weighing ≥25kg (typically eight years and older) can be offered 3HP if the regimen is available since they can receive adult doses of TB medications. These include children living with HIV, if they are on a dolutegravir-based regimen with a suppressed viral load (VL <1000 in the last six months). Accordingly, the guidelines have been stratified into two weight groups: children under 25kg, and everybody else above or equal to 25kg, including older children, adolescents and adults. If 3HP is not available, 3RH (in HIV-negative individuals) should be used as the priority regimen. 6H also remains an option for people who are not living with HIV, if preferred. 12H should be offered to all PLHIV who

are starting a dolutegravir-containing regimen (6H in children with HIV). For individuals already virally suppressed or who are not starting a dolutegravir-containing regimen, 3HP is preferred.

It should be noted that shorter TPT regimens in general, in all people, usually have better completion rates, are safer and are better tolerated than longer regimens, in adults, children, adolescents, pregnant women and PLWH.

Children <25kg:

3RH is the preferred regimen for children under 25kg not living with HIV. 6H is preferred (above 3RH) for children under 25kg living with HIV and in infants/children born to pregnant women living with HIV, due to the risk of drug-drug interactions with ART and the potential for decreasing the effectiveness of prevention of mother-to-child transmission (PMTCT). Once child-friendly rifapentine (P) formulations become available and the appropriate dose and safety of 3HP is known in young children, 3HP may in future become an available option for children < 25 kg.

Where possible, when considering a TPT regimen, preference should be given to individuals in one household or group receiving the same type of regimen. This should be done to lessen the burden and complexity of TPT on the individuals and the family/group; reduce the chances of being stigmatised; and facilitate support, monitoring and evaluation of TPT at the programme level.

While the **same test and treat** approach as that for drug-susceptible TB (DS-TB) should be applied for **people exposed to drug-resistant TB** (DR-TB), the management of DR-TB contacts must consider all available M. tuberculosis resistance data. Additional drug susceptibility testing should be attempted for known sources/index patients. Please refer to the latest *National Drug-resistant TB Treatment Guidelines* for the management of DR-TB exposed individuals.

Support for people on TPT

Individuals offered TPT require appropriate education and counselling prior to TPT initiation, with continued support during their TPT journey. Individuals should be educated about the potential options for TPT and about TB testing strategies. A family-centred, household-based approach may support adherence and improve TPT acceptability. Community health workers (CHWs) can and should play a key role in providing home-based person-centred treatment support, as they already do for active TB treatment and for ART. All care providers need to be trained on the updated guidelines, with a special emphasis on scaling up access among previously neglected groups (e.g. in HIV-negative contacts older than five years).

After TPT initiation, clinical follow-up is important to monitor for safety, support adherence, checking the weight and adjusting the dose as needed, and to re-evaluate for TB disease. Monthly monitoring for adherence and adverse effects of TPT is recommended. Patients should be carefully assessed for adverse effects, using standard reporting tools as per the National Pharmacovigilance Centre (Tel: (012) 501 0311 and e-mail: adr@sahpra.org.za).

After completing a course of TPT, individuals should be informed that subsequent TPT is required if another significant TB exposure occurs and that they should access care for TB evaluation.

Children should be weighed at every visit and dosages adjusted based on actual weight to prevent under- or overdosing. Patients and children's caregivers should be counselled regarding side effects of TB medications. They must be actively encouraged to present for evaluation should they develop new symptoms, such as fever, night sweats or cough, that could indicate TB disease or immune reconstitution inflammatory syndrome (IRIS), or if weight loss (or failure to gain weight, in children) occurs.

Monitoring and evaluation

It is important that programmatic assessments should be conducted to determine whether TPT delivery targets are being met, using existing data collection tools. These include available electronic or other registers, and cascade analysis. Such assessments should establish indicators and outcomes. Refer to Section 12 for more details.

1. INTRODUCTION AND RATIONALE

1.1 Background

South Africa, with 13 other countries, carries the major triple burden of drug-susceptible TB (DS-TB), multidrug-resistant TB (MDR-TB) and TB co-infected with HIV (TB/HIV), and is among the top 30 high TB burden countries identified by the World Health Organization (WHO). The WHO estimated that, in 2019 there were 360 000 new people with TB disease in South Africa, of whom 58 per cent were living with HIV[2]. TB is the leading cause of death in South Africa[3].

The COVID-19 pandemic has put the gains made for TB at risk. Not only does SARS-CoV-2 pose an increased risk to people with TB, but it has severely disrupted services. An estimated 1.4 million fewer people received care for TB last year – 21 per cent less than in 2019. The Director-General of the WHO announced in June 2021 at the WHO high-level event on a global drive to scale up TB prevention that the disruption of TB services could cause an additional half a million deaths[4]. He reiterated the urgency to preventive treatment for household contacts of people with TB, including children, alongside efforts to find people with TB disease among people living with HIV.

Significant exposure to TB in all age groups, people living with HIV (PLHIV), miners, inmates, pregnant women, immunocompromised individuals, those with silicosis and healthcare workers are at especially high risk of developing TB disease – with reported rates of infection ranging from 26 per cent up to 89 per cent. [5-11]

Prevention of TB disease is enshrined in South Africa's *National Strategic Plan for HIV, TB and STIs (Sexually Transmitted Infections) 2017-2022*[12]. It is a critical component of the WHO End TB Strategy, which together with the United Nations (UN) Sustainable Development Goals (SDGs), commits to end the global TB epidemic by 2030 or sooner[13]. This commitment was endorsed at the first UN High Level Meeting (HLM) on TB in New York, also attended by representatives and the President of South Africa in September 2018. The meeting set a target of 30 million people (including PLHIV and household contacts) to be provided with TPT between 2018 and 2022. From estimates computed by the Stop TB Partnership, South Africa's contribution to this global target is 2 572 100 people.

1.2 TB Preventive Treatment (TPT)

TPT is an effective and safe intervention to reduce the risk of developing TB disease for all age groups with TB exposure. TPT is also an effective intervention to reduce the risk of developing TB disease amongst PLHIV[14] and those with silicosis[15], regardless of documented TB exposure.

The overall guiding principle is therefore that: **TPT should be offered to all people (regardless of age and HIV status) after significant TB exposure and those who are immunocompromised (regardless of known exposure), after TB disease has been ruled out, i.e., a TB test and treat approach. Figure 1** describes the overall principle of eligibility for TPT.

Even those who previously completed TB treatment may experience multiple significant exposures or acquire/develop immunocompromising conditions over their life course. **TPT is indicated at each new TB exposure or each period of immunocompromise.**

The TPT regimen chosen will depend on the weight (for children), the HIV status, the type of patient and their circumstances, household or family considerations, other medications including ART, the availability of formulations and current evidence. **Where possible, individuals in one household or group should receive the same type of TPT regimen** to lessen the burden and complexity of TPT on the individuals and family/group, reduce the chances of being stigmatised and facilitate support, monitoring and evaluation.

In South Africa, the current TPT options include:

- **3HP:** three months of isoniazid and rifapentine given once **weekly**
- **3RH:** three months of **daily** rifampicin and isoniazid
- **6H:** six months of **daily** isoniazid
- **12H:** 12 months of **daily** isoniazid

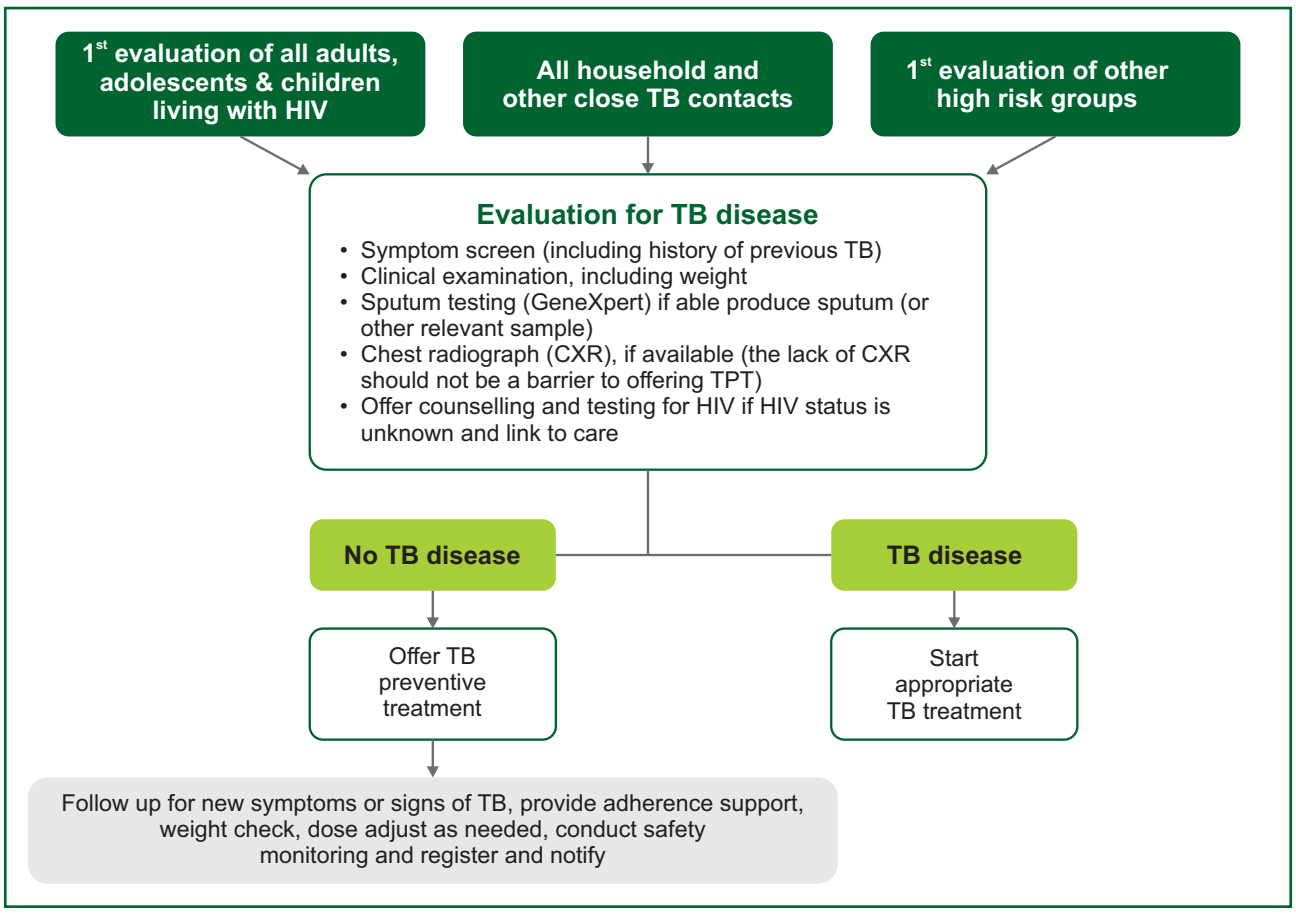
The 3HP regimen is as safe and effective, achieves significantly higher treatment completion rates and has a significantly lower risk of hepatotoxicity than 6H[16, 17]. It is therefore the preferred option if there are no contra-indications. The isoniazid-only regimens (6H and 12H) also have very low rates of adverse events[18] and do not lead to isoniazid resistance[19].

In asymptomatic children, sputum testing or CXR is NOT a requirement to start TPT. Tests of TB infection (tuberculin skin test/TST or IGRA) are not required to initiate TPT.

Once the dolutegravir levels from trials like the DOLPHIN-2, DOLPHIN-kids and Tuberculosis Trials Consortium (TBTC) Study 35 trials are known and a child-friendly rifapentine formulation is available, 3HP will likely be the preferred option in all PLHIV, regardless of age and weight. In general, in PLHIV, if 3HP is not suitable, use either 6H (children) or 12H (adults).

Options for TPT regimens will be revised as new evidence regarding safety, efficacy, appropriate dosing and patient friendly formulations become available in South Africa. **Table 1** summarises the current treatment options and their duration. **Where possible, shorter TPT regimens should be prioritised.**

Figure 1. General algorithm for provision of TB preventive treatment using the test and treat approach



1.3 Tests of TB infection: Tuberculin Skin Tests (TST) and Interferon-Gamma Release Assays (IGRA)

It is important to recognise the difference between testing for TB infection (e.g., tuberculin skin test; TST, interferon-gamma release assay; IGRA) and testing for TB disease (Xpert/culture, chest x-ray, Urine LF-LAM). Tests for TB infection are useful to detect TB infection but are not a requirement to starting TPT. A positive test of infection means that the person is (or was previously) infected with *M.tb*, but does not indicate (or exclude) TB disease. Also, a negative test of infection does not mean that the person is not actually infected with *M.tb* or is not at risk for developing TB disease in the near future. Therefore, tests for TB infection are no longer listed in these algorithms and any lack of availability should not impact whether somebody is offered TPT or not. Tests of TB infection may be used in individual care settings at clinician discretion.

TPT should be offered to all people after significant exposure to an adult or adolescent with active pulmonary TB disease (TB contacts) or if the individual is immunocompromised (regardless of known *M.tb* exposure). In the past, the lack of TST or IGRA availability was a barrier to TPT access – this requirement has now been replaced with testing for TB disease, before disease can be ruled out and TPT started. Xpert should be available at all healthcare facilities as a minimum with or without urine LF-LAM and chest x-rays.

Table 1. Summary of TPT regimen options by patient type

PATIENT CATEGORY		WHAT TO DO	REGIMEN
Adults and adolescents including children ≥25kg	HIV-positive	**PLHIV**: Test for TB regardless of ART status and give TPT once TB disease is excluded. If newly diagnosed with HIV, start ART immediately and TPT within the next two weeks.	3HP* or 12H
		Post TB treatment: Offer TPT to all PLHIV ≥25 kg after successfully completing treatment for TB disease, after active TB disease has again been excluded.	
		Previously treated with TPT: If re-exposed to any close contact with TB, retest for TB and give TPT once TB disease has been excluded.	
		Evaluate all **HIV-positive pregnant women** regardless of CD4 count and give TPT once TB disease has been excluded.	12H
	HIV-negative	**Contacts:** Evaluate all HIV-negative adults, adolescents and children ≥25kg in close contact with people diagnosed with TB and start TPT once TB disease has been excluded.	3HP, 3RH or 6H
		Evaluate all HIV-negative **at-risk groups** (on anti-TNF treatment, on dialysis, diabetes, preparing for organ or haematological transplant, or with silicosis). Once TB disease is excluded, start TPT.	
		Evaluate HIV-negative adults and adolescents who **previously received TPT**, if re-exposed to a close contact with TB and start TPT once active TB has been excluded.	
		Evaluate all TB exposed **HIV-negative pregnant women** and give TPT once TB disease has been excluded.	3RH or 6H
Infants and children <25kg	HIV -positive	Children living with HIV (CLHIV): Evaluate all children older than 14 weeks of age living with HIV for TB and start TPT once active TB has been excluded. ART should be started immediately if newly diagnosed with HIV. TPT should be started within two weeks of ART initiation.	6H**
		Contacts: Evaluate all TB-exposed CLHIV and start TPT after TB disease has been excluded, regardless of previous treatment or TPT.	
	HIV-negative	**Contacts:** Evaluate HIV-negative children in close contact with a TB patient and start TPT after active TB disease has been excluded.	3RH
		Test other **HIV-negative at-risk children** (weakened immune system e.g., cancer, diabetes, autoimmune diseases, transplant patients on immunosuppressive drugs, receiving dialysis, or inherited immunodeficiencies) for TB and start TPT once TB disease has been excluded	

* For adults, adolescents and children ≥25kg *initiating* a dolutegravir-containing ART regimen, 12H is preferred. For PLHIV who are virally suppressed (VL<50 copies/mL) on a dolutegravir-containing regimen, 3HP is preferred.,

** In children <25kg initiating a dolutegravir-containing ART regimen, 6H is preferred.

Once the dolutegravir levels from the DOLPHIN-2, DOLPHIN-kids and TBTC Study 35 trials are available, 3HP will likely be the preferred option in all PLHIV. If 3HP is not available, use either 6H (children<25kg) or 12H (adults, adolescents and children ≥25kg).

2. PURPOSE OF THE GUIDELINES

These guidelines provide evidence-based practices for TPT to reduce the risk of progressing to TB in people who experience significant exposures or are immunocompromised, thus reducing the overall burden of TB in South Africa. These guidelines are informed by the latest WHO guidance for TB screening[20] and treatment of latent TB infection[21] and are adapted to South Africa's TB epidemiology, local evidence, the availability of regimens, formulations, resources, health infrastructure and other national determinants.

3. ORGANISATION OF THE GUIDELINES

The guidelines are organised into sections by TPT patient type (Sections 4 to 9). Within each section, there are considerations listed for (a) eligibility criteria that define the patient type in that section, and (b) management of TPT patients described in that section including: (i) the TPT test and treat algorithm, (ii) regimen options, and (iii) dosing instructions per regimen.

There are three groups of potential TPT patients:

1) those (regardless of age and HIV status) who experience a *significant exposure* to TB (contacts),
2) those who are living with HIV and
3) other high-risk groups (people with silicosis, on dialysis, on anti-TNF treatment, on dialysis, preparing for organ or haematological transplant, or other risk groups in national guidelines).

There is some overlap between sections and readers are encouraged to follow the text directing them to other sections as appropriate.

The overall guiding principle is a test and treat approach: **TPT must be offered to all people (regardless of age and HIV status) who experience significant TB exposure or who are immunocompromised, after TB disease has been excluded** – see **Figure 1** for the overarching principles and groups of individuals requiring TPT.

Further, where feasible, a '**family-centred' or 'household-centred' approach to integrated TB treatment and TPT should be followed** to simplify adherence support, reduce the risk of stigmatisation and minimise the therapeutic burden on families. As significant TB exposure occurs in places like households, some residents will be on TB treatment (for active disease) and the others on TPT concurrently.

The management of contacts of DR-TB is addressed in the latest *South African National DR-TB Guidelines*.

4. ADULT, ADOLESCENT AND OLDER CHILD CONTACTS

This group of potential TPT patients were previously called “household contacts”. Significant TB exposure can however occur both within and outside the household. Therefore, the term “household contact” is confusing and should no longer be used. Instead, these guidelines use the term “contacts” for “those with significant TB exposure”, defined as:

Significant exposure: (Documented) exposure to a person (adult or adolescent) with pulmonary TB who shared the same enclosed space for one or more nights or for frequent or extended daytime periods during the three months before the index patient started TB treatment.

4.1 TPT should be offered to:

All adult, adolescent, and child contacts. TPT should be offered regardless of HIV status and age. 3HP can be used for children ≥25kg, adolescents and adults.

Prior completion of either TB treatment or TPT does not exclude a new course of TPT for a new exposure.

4.2 TPT should be deferred or not offered if the individual:

- is diagnosed with TB disease
- has active liver disease (acute or chronic)
- has symptoms and signs of severe peripheral neuropathy (could consider rifampicin only [4R] regimen)
- has a history of adverse reactions to any of the drugs (medications) used for TPT
- drinks excessive alcohol, and is unwilling or unable to scale down use:
- *for men:* more than five standard drinks on any day or 15 drinks per week
- *for women:* more than four standard drinks on any day or eight drinks per week

For individuals with abnormal baseline liver function test results, sound clinical judgement is required to ensure that the benefit of TB preventive treatment outweighs the risks, and they should be tested routinely at subsequent visits.

4.3 Management of TPT in adult, adolescent, and older child (weighing more than25 kilograms) contacts

All adult, adolescent and child contacts require TPT once TB disease has been excluded through evaluation and testing. When an adult or adolescent is diagnosed with pulmonary TB disease it is essential for thorough contact investigations to establish who has had significant exposure to this index patient. Each person with significant exposure should be documented, evaluated for TB disease and offered either TPT or TB treatment – i.e., the TB test and treat approach.

If contacts decline TPT (despite counselling), they should be counselled further regarding TB symptoms and should be offered TPT again at the next opportunity. If they develop symptoms suggestive of TB, they should be evaluated for TB disease again, and be offered TB treatment (if diseased) or offered TPT once more (if TB disease has been excluded).

4.3.1 Evaluation for TB disease amongst adult, adolescent, and older child contacts

Evaluation for TB disease includes symptom screening, physical examination **and diagnostic testing irrespective of reported symptoms**. TB can either be bacteriologically confirmed or clinically diagnosed. Amongst adults, adolescents, and older children (≥25kg), at least symptom screening **and a sputum test are required prior to initiating TPT.**

Please refer to **Figure 2** for the overall approach to the management of adults, adolescents and older children with TB exposure.

Symptom screening for TB disease amongst adults, adolescents, and older children include one or more of the following:

- current cough
- weight loss
- fever
- night sweats
- haemoptysis

Diagnostic tests for TB disease amongst adults, adolescents, and older children, *regardless of the presence of symptoms:*

- a sputum sample for testing using Xpert
- if no sputum sample can be collected, a chest radiograph should be obtained to rule out TB disease
- tests of TB infection (TST/IGRA) are not a requirement to initiate TPT
- most children ≥25kg can spontaneously expectorate sputum. If children cannot expectorate sputum and are well (no signs or symptoms), sputum testing is not

required. CXR should be used as available to rule out TB. If a child is well and CXR is not available, TPT should still be initiated, and the child followed

- in a child with suggestive signs or symptoms, a CXR should be obtained where possible and sputum sampling attempted

4.3.2 TPT regimens for adult, adolescent, and older child (≥25kg) contacts

There are currently four potential regimens for this group: **3HP, 3RH, 6H or 12H**. The short course 3HP regimen should be prioritised if possible. This applies to adults, adolescents and older children who are NOT living with HIV.

If **3HP** is not available for HIV-negative children ≥25kg, adolescents and adults, use **3RH**. Also consider 3RH use as an alternative to 6H, especially to harmonise treatments in a household or family setting.

For adults, adolescents and children ≥25kg living with HIV and initiating dolutegravir-containing ART, **12H** is preferred.

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.

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

4.3.2.3 Recommended daily dosages for the 12H regimen in adults, adolescents and children ≥25kg living with HIV

Drug	Dose	Maximum Dose/day	Duration	Interval
Isoniazid (H)	5mg/kg	300mg*	12 months	Daily

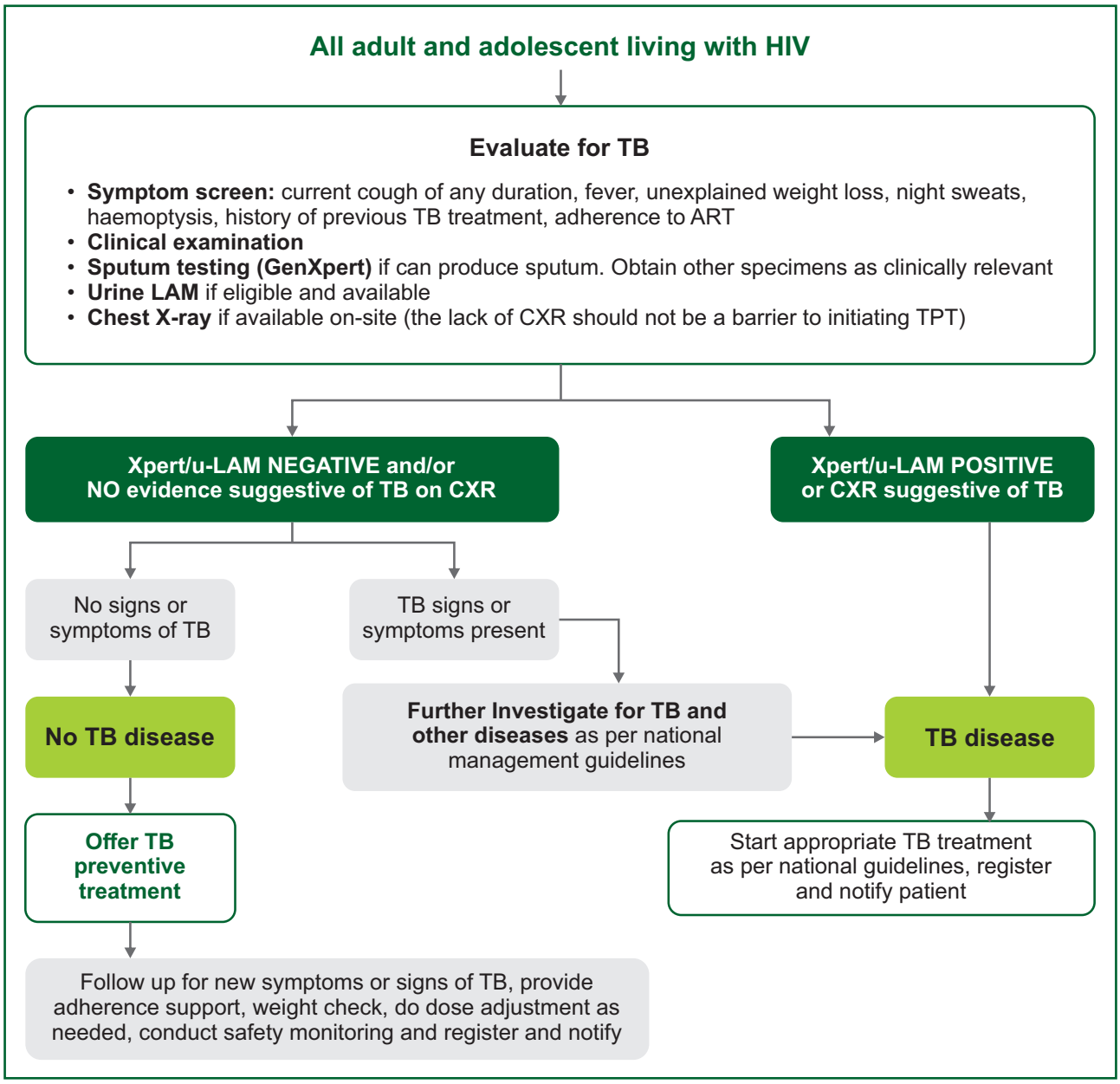
* If 300mg tablets are not available, use 100mg x 3

4.3.2.4. Recommended daily dosages for the 12 months once-daily Isoniazid 12H regimen (only adults living with HIV)

Drug	Dosage	Number of tablets (daily)	Duration
Isoniazid(H)	300mg tablet	1	12 months
	Or 100mg tablet	3	12 months

All people receiving TPT should be offered pyridoxine (vitamin B6) for the duration of their TPT: 25mg/day if five years or older, 12.5mg/day if younger than five years of age. Lack of pyridoxine supply should not be a reason to withhold or postpone TPT.

Figure 2. Algorithm for provision of TB preventive treatment for adult, adolescent and older child (≥25kg) TB contacts



- *Tests of TB infection (tuberculin skin test/TST or IGRA) not required to initiate TPT in adult or adolescent TB contacts*
- *For management of DR-TB exposure, refer to the latest National DR-TB Guidelines*

5. CHILD CONTACTS: CHILDREN WEIGHING LESS THAN 25 KILOGRAMS AND INFANTS

Significant exposure is known (documented) exposure to a person (adult or adolescent) with pulmonary TB who shared the same enclosed space for one or more nights (e.g. at home or similar) or for frequent or extended daytime periods (e.g. at a school, crèche or similar) during the three months before the index patient started TB treatment.

5.1 TPT should be offered to

All children <25 kg with significant TB exposure (child contacts – for older contacts, refer to Section 4).

TPT should be offered regardless of the child's HIV status and age. The practical 25kg cut-off is used since heavier children can be offered 3HP if available. There is not enough evidence yet on dosing or safety or the appropriate formulations available to recommend 3HP in children <25kg.

The prior completion of either TB treatment or TPT does not exclude a new course of TPT in a child.

5.2 TPT should be deferred or not offered if the child:

- is diagnosed with TB disease
- has active liver disease (acute or chronic)
- has symptoms and signs of severe peripheral neuropathy (a clinician may consider a rifampicin only regimen on and individual basis)
- has a history of adverse reactions to any medication used for TPT

5.3 Management of TPT in children weighing less than 25 kilograms

All children (HIV-negative and HIV-positive) with significant exposure to TB require TPT once TB disease has been excluded through clinical evaluation and testing.

When an adult or adolescent patient is diagnosed with pulmonary TB disease it is essential to conduct a thorough contact investigation to establish who had significant exposure to this index patient. Each child with TB exposure is evaluated for TB disease and offered either treatment or TPT (if disease excluded), i.e., the TB test and treat approach.

5.3.1 Evaluation of child contacts

Evaluation for TB disease includes symptom screening, clinical examination and diagnostic testing. These are similar for HIV-negative children and in children living with HIV (see Figure 3).

TB testing strategies are different in older children and younger children, who typically cannot spontaneously expectorate sputum. Sputum testing or CXR in well young children (i.e. without symptoms or signs suggestive of TB) is therefore not a requirement for the initiation of TPT. Sputum testing (and Xpert) should be attempted in older children, who can expectorate spontaneously. Sputum should also be collected in a young child if they are able to expectorate sputum (such children are usually symptomatic).

If parents or guardians of child contacts decline TPT (despite counselling) then they should be counselled further regarding potential TB symptoms and should be offered TPT again at the next opportunity. If the child develops symptoms suggestive of TB, the child should be evaluated for TB disease and be offered TB treatment (if diseased) or be offered TPT again if TB disease has been excluded.

5.3.1.1 Symptom screening for TB disease amongst children – regardless of HIV status:

- current cough
- poor weight gain or failure to thrive or documented weight loss
- fever or night sweats
- lethargy/fatigue (decreased playfulness)
- visible neck mass or swelling

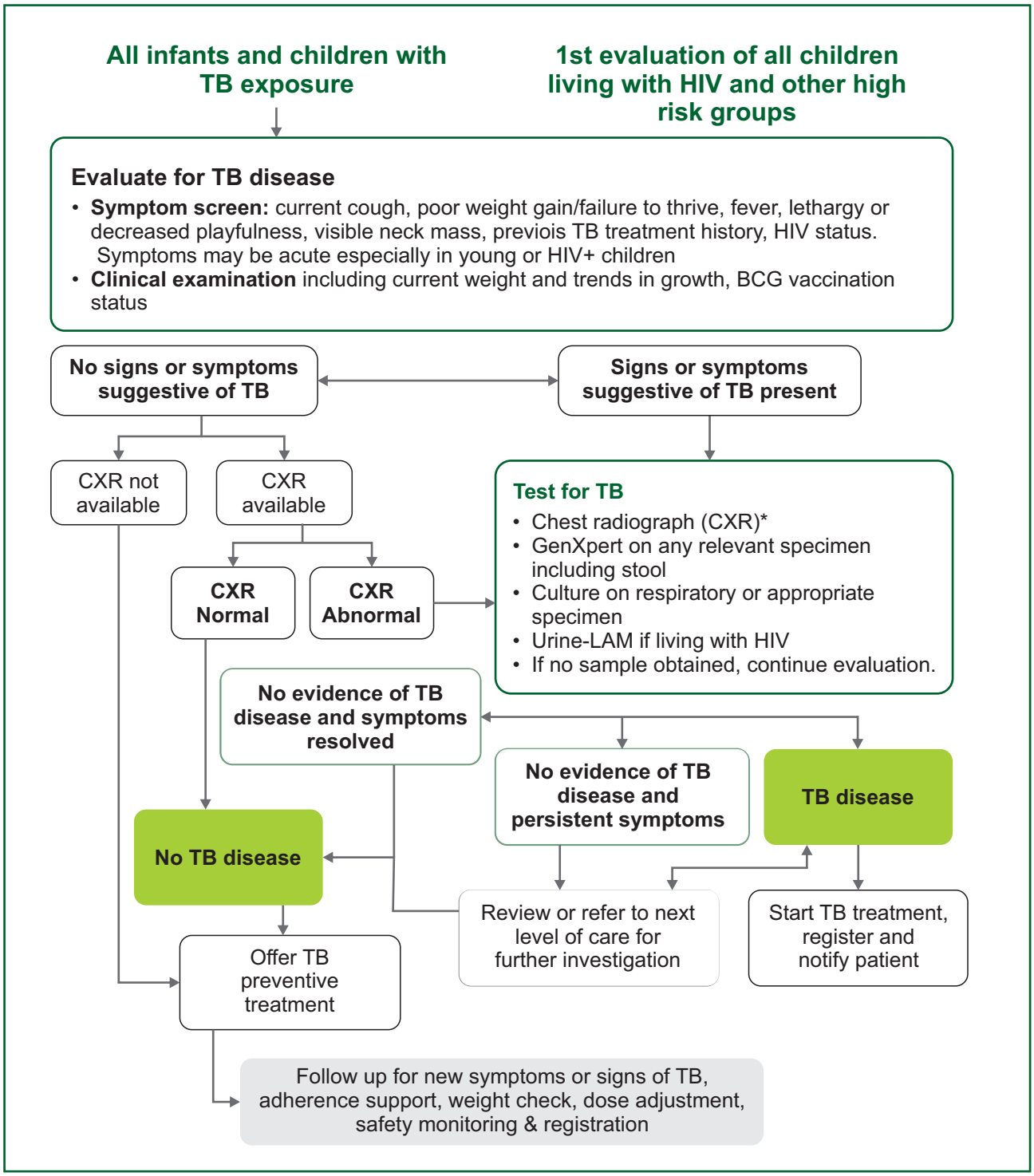
Note that symptoms may be acute in young children, in severely malnourished children and in those living with HIV.

5.3.1.2 Diagnostic tests for TB disease amongst children – regardless of HIV status:

- sputum testing (and Xpert) should be attempted in older children, who can expectorate spontaneously and in any other children who can expectorate spontaneously. If a young child can expectorate sputum, a sample should also be attempted

- CXR is a valuable tool to rule out TB disease in children. The absence of a CXR should however not pose a barrier to starting TPT in well children. In a well child with no TB signs or symptoms, a CXR is therefore not required to initiate TPT. Clinical follow-up remains important
- in any child with signs or symptoms suggestive of TB, either at initial screening or at follow-up, a CXR should be obtained if available
- tests of TB infection (TST/IGRA) are not a requirement to initiate TPT. A positive test of infection in a well child however indicates a higher risk of future TB disease progression. Tests of infection may be used at clinician discretion

Figure 3. Algorithm for provision of TB preventive treatment for infant and child contacts, children living with HIV and other high-risk groups



- If a CXR has already been done recently in a child who presented with no signs or symptoms, do not repeat the CXR
- Culture should NOT be attempted from stool given high contamination rates
- Tests of TB infection (tuberculin skin test/ TST or IGRA) are not required to initiate TPT in children who are TB contacts
- For the management of DR-TB exposure, refer to the latest National DR-TB Guidelines

5.3.2 TPT regimens for children weighing less than 25 kilograms

There are three potential regimens for children: **3RH, 3HP, and 6H**. The choice depends on the child's weight, HIV status or HIV exposure (maternal HIV) status:

- in HIV-negative children <25kg, the priority regimen is **3RH**
- in children living with HIV and on DTG (dolutegravir) containing ART, the preferred regimen is **6H** to avoid drug-drug interactions with ART
- in infants born to HIV-positive women (HIV-exposed but HIV-negative infants) on nevirapine, **6H** is the priority regimen as rifampicin lowers nevirapine levels below efficacy

All children and breastfeeding infants require pyridoxine (vitamin B6) for the duration of their TPT as follows: Children younger than five years 12.5mg and children five years or older 25mg, once daily. Lack of pyridoxine access should not be a barrier to receiving TPT.

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

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		

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)	

5.4 Management of TPT in children living with HIV (irrespective of TB exposure)

All children living with HIV (irrespective of significant TB exposure), require a course of TPT once TB disease has been excluded through evaluation and testing.

For any new TB exposure, TB evaluation is again required along with offering TPT or TB treatment.

Evaluation for TB disease is identical to that described under HIV-negative children (Figure 3). Refer to Section 7 for more information.

5.5 Management of TPT in TB-exposed newborns (babies born to mothers diagnosed with pre-natal or peri-partum TB or with other significant TB exposure)

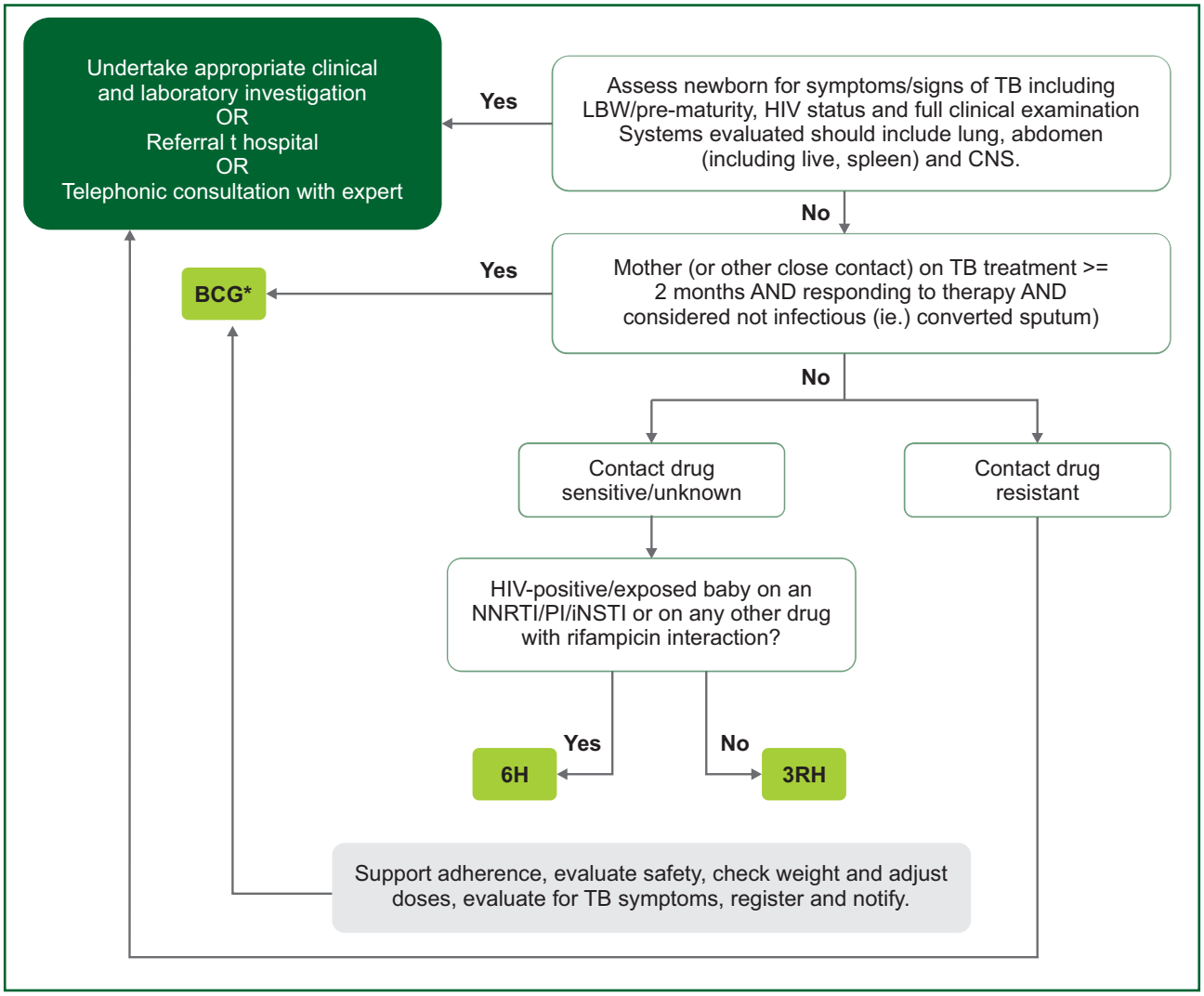
Infants have a high risk of developing severe and disseminated TB if exposed to TB and if not given TPT. Babies born to mothers diagnosed with TB in the last two months of pregnancy or at/after birth, or who are still infectious (culture positive), or who are not clinically responding to TB treatment at the time the baby is born, are classified as TB exposed. Infants may also be exposed to another person with TB inside or outside the household.

In newborns, TB disease should be excluded by thorough clinical evaluation of the baby, including respiratory and abdominal examination; respiratory sampling (gastric aspirates) for Xpert and mycobacterial culture and CXR should be done. An abdominal ultrasound is needed in case of abnormal clinical findings (distension or hepatomegaly).

The newborn should be managed according to the algorithm outlined in **Figure 4.** Referral for further evaluation should be done if disease is suspected, TPT is not well tolerated or new symptoms develop. There should be a low threshold for rapidly referring an unwell TB-exposed neonate or infant for further evaluation given the high risk of TB and non-specific clinical presentation of TB in infants.

BCG vaccination should be deferred in newborns starting TPT to after TPT completion since TB drugs impair the effect of live BCG (M.bovis BCG) vaccine. It is important that BCG vaccination is given after completion of TPT.

Figure 4. Algorithm for TB preventive treatment for TB-exposed newborns



- These infants must be investigated for TB disease – if TB disease is definitely excluded, infants should also return to algorithm for TPT
- It is critical that BCG should be given *immediately after the completion of TB preventive treatment or TB treatment. BCG is a live attenuated M.bovis vaccine and is killed by TB medications. If the child is also living with HIV, discuss with HIV clinician to decide when BCG should be given.*
- ART=antiretroviral treatment; BCG=Bacillus Calmette-Guérin; CNS=central nervous system; DST=drug susceptibility testing; INH=isoniazid; RIF=rifampicin; Rx=treatment; TPT=tuberculosis preventive treatment; NNRTI=Non-nucleoside reverse transcriptase inhibitors; PI=Protease Inhibitor; iNSTI=Integrase strand transfer inhibitors.
- For management of DR-TB exposure, refer to the latest National DR-TB Guidelines

6. TPT IN PREGNANT AND BREASTFEEDING WOMEN WITH TB EXPOSURE OR LIVING WITH HIV

6.1 TPT should be offered to all pregnant and breastfeeding women (regardless of their HIV status) with significant TB exposure

All pregnant and breastfeeding women with significant exposure to TB require TPT once TB disease has been excluded through careful evaluation, **including TB testing for all, regardless of symptoms.**

TPT should not be deferred in a pregnant or breastfeeding woman with significant TB exposure, defined as sharing the same enclosed space with a person (adult or adolescent) known to have had pulmonary TB during the three months before this index patient starting his/her TB treatment. Sharing enclosed space includes one or more nights (e.g., a home, correctional facility or similar) or for frequent and extended periods. The prior completion of either TB treatment or TPT does not exclude a new course of TPT, if there has been a new source of TB exposure.

TPT should be offered to pregnant women with significant TB exposure, regardless of HIV status. Conversely, **TPT should also be offered to all pregnant or breastfeeding women living with HIV, regardless of TB exposure.**

6.2 TPT should be deferred or not offered if the pregnant woman:

- is diagnosed with TB disease
- has active liver disease (acute or chronic)
- has symptoms and signs of severe peripheral neuropathy (could consider rifampicin only regimen)
- has a history of adverse reactions to any medications used for TPT
- makes excessive use of alcohol (and is unwilling or unable to scale down), defined as four or more standard drinks on a day or eight or more per week

For individuals with abnormal baseline liver function test results, sound clinical judgement is required to ensure that the benefit of TB preventive treatment outweighs the risks, and they should be tested routinely at subsequent visits.

TPT should not be deferred to the postpartum period in pregnant women living with HIV.

Breastfeeding is NOT a contraindication to TPT.

6.3 Management of TPT amongst HIV-negative and HIV-positive pregnant and breastfeeding women with TB exposure

When an adult or adolescent patient is diagnosed with pulmonary TB disease, thorough contact investigation is essential to establish who may have had a significant exposure to this index patient.

For subsequent TB exposures, TB evaluation is again required followed by either TPT or TB treatment, as appropriate, i.e., TB test and treat approach (see also Section 4).

6.3.1 Evaluation for TB disease amongst pregnant and breastfeeding women

Evaluation for TB disease in pregnant women includes symptom screening, physical examination, and diagnostic testing. TB can either be bacteriologically confirmed or clinically diagnosed. A minimum of symptom screening and a sputum test (regardless of the presence of symptoms) are required prior to initiating either TPT in a pregnant or breastfeeding woman.

Evaluation for TB disease is required at the first antenatal care (ANC) booking or visit and each subsequent ANC and postpartum follow-up visit. Sputum should always be collected from those who are symptomatic during follow-up visits.

6.3.1.1 Symptom screening for TB disease amongst pregnant or breastfeeding women include the presence of any one or more of the following:

- current cough
- weight loss or poor weight gain
- fever
- night sweats
- haemoptysis

6.3.1.2 Diagnostic tests for TB disease amongst pregnant or breastfeeding women:

- a sputum sample should be obtained and tested using GeneXpert
- tests of TB infection (TST/IGRA) are not a requirement to initiating TPT
- if CXR is needed (e.g., sputum not obtained), precautions are required to protect the foetus from radiation exposure

Pregnant or breastfeeding women declining TPT (despite counselling), should be followed up and screened for TB symptoms at every antenatal and postpartum visit, and offered TPT again after TB disease was excluded.

6.3.2 Considerations for TPT initiation in pregnant and breastfeeding women living with HIV:

- TPT should not be deferred in pregnant and breastfeeding women living with HIV
- newly pregnant women living with HIV and already on TPT should continue TPT

6.3.3 TPT treatment options for pregnant and breastfeeding women

For HIV-negative pregnant and breastfeeding women there are two regimen options: **3RH** or **6H**.

For HIV-positive pregnant and breastfeeding women there is one option: **12H**.

For ALL pregnant and breastfeeding women pyridoxine (vitamin B6) 25mg is added for the duration of TPT – irrespective of HIV status.

6.3.3.1 Recommended daily dosages for the 6H regimen amongst HIV-negative pregnant and breastfeeding women

Drug	Dose	Maximum Dose/day	Duration	Interval
Isoniazid (H)*	5mg/kg	300mg	6 months	Daily

* If 300mg tablets are not available, use 100mg

6.3.3.2 Recommended daily dosages for the 3RH regimen amongst HIV-negative pregnant and breastfeeding women: Please refer to Section 4.

6.3.3.3 Recommended daily dosages for the 12H regimen amongst HIV-positive pregnant and breastfeeding women. All HIV-positive women initiated on DTG should receive 12H.

Drug	Dose	Maximum Dose/day	Duration	Interval
Isoniazid (H)*	5mg/kg	300mg	12 months	Daily

* If 300mg tablets are not available, use 100mg

7. PEOPLE LIVING WITH HIV (PLHIV): ADULTS, ADOLESCENTS, AND CHILDREN IRRESPECTIVE OF AGE

All immunocompromised people have a significant risk for developing TB disease and require an initial TPT course, regardless of significant exposure, once TB disease has been excluded. This includes people of all ages living with HIV (adults, pregnant and breastfeeding women, adolescents, and children including infants older than 14 weeks of age).

See Section 6 for pregnant women living with HIV and Section 5 for children living with HIV. After any new TB exposure, TB evaluation is again required along with a decision to start either TPT or TB treatment, i.e., the TB test and treat approach (see Section 4).

7.1 Who TPT should be offered to

TPT should be offered to all people on ART and people newly diagnosed with HIV (adults, pregnant and breastfeeding women, adolescents, and children of all weights) should be evaluated for TB disease and offered TPT, regardless of a TB exposure, once TB disease has been excluded.

Prior completion of either TB treatment or TPT do not exclude being offered TPT again if there is a new significant TB exposure.

7.2 TPT should be deferred or not offered if the individual living with HIV:

- is diagnosed with TB disease
- has active liver disease (acute or chronic)
- has symptoms and signs of severe peripheral neuropathy (could consider rifampicin only regimen)
- has a history of adverse reactions to any of the drugs used for TPT
- Uses alcohol excessively (and is unwilling or unable to scale down), defined as:
  - *for men:* Five or more standard drinks on any day or 15 or more per week
  - *for women:* Four or more standard drinks on any day or eight or more per week

For individuals with abnormal baseline liver function test results, sound clinical judgement is required to ensure that the benefit of TB preventive treatment outweighs the risks, and they should be tested routinely at subsequent visits.

7.3 Management of TPT for PLHIV

If PLHIV (or their caregivers in the case of children) decline TPT (despite counselling) then they should be counselled further regarding TB symptoms and should be offered TPT again at the next opportunity. If they develop symptoms suggestive of TB, they should be evaluated for TB disease and be offered either TB treatment, or be offered TPT again if TB disease has been excluded.

7.3.1 Evaluation for TB disease amongst PLHIV

Evaluation for TB disease includes symptom screening, physical examination, and diagnostic testing (regardless of symptoms). TB can either be bacteriologically confirmed or clinically diagnosed.

Amongst PLHIV adults (including pregnant and breastfeeding women), adolescents and older children, a Xpert sputum test is required irrespective of symptoms prior to initiating either TB treatment or TPT, i.e., the TB test and treat approach.

PLHIV already in care should be screened for TB symptoms at each visit, with those symptomatic being tested for TB disease again (Figure 5).

PLHIV who complete TB treatment and have bacteriological proof of cure should be screened for TB symptoms and assessed for TPT eligibility if there is repeated exposure to TB or they have not taken TPT before. If bacteriological cure is not demonstrated after treatment completion, reassess for TPT eligibility three months after completion of TB treatment.

After completing a TPT course, PLHIV are eligible for TPT again after a significant TB exposure (see Section 4).

7.3.1.1 Symptom screening for TB disease amongst PLHIV (adults, adolescents, and children ≥25kg):

- current cough
- weight loss
- fever
- night sweats
- haemoptysis

7.3.1.2 Symptom screening for TB disease amongst PLHIV (children <25kg):

- current cough
- poor weight gain or failure to thrive or documented weight loss
- fever or night sweats
- lethargy/fatigue (decreased playfulness)
- visible neck mass/swelling

7.3.1.3 Diagnostic tests for TB disease amongst PLHIV (adults, adolescents, and children ≥25kg):

- a sputum sample should be obtained and tested using Xpert
- if no sputum sample can be obtained, then a chest radiograph should be obtained to rule out TB disease
- a urine sample can also be obtained from those who are eligible and tested using LF-LAM
- test of TB infection (TST/IGRA) are not a requirement to initiating TPT

7.3.1.4 Diagnostic tests for TB disease amongst children weighing less than 25 kilograms living with HIV

Refer to Section 5.

7.3.2 TPT regimens for PLHIV (adults, pregnant and breastfeeding women, adolescents, and children 25 kilograms or more)

For adults, adolescents and children ≥25kg living with HIV and initiating dolutegravir-containing ART, 12H is the preferred regimen. For those taking ART that are already virally suppressed (VL<50 copies/mL in the last six months) or those starting ART not containing Dolutegravir, 3HP is preferred.

7.3.2.1 Recommended daily dosages for 12H in adults, pregnant and breastfeeding women, adolescents and children weighing 25 kilograms or more living with HIV

Drug	Dose	Maximum Dose/day	Duration	Interval
Isoniazid (H)*	5mg/kg	300mg	12 months	Daily

* If 300mg tablets are not available, use 100mg

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)

7.3.3 TPT regimens for children weighing less than 25 kilograms living with HIV

In children living with HIV initiating a dolutegravir-containing ART regimen, 6H is the preferred regimen.

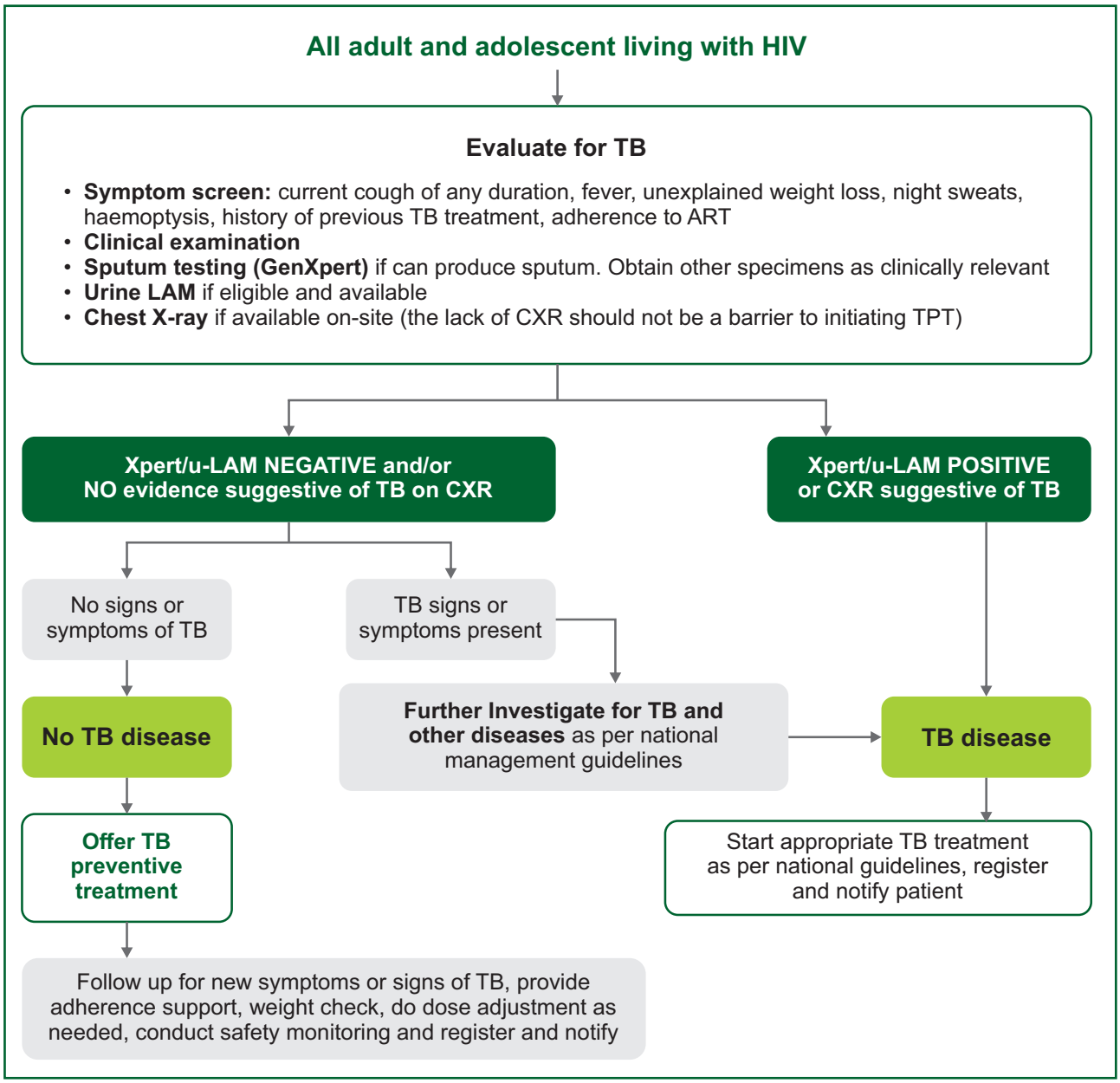
7.3.3.1 Recommended daily dosages for 6H regimen amongst children living with HIV weighing less than 25 kilograms

Drug	Dose	Maximum Dose/day	Duration	Interval
Isoniazid (H)*	5mg/kg	300mg	6 months	Daily

* If 300mg tablets are not available, use 100mg

For managing the TB-exposed infant, please refer to Section 5.

Figure 5. Algorithm for provision of TB preventive treatment for adults and adolescents living with HIV



- *Tests of TB infection (tuberculin skin test/TST or IGRA) not required to initiate TPT in adults or adolescents with known TB exposure*
- *For management of DR-TB exposure, refer to the latest National DR-TB Guidelines*

8. SILICOSIS

People with confirmed silicosis have a significant risk for developing TB disease and require initial TPT regardless of significant exposure.

After new TB exposure, TB evaluation is again required along with a decision to offer TPT or TB treatment (see Section 4).

8.1 Who TPT should be offered to

TPT should be offered to all people with confirmed silicosis regardless of whether they have a known significant exposure (regardless of prior TB treatment or TPT unrelated to silicosis).

People with silicosis who have completed TB treatment and have bacteriological proof of cure should be screened for TB symptoms and assessed for TPT eligibility if they have not previously received TPT or if they are re-exposed. If bacteriological cure is not demonstrated after completion of treatment, reassess the patient for TPT eligibility three months after completion of TB treatment.

People with silicosis who have completed a TPT regimen are eligible for subsequent TPT (again) if they experience a significant exposure (see Section 4).

8.2 TPT should be deferred or not offered if the individual:

- is diagnosed with TB disease
- has active liver disease (acute or chronic)
- has symptoms and signs of severe peripheral neuropathy (could consider rifampicin only regimen)
- has a history of adverse reactions to any of the drugs used for TPT
- uses alcohol excessively (and is unwilling or unable to scale down), defined as:
  - *for men:* Five or more standard drinks on any day or 15 or more per week
  - *for women:* Four or more standard drinks on any day or eight or more per week

For individuals with abnormal baseline liver function test results, sound clinical judgement is required to ensure that the benefit of TB preventive treatment outweighs the risks, and they should be tested routinely at subsequent visits.

8.3 Management of TPT for people with silicosis

If TPT is declined (despite counselling) re-counsel regarding TB symptoms and offer TPT again at the next opportunity. For symptoms suggestive of TB, re-evaluate for TB disease and offer either TB treatment or TPT again, if TB disease has been excluded.

8.3.1 Evaluation for TB disease amongst silicosis

Evaluation for TB disease includes symptom screening, physical examination, and diagnostic testing, regardless of symptoms. TB can either be bacteriologically confirmed or clinically diagnosed. Amongst people with silicosis a minimum of symptom screening and a sputum test are required prior to initiating either TB treatment or TPT.

People with silicosis will present with similar symptoms and signs of TB. Therefore, it is imperative that all adults presenting with TB symptoms should always be asked about history of working in the mines and silicosis.

8.3.1.1 Symptom screening for TB disease amongst adults with silicosis:

- current cough
- weight loss
- fever
- night sweats
- haemoptysis

8.3.1.2 Testing for latent tuberculosis infection (LTBI) amongst adults with silicosis

Where available, tuberculin skin test (TST) or interferon gamma release assay (IGRA) may be useful to distinguish silicosis from TB disease.

8.3.2 TPT regimens for adults with silicosis

There are currently three potential regimens for this group: **3HP, 3RH** or **12H**. In general, the short course **3HP** regimen should be prioritised where possible. Patients should also receive pyridoxine (vitamin B6) 25mg for the duration of their TPT.

8.3.2.1 Recommended weekly dosages for the 3HP regimen for adults with silicosis

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

8.3.2.2 Recommended daily dosages for 12H for adults with silicosis

Drug	Dose	Maximum Dose/day	Duration	Interval
Isoniazid (H)*	5mg/kg	300mg	12 months	Daily

* If 300mg tablets are not available, use 100mg

8.3.2.3 Recommended daily dosages for 3RH for adults with silicosis – see Section 4.

9. OTHER HIGH-RISK GROUPS

Additional specific TPT guidelines need to be developed for groups at increased risk of TB infection and/or progression to TB disease, such as:

1) inmates in correctional facilities remain a priority for TPT because the confined indoor spaces they share with other people often mean they meet the criteria of 'significant TB exposure'
2) healthcare workers also have a high risk of TB and should be considered for TPT during a routine occupational TB screening programme. At the minimum, annual testing for active disease is recommended and additional evaluation based on clinical indications (e.g. symptoms, new TB exposure) should be undertaken
3) people who have previously had TB are at higher risk of getting TB again. TPT is therefore also indicated in those with previous TB after another significant exposure

10. PATIENT CATEGORISATION AND TREATMENT OUTCOMES

Patients treated for TB infection may be categorised either as new or previously treated. The treatment outcome possibilities are completed, lost to follow-up, stopped or died as described in **Table 2**.

Table 2. Patient categories and treatment outcomes

Category definition	
New	Never had TPT or who took treatment for less than four weeks.
Previously treated	Past TPT or another regimen for four or more weeks and either completed or stopped for any reason (e.g. due to adverse events, developed TB, lost to follow-up)
TB Preventive Treatment (TPT) outcomes	
Treatment completed	Individual who has taken treatment and completed preventive treatment within the prescribed period.
Lost to follow-up	An individual whose treatment was interrupted for four weeks or more (if on four or more months regimen) OR two consecutive months (if on a six-month regimen) OR three consecutive months (if on a 12-month regimen) during the treatment period.
Treatment stopped	An individual whose treatment was stopped during the treatment period, because of serious adverse events or development of TB disease.
Died	Death for any reason during the treatment

11. CLINICAL MONITORING OF PEOPLE ON TREATMENT

11.1 Education and counselling of eligible individuals

Education and counselling at treatment initiation should cover the following:

- what is TB exposure and infection?
- who is eligible for TPT?
- benefits of TB preventive treatment
- risks of TB preventive treatment
- importance of adhering to treatment
- duration of treatment
- taking the medication - advice for the patients and caregivers:
- 3RH: Given on an empty stomach (before a meal)
- Isoniazid regimen only (6H or 12H): Give on an empty stomach (before a meal). Isoniazid is best absorbed on an empty stomach; there is an up to 50 per cent reduction in peak concentration with a fatty meal
- 3HP: Give with a meal or directly after a meal (Rifapentine is better absorbed with food)
- medicines they will be taking, frequency and timing
- possible side effects such as unexplained loss of appetite, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools and jaundice
- infection control, including cough hygiene and adequate ventilation
- undesirable effects of using alcohol and smoking while on treatment
- what to do when experiencing adverse effects, which could include returning to a health facility
- develop an adherence plan together with the patient focusing on weekly or daily adherence strategies, depending on individual's treatment regimen and support required during the treatment period (for an example of an adherence plan, see Annexure B).

11.2 Follow-up visits

Individuals should be monitored monthly (three or six months depending on the duration of treatment). For individuals with co-morbidities, try to align appointments with other scheduled chronic disease or ART visits to avoid multiple visits for care. At each visit the following must be done:

- screen individuals for signs and symptoms of TB. If symptomatic, investigate per *National TB Management Guidelines,* stop treatment. If asymptomatic, continue treatment
- provide on-going counselling and education of the individual
- monitor adherence (including pill count and missed appointments). If poor adherence or treatment interruption, ask about the possible reasons and counsel the individual. For children, counsel the parent/ guardian
- assess for need of social support and refer accordingly to social worker, community development officer, etc.
- assess individual for side effects of the medicines used for treatment, if any are present manage them
- people on the three-month treatment regimen can be given three months' supply of treatment as part of multi-month dispensing (MMD). Those on longer treatment regimens (≥6 months) may be enrolled on central chronic medicine dispensing and distribution (CCMDD). Refer to the *CCMDD Standard Operating Procedure (SOP) 12: Enrolment and management of patients on treatment for latent TB infection, treatment for DS-TB or drug resistant TB onto the CCMDD programme,* for guidance.

11.3 Adverse events

While most of the adverse events are minor and occur rarely, specific attention should be paid to drug-induced hepato-toxicity, severe peripheral neuropathy as well as hypersensitivity. Assess individual for signs and symptoms suggestive of hepatitis such as new-onset vomiting, right upper quadrant pain and jaundice – if any of these are present, stop treatment immediately and refer to hospital for further assessment.

All adverse events should be reported using the standard reporting form as per the National Pharmacovigilance Centre (NPC) Guidelines (Annexure A).

Table 3. Management of common adverse events

Adverse event	Drug(s) responsible	Signs/symptoms	Management
Peripheral Neuropathy	Isoniazid(H)	Tingling or burning sensation of the fingers and/or toes that usually occurs in a glove and stocking distribution	Vitamin B6 (pyridoxine) must be increased from 25mg to 100mg daily until the symptoms disappear. If the peripheral neuropathy is severe or worsens, then H should be discontinued immediately. Consider a Rifampicin only alternative TPT regimen.
Hepatotoxicity	Isoniazid(H) Rifapentine (P) Rifampicin (R)	**Symptoms:** Nausea, vomiting, abdominal tenderness, discomfort near the ribs on the right upper abdomen, jaundice (yellowing of skin and whites of the eyes) **Signs:** Hepatic enlargement, increased liver function tests (LFTs)	Stop Isoniazid and Rifampicin or Rifapentine immediately. Refer the individual to the hospital/ medical officer immediately for further evaluation.
Gastrointestinal Uncommon at recommended daily doses	Isoniazid(H) Rifampicin (R) Rifapentine (P)	**Symptoms:** Nausea, vomiting, diarrhoea	Rule out other causes. Conduct LFTs to rule out drug-induced hepatic dysfunction. Continue treatment based on severity of symptoms. Treat symptomatically (if no other cause is found).
Flushing reaction	Isoniazid(H)	**Symptoms:** Flushing and/or itching of the skin with or without a rash, hot flushes, palpitations, headache **Signs:** Increased blood pressure	Reassure individual and inform about avoiding tyramine and histamine-containing foods (e.g. tuna, cheese, red wine) while receiving Isoniazid – consider a referral to a dietitian. Flushing is usually mild and resolves without treatment. If flushing is bothersome to the individual, an antihistamine may be administered to treat the reaction.
Mild itching rash	Isoniazid(H) Rifapentine (P)	Mild rash and itching	Treat with antihistamine and topical steroid creams.
Hypersensitivity uncommon usually occurs –three to seven weeks after initiation of treatment	Isoniazid(H)	**Symptoms:** Hives (raised, itchy rash), fever (may occur)	Discontinue treatment until the reaction resolves.

Adverse event	Drug(s) responsible	Signs/symptoms	Management
Hypersensitivity reaction occurs after the first three to four doses and begins approximately four hours after ingestion of medication	Rifapentine (P)	**Symptoms:** Flu-like symptoms, fever, headache, dizziness, shortness of breath, wheezing, nausea, muscle and bone pain, rash, itching, red eyes, hypotension or shock	If mild reaction e.g. rash, dizziness, fever: Continue treatment and manage the adverse events. If severe reaction e.g. thrombocytopenia or hypotension, discontinue treatment and refer to hospital.

11.4 Drug-drug Interactions

Points to note:

- Daily Rifampicin plus Isoniazid for three months (3RH) should not be given to infants and children on protease inhibitors (PI) or nevirapine-based ART due to drug-drug interactions.
- Rifapentine and INH (3HP) should not be offered to ART-naïve individuals starting Dolutegravir-containing ART due to lack of evidence at this stage. 3HP should be deferred until individuals have been on ART with a Dolutegravir-containing regimen until virally suppressed.

Table 4. Drug-drug interactions

TPT drug	Drug-Drug interaction	Recommendation
Rifampicin decreases the levels of:	Dolutegravir	Double Dolutegravir dose to 50mg 12-hourly Offer Isoniazid monotherapy
	Efavirenz	Offer Isoniazid monotherapy
	Protease inhibitors e.g. Lopinavir/Ritonavir	Offer Isoniazid monotherapy
Rifapentine decreases the levels of:	Protease inhibitors e.g. Lopinavir/Ritonavir	Offer Isoniazid monotherapy
	Nevirapine	Offer Isoniazid monotherapy
	Oral and implantable contraceptives	Use barrier method Offer injectable contraceptive method
	Dolutegravir	Offer Isoniazid monotherapy to ART naïve PLHIV

Treatment adherence and completion of treatment

Adherence and completion of treatment are important for ensuring successful treatment and preventing the development of TB disease. Education and counselling must be provided on an ongoing basis.

11.5 Treatment interruption and discontinuation

Categorisation of treatment interruption

- Individuals who are initiated on the longer treatment regimens (six or more months) who interrupt treatment should be categorised as follows:
- interrupted treatment for less than three consecutive months
- interrupted treatment for more than three consecutive months
- interrupted treatment for a second time regardless of duration of interruption, despite adherence counselling
- Individuals who are initiated on the shorter regimens (three to four months) who interrupt treatment should be categorised as follows:
  - interrupted treatment for less than four consecutive weeks

- interrupted treatment for more than four consecutive weeks
- interrupted treatment for a second time regardless of duration of interruption, despite adherence counselling

Individuals who interrupt treatment should be managed as outlined in **Table 5**.

Table 5. Management of individuals who interrupt treatment

Duration of interruption	Management
If an individual misses one dose	For daily doses: The individual should take the missed dose as soon as they remember within the same day. If this is on the following day, take the next scheduled dose and continue with the regular schedule. Do not take two doses on the same day. For weekly doses: The individual should take the missed dose as soon as they remember within three days, continue the next dose as scheduled or start a new weekly schedule based on the day you took the missed dose.
If an individual interrupts treatment for less than one month for a short regimen or less than three consecutive months for a longer TPT regimen	• Enquire about the reasons for treatment interruption. • Address individual's concerns. • Counsel the individual on the importance of adherence. • Screen clinically for TB symptoms. • If signs and symptoms of TB are present, conduct investigations to exclude TB. • If asymptomatic and no signs of TB disease, continue treatment including missed doses.

If an individual interrupts treatment for one or more month for a short regimen or three or more consecutive months for a longer TPT regimen	• Enquire about the reasons for treatment interruption.
	• Address individual's concerns.
	• If this is the first interruption and the individual commits to taking treatment:
	  • reassess for eligibility
	  • provide intensive counselling
	  • restart treatment
	  • refer to relevant services (psychologist, dietitian, social worker etc.) based on the patient's need

If an individual interrupts treatment for a second time regardless of duration of interruption, despite adherence counselling	Do not consider for retreatment.

12. MONITORING AND EVALUATION

Monitoring is the periodic assessment of programme activities to determine whether they are proceeding as planned. It provides managers with continuous feedback on implementation, to make informed decisions regarding service delivery and ensure effective and efficient use of resources for maximum impact. Evaluation, on the other hand, is a periodic in-depth time-bound analysis which aims to assess performance and overall impact of the programme systematically and objectively.

Data collection tools

Patient record folder - this is a standard record where all patient clinical information is recorded for each visit. It serves as a source document for capturing in the electronic register.

Primary healthcare (PHC) tick register - this register is used to collect the data elements needed to compile routine monthly statistics. This includes information on TB screening, eligibility and initiation of TPT.

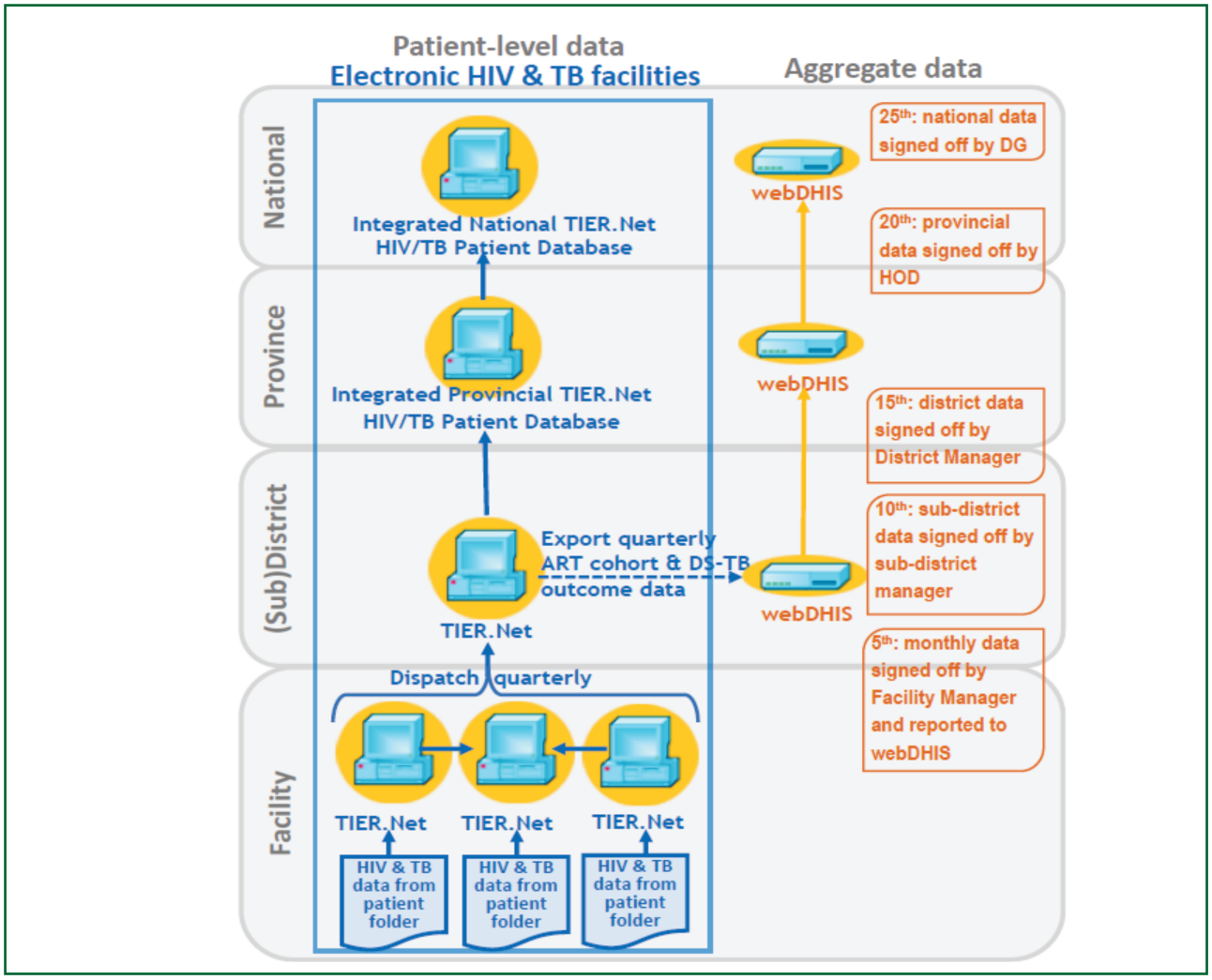
TB identification register – this register is used to record all presumptive TB patients.

TIER.Net - This is an electronic information system used to capture patients started on treatment and to monitor outcomes.

Data flow processes and reporting

- Facilities, districts and provinces are expected to report according to the *District Health Management Information System (DHMIS) Policy* and processes illustrated in Figure 6.
- With facility level digitisation, data from the patient folders is captured directly into the three interlinked electronic registers (TIER) system at facility level daily. It is then dispatched to the next level on a monthly or quarterly basis.
- At each level the data should be checked and signed off by the manager before reporting to the next level.

Figure 6. Illustration of the data flow process from the facility to national level and reporting timeline



Cascade analysis at facility level

- Facilities must conduct a care cascade analysis of aggregated data from screening to treatment outcomes. This will help to identify gaps/leakages within the cascade and develop plans to address the gaps using the quality improvement methodology. Examples of TB evaluation cascades for HIV-positive clients and contacts of TB index patients are illustrated in **Figures 7 and 8**.
- District, provincial and national levels must monitor progress against their cascades. The managers at these levels should identify facilities, districts and provinces that are struggling to meet targets using the dashboards and develop plans to provide intensive support.

Figure 7. Illustration of a cascade for HIV-positive clients

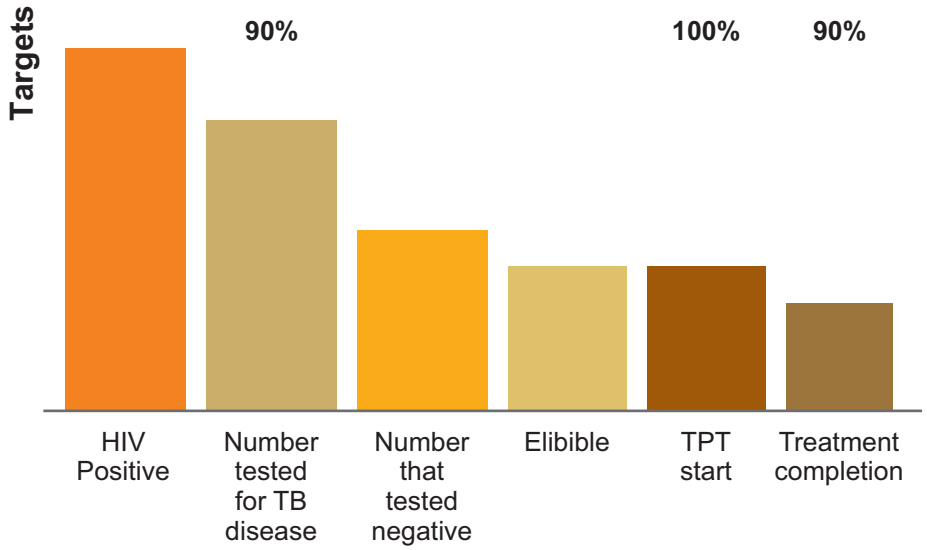
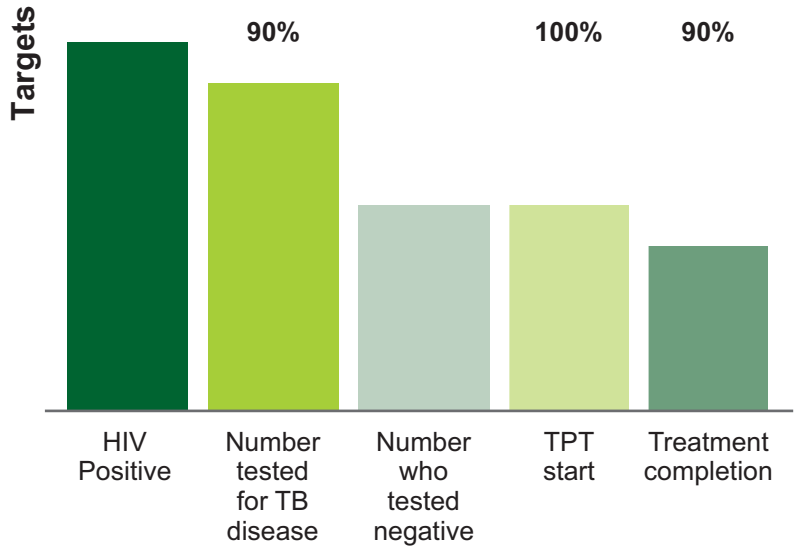


Figure 8. Illustration of a cascade for contacts



Proposed data elements

- Number of individuals eligible for TPT.
- Number of individuals started on TPT.
- Number of individuals who successfully completed treatment.
- Number of individuals lost to follow-up during treatment.
- Number of individuals who died during treatment.

ANNEXURES

Annexure A: Pharmacovigilance Form

SAHPRA South African Health Products Regulatory Authority

ARF 1

ADVERSE DRUG REACTION (ADR)/PRODUCT QUALITY PROBLEM REPORT FORM
(PUBLIC AND PRIVATE SECTOR) (Including Herbal Products)

Reporting Health Care Facility/Practice					
Tel: (012) 501 0311 **E-mail:** adr@sahpra.org.za	Facility/Practice				
	District		Tel		
	Province		Fax		

Patient Details							
Patient Initials		File/Reference Number		Date of Birth/Age			
Sex	□ M □ F □ Unk	Race		Weight (kg)		Height (cm)		Pregnant?	□ N □ Y
Allergies		Estimated Gestational Age at time of reaction					

Suspect Medicine(s) [Medicines suspected to have caused the ADR]

Trade Name [Generic Name if Trade Name is unknown]	Route	Dose (mg) and Interval	Date Started/Given	Date Stopped	Reason for use	Batch Number	Expiry Date

All other Medicines Patient was taking at time of reaction [Including over-the-counter and herbal products]

Trade Name [Generic Name if Trade Name is unknown]	Route	Dose (mg) and Interval	Date Started/Given	Date Stopped	Reason for use	Batch Number	Expiry Date

Adverse Drug Reaction/Product Quality Problem

Date and time of onset of reaction		Date reaction resolved/duration	

Please describe Adverse Reaction/Product Quality Problem: (kindly add as much clinical information as possible)

Intervention(tick all that apply)	**Patient Outcomes (tick all that apply)**
□ No intervention	□ ADR recovered/resolved□ recovering/resolving
□ Intervention unknown	□ not recovered/not resolved
□ Patient Counselled/non-medical treatment	□ Patient Died: Date of death: _____
□ Discontinued Suspect Drug; **Replaced with**: _____	□ Impairment/Disability □ Congenital Anomaly
□ Decreased Suspect Drug Dosage; **New Dose**: _____	□ Patient Hospitalised or Hospitalisation prolonged
□ Treated ADR - with: _____	□ Life Threatening □ Other: _____
□ Referred to Hospital: **Hospital Name**_____	□ ADR reappeared after restarting suspect drug/similar drug (rechallenge)?: □ N □ Y □ Not done □ Unknown
□ Other Intervention (e.g. dialysis): _____	

Laboratory Results			**Additional Laboratory Results**		
Lab Test	**Test Result**	**Test Date**	**Lab Test**	**Test Result**	**Test Date**

Co-morbidities/Other Medical Condition(s)

Reported by			
Name		E-mail	
Designation	□ Nurse □ Pharmacist □ Doctor □ Other:	Telephone	
Date reported:		Signature	

THIS ADR REPORT IS NOT A CONFIRMATION THAT THE REPORTER OR THE SUSPECT MEDICINE(S) CAUSED THE ADR **V5.1 01/20**

Annexure B: Adherence Plan

Adherence Step 1: Education of patient

- How treatment for TB infection differs from treatment for TB disease.
- Type of treatment regimen suitable for the patient and why.
- Risk factors associated with treatment, such as:
  - side effects of treatment regimen chosen
  - interactions with other medicines
  - risk of getting infected with TB whilst on treatment
  - risk of developing TB disease whilst on treatment
  - the importance of completing the full course of treatment

Adherence Step 2: Life goals:

My motivations to stay healthy are:

(1) .....

(2) .....

(3) .....

It is important for the client to have a health goal to motivate him- or herself to not interrupt their treatment. The long-term benefit of TPT to their overall health should override the inconvenience of taking treatment before they feel sick.

Adherence Step 3: Patient support system

Agree for home visit (where possible): Yes No

Who can support me during my treatment? .....

Adherence Step 4: Getting to appointments

How will I get to my clinic appointments: .....

The best time to collect my treatment will be: .....

If I face difficulties with keeping clinic appointments my alternative plan will be: .....

.....

Adherence Step 5 - Treatment schedule

The best time for me to take my treatment is: .....

I am taking the following treatment and I will add this treatment to my daily dose: .....

.....

I am not taking any other medication and will need a reminder to take my weekly/daily dose: .....

.....

Adherence Step 6: Reminder strategies

To remind me to take treatment, I will use: .....

Adherence Step 7: Managing missed doses

If I miss a dose, I know exactly what to do to get back to my regular treatment schedule: Yes No

Adherence Step 8: Storing medication and extra doses

I will store my medication in: .....

I will carry extra supply and keep it in: .....

Adherence Step 9: Dealing with side-effects

I know what side effects to expect Yes ..... No .....

If I experience side effects, I will: .....

Adherence Step 10: Planning for trips

If I have some trips planned, before going away I will: .....

In case I cannot come to the health facility before going away, I will: .....

Adherence Step 11: Dealing with substance use

I am aware of the implications of taking alcohol with the treatment

Yes ..... No .....

My plan is to .....

.....

.....

.....

.....

Annexure C:

TPT INTEGRATION INTO REPEAT PRESCRIPTION COLLECTION STRATEGIES FOR CLINICALLY STABLE PLHIV ON ART

Background

South African Adherence Guidelines enable clinically stable ART patients to access multi-month ART supply and easier drug supply collection through Repeat Prescription Collection Strategies (RPCs), namely facility pick-up points, adherence clubs and external pick-up points, from six months on ART and other chronic conditions. These RPCs are either based at their health facility or in the community, including at private pharmacies, private general practitioners and community venues.

Patients should not be prevented from accessing RPCs, which support long-term adherence and retention, when completing their course of TPT. In addition, patients already enrolled in RPCs who previously missed TPT should be provided with access to TPT without being removed from their RPCs.

Completion of TPT prior to enrolment in differentiated service delivery (DSD) model

Where patients have started TPT at ART start and the TPT treatment course is shorter than six months (e.g., 3HP), TPT should be completed prior to the assessment for and enrolment in RPCs (facility pick-up points, adherence clubs or external pick-up points).

Where patients have started TPT at ART start or after ART start but not completed their TPT course prior to enrolment in an RPCs, at least three months of TPT must have been completed and clinical assessment for adverse events undertaken. Where a patient is assessed as clinically stable on TPT, TPT treatment supply can be provided on the same multi-month basis as ART supply and can be provided through the same RPCs.

TPT initiation and completion within DSD model

Where adult patients are already enrolled in a RPCs (facility pick-up point, adherence club or external pick-up point) and have previously missed TPT, these patients should be supported to complete a course of 12H within their RPCs model. These patients should be assessed at their annual comprehensive clinical consultation visit by their clinician for TPT eligibility and if eligible, initiated on TPT and scripted for six months of ART and TPT treatment supply. Patients will collect their TPT supply within their RPCs model but will be required to return to the health facility one month after TPT start for clinical follow-up. Thereafter, RPCs patients will be screened for any TB symptoms or side effects by their RPCs service provider and referred to their health facility should any side effects or ill health be identified for follow-up. Emphasis must be placed on patient treatment literacy, especially at TPT start, to support patients to identify any side effects and return to their health facility outside of scheduled appointment dates if necessary. Patients will have a further TPT clinical follow-up assessment at six months when returning for their RPCs rescripting visit and for their TPT completion assessment at their next annual comprehensive clinical consultation visit.

Transition to TLD regimen

For patients making use of RPCs who are eligible and opting to switch to TLD, TPT eligibility should be assessed at switch. For TPT eligible patients, 3HP could be offered to the patient to be started with TLD, provided the patient agrees to additional facility clinical review dates. Alternatively, 12H can be scripted and aligned with RPCs review dates.

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