Republic of Rwanda
Ministry of Health

Rwanda Biomedical Centre
Healthy People, Wealthy Nation

# TUBERCULOSIS PREVENTIVE TREATMENT GUIDELINES

Edition | 2022

**Tuberculosis and others respiratory communicable diseases division**

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# FOREWORD

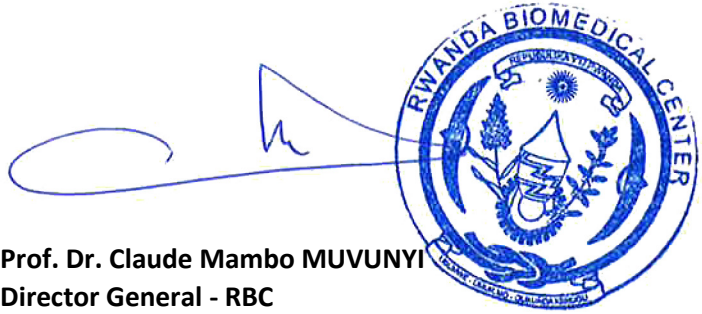
About one fourth of the world's population is estimated to have the Latent Tuberculosis Infection (LTBI), and 5–10% of them develop active TB disease in their lifetime. TB Preventive Treatment (TPT) stops TB infection from progressing to disease in those who are infected and can protect both the individual and the community from TB. Even though Rwanda is among countries with low TB incidence rate, it still counting around 6,000 patients with active tuberculosis disease every year. In the line of the global targets of the End TB strategy, the identification of people who may have latent tuberculosis infection and provide them Tuberculosis Preventive Treatment to break the progression to active TB disease in their lifetime, are among the top priorities of the Ministry of Health.

The Latent Tuberculosis Infection is when a person is infected with *mycobacterium tuberculosis*, but does not have tuberculosis disease and he is asymptomatic. The progression to active TB disease depends on several factors, the most important being weakened immunological status. The WHO End TB Strategy prioritized TPT among persons at high risk of developing active TB disease. Persons at high risk for progression from the latent tuberculosis infection to active TB disease are PLHIV, household contacts of TB confirmed patients, patients initiating anti-TNF treatment and other immune compromised persons.

In 2018, Heads of States in the United Nations High Level Meeting on TB (UNHLM), committed to accelerate efforts in ending TB and reach all affected people through the provision of the Tuberculosis Preventive Treatment and targets for this purpose were set.

This technical guideline for TPT, 2022 edition, was elaborated based on the WHO consolidated guidelines on tuberculosis: Tuberculosis preventive treatment version 2022. It responds to the need by the Ministry of Health to improve skills of actors in the health sector as well as the quality of TPT services offered in health facilities countrywide.

The Ministry of Health is grateful to all individuals and institutions (District Hospitals, WHO, CDC, Maryland University/Rwanda), for their contribution to the elaboration of this document.




**Prof. Dr. Claude Mambo MUVUNYI**
**Director General - RBC**

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Special gratitude goes to the WHO-Rwanda, for the technical and financial support in hiring the consultant for developing these guidelines. Our thanks specially go to the consultant Dr Regina Osih, who spent days and nights for having the last version of this handbook.

Tuberculosis Preventive Treatment guidelines would not have been finalized without the usual support of all the stakeholders who are involved in TB response in Rwanda. We give our sincere thanks and appreciation to the following organizations, for their technical support:

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- To the local and international NGO supporting HIV and TB control in Rwanda
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- To all TB experts (members of technical working groups, clinicians, researchers and other stakeholders) who participated actively in reviewing the different chapters.

Our appreciation also goes towards all persons, who, from near or far, contributed to the realization of these guidelines; please accept our heartfelt gratitude.

**Dr Patrick MIGAMBI**
**TB&ORD Division Manager**

## ABBREVIATIONS & ACRONYMS

| | |
|---|---|
| 1HP | One month of daily rifapentine plus isoniazid |
| 3HP | Three months of weekly rifapentine plus isoniazid |
| 3HR | Three months of daily rifampicin plus isoniazid |
| 4R | Four months of daily rifampicin monotherapy |
| 6H | Six months of daily isoniazid monotherapy |
| 9H | Nine months of daily isoniazid monotherapy |
| ACF | Active TB case finding |
| ACT | Artemisin combination therapy |
| AIDS | Acquired immunodeficiency syndrome |
| ALT | Alanine aminotransferase |
| ART | Antiretroviral therapy |
| ARV | Antiretrovirals |
| AST | Aspartate aminotransferase |
| BCG | Bacille Calmette-Guérin (vaccine) |
| DDI | Drug-drug interaction |
| DSD | Differentiated HIV service delivery |
| ELISA | Enzyme-linked immunosorbent assay |
| FDC | Fixed-dose combination |
| HIV | Human immunodeficiency virus |
| ICF | Intensified TB case finding |
| IFN-g | Interferon-gamma |
| IGRA | Interferon-gamma release assay |
| INSTIs | Integrase strand transfer inhibitors |
| IPT | Isoniazid preventive treatment |
| LFT | Liver function test |

| | |
|---|---|
| LFX | Levofloxacin |
| LMIC | Low and middle-income countries |
| LTBI | Latent tuberculosis infection |
| MDR-TB | Multidrug-resistant tuberculosis |
| NNRTI | Non-nucleoside reverse transcriptase inhibitor |
| NRTI | Nucleotide reverse transcriptase inhibitor |
| PIs | Protease inhibitors |
| PLHIV | People living with HIV |
| PMTCT | Prevention of mother-to-child transmission (of HIV) |
| PMTPT | Programmatic management of tuberculosis preventive treatment |
| PPD | Purified protein derivative |
| RCT | Randomized controlled trial |
| SSRI | Selective serotonin reuptake inhibitor |
| STBP/GDF | Stop TB Partnership's Global Drug Facility |
| TB | Tuberculosis |
| TNF | Tumour necrosis factor |
| TPT | Tuberculosis preventive treatment |
| TPT | Tuberculosis preventive treatment |
| TST | Tuberculin skin test |
| UNHLM | United Nations High-Level Meeting on Tuberculosis (2018) |
| WHO | World Health Organization |

## DEFINITIONS

*Note:* Unless otherwise specified, the definitions listed below apply to the terms used in this guideline. They may have different meanings in other contexts.

**Active case finding** (ACF): is synonymous with systematic screening for TB disease, although it normally implies screening that is implemented outside of health facilities.

**Adolescent:** is a person aged 10–19 years.

**Adult:** is a person over 19 years of age.

**Bacteriologically confirmed TB:** is TB diagnosed in a biological specimen by smear microscopy, culture or a WHO-approved molecular test such as Xpert MTB/RIF®.

**Child:** is a person under 10 years of age.

**Contact:** is any individual who was exposed to a person with TB disease.

**Contact investigation:** is a systematic process for identifying previously undiagnosed people with TB disease and TB infection among the contacts of an index TB patient and/or other comparable settings where transmission occurs. Contact investigation consists of identification, clinical evaluation and/or testing and provision of appropriate anti-TB therapy (for people with confirmed TB) or TB preventive treatment (for those without TB disease).

**Close contact**: is a person who is not in the household but shared an enclosed space, such as a social gathering, workplace or facility, for extended periods during the day with the index patient during the three months before the commencement of the current TB treatment episode.

**Differentiated HIV service delivery (DSD) models:** is a person-centered approach to simplify the provision of HIV services across the cascade, in ways that both serve the needs of PLHIV better and reduce unnecessary burdens on the health system.

**High TB transmission setting**: is a setting with a high frequency of individuals with undetected or undiagnosed TB disease, or where infectious TB patients are present and there is a high risk of TB transmission. TB patients are most infectious when they are untreated or inadequately treated. Transmission will be increased by aerosol-generating procedures and by the presence of susceptible individuals.

**Household contact:** is a person who shared the same enclosed living space as the index patient for one or more nights or frequent or extended daytime periods during the three months before the start of current treatment.

**Index patient (index case) of TB:** is the initially identified person of any age with new or recurrent TB in a specific household or other comparable settings in which others may have been exposed. An index patient is a person on whom a contact investigation is cantered but is not necessarily the source.

**Infant:** is a child under one year (12 months) of age.

**Latent tuberculosis infection (LTBI):** is a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest TB disease. There is no gold standard test for direct identification of *M. tuberculosis* infection in humans. Most infected people have no signs or symptoms of TB but are at risk for TB disease. Given that the main difference from active TB is the absence of disease and given that infection cannot always be considered latent, LTBI is sometimes referred to as just “TB infection”.

**People who use drugs:** are those who engage in the harmful or hazardous use of psycho active substances, which could impact negatively the user’s health, social life, resources and legal situation.

**Programmatic management of TB preventive treatment (PMTPT):** includes all coordinated activities by public and private health caregivers and the community aimed at scaling up TB preventive treatment to people who need it.

**At-risk group**: is any group of people in which the prevalence or incidence of TB is significantly higher than in the general population.

**Systematic screening for TB disease**: is a systematic identification of people with presumed TB disease, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly. Among those screened positive, the diagnosis needs to be established by one or several diagnostic tests and additional clinical assessments, which together have high accuracy.

**TB preventive treatment (TPT):** Treatment offered to individuals who are considered to be at risk of developing TB disease, to reduce that risk. Also referred to as the treatment of TB infection or LTBI treatment.

**Tuberculosis (TB):** is the disease that occurs in someone infected with *M. tuberculosis*. It is characterized by signs or symptoms of TB disease, or both, and is distinct from TB infection, which occurs without signs or symptoms of TB. In this document, it is commonly referred to as "active" TB or TB "disease" to distinguish it from LTBI or TB infection.

**Underweight:** among adults, this usually refers to a body mass index < 18.5 and among children< 10 years of age to a weight-for-age < –2 z-scores.

# EXECUTIVE SUMMARY

Latent tuberculosis infection (LTBI) occurs when the immune system is able to control a tuberculosis (TB) exposure, and is estimated to affect over 2 billion persons worldwide. Treatment of latent TB would significantly impact the development of TB and help eliminate TB through a decrease in the pool of persons who can eventually reactivate TB and transmit it to others. The UN high level meeting on TB in late 2018 renewed the global commitment to prevent tuberculosis and put forward a target of 30 million people (4 million children under 5 and 20 million household contacts, and 6 million persons living with HIV[1])to receive preventive treatment by 2022.

Rwanda has a relatively low TB burden when compared to its immediate neighbors, with an incidence of 57 per 100 000 population[2], which has been steadily decreasing. The total case notifications of 2019 were 5766. However, Rwanda has a generalized HIV epidemic with a prevalence of 3%, and a higher concentration in key populations. The PLHIV population is estimated at 229,245 in 2018[3,4], of which 190,477 were on ART by 2018. Rwanda has been providing TB preventive treatment to children under 5 and PLHIV. In 2018, 61% of household contacts <5 years of age were estimated to have received treatment. Rwanda's UNHLM minimum target for TB prevention by 2022 is 85 560 persons, of which 11 610 are children under 5, 14 352 are household contacts over 5, and 59 593 are persons living with HIV[5].

It is therefore imperative that progress be made towards reaching and exceeding the UNHLM LTBI treatment goals, and these guidelines have been developed with this in mind. Given the paradox in Rwanda's TB epidemic – a low TB burden coupled with a high HIV burden, and the resources available to treat latent TB infection, these guidelines recommend the following:

**Phase 1:**

- Treatment of all persons living with HIV regardless of age and test of infection.
- Treatment of all household contacts under the age of 5
- Treatment of all household contacts over the age of 5 if a test of infection is positive or if their body mass index is <18.5 kg/m2 or if they are immunocompromised for reasons other than HIV
- Operational research to determine benefit of test of infection given the epidemiology of Rwanda and geographic distribution of TB

**Phase 2**

- Treatment of all persons living with HIV regardless of age and test of infection
- Expansion of TPT to all household contacts of persons with TB, guided by the operational research results

Test of infection will ideally be done with a Mantoux test (tuberculin skin test) that is readily available in the primary health care setting, and which nurses are trained to use. If in due course the interferon gamma release assay test (IGRA) becomes available, this will be the preferred modality due to its ability to detect latent TB infection in the setting of a previous BCG vaccine.

After review of the literature and in keeping with the resource constraints, the following regimens are proposed for latent TB treatment:

- Isoniazid for 6 months, in combination with Cotrimoxazole and B6 for persons living with HIV
- Rifapentine and Isoniazid for 3 months
- Rifampicin and isoniazid in a dispersible fixed dose combination for children under the age of 2 or those who cannot swallow tablets. This combination is readily available as the second phase of TB treatment.

These guidelines will enable Rwanda to enroll a significant number of PLHIV and household contacts on TB preventive treatment, thereby accelerating the progress towards TB elimination in the country.

# 1. INTRODUCTION

Latent TB infection (LTBI) is a significant driver of the TB epidemic, which, affected 10 million persons and carried a mortality of 1.4 million persons globally in 2019[6]. The World Health Organization (WHO) has set ambitious targets for reducing TB incidence and mortality in the next 10–20 years, with an aim of eliminating TB by 2035. Elimination of TB, however, cannot be considered without a discussion of latent TB infection (LTBI) and its diagnosis and treatment. People with latent TB infection are unlikely to know if they are infected, manifest no symptoms, and, while their disease remains dormant, do not contribute to ongoing disease transmission.

Latent TB infection can progress to active disease, and it is likely to do so in people with certain risk factors such as reduced immunity. As such, one of the global priority indicators for tracking progress towards the End TB goals is for ≥90% of people living with HIV and children who are contacts of TB cases to be started on preventive treatment for TB infection[7]. At present, most high-burden countries follow a two-pronged approach, using the Bacille Calmette-Guérin (BCG) vaccine for all children at birth (to prevent infection and reduce the risk of transmission)[8] and treatment of groups who are at high risk for progression to active disease (household contacts aged under five years and HIV-positive people of any age) with 6–36 months of daily isoniazid preventive therapy (IPT)[9]. In 2018, only around 27% of eligible household contacts aged under five years and around 49% of HIV- positive people newly enrolled in care were started on TB preventive therapy. However, by 2019, only 6.3 Million people were started on TPT, 21% of the five year 30 million target.

The consolidated 2018 WHO guidelines[10]recommend at least six months of daily Isoniazid (INH or H) for HIV-positive children (for HIV-positive children aged <12 months, only if contact with a case of TB; for HIV-positive children aged ≥12 months, even without a case of TB; and for all HIV-positive children after successfully completing treatment for TB), and at least 6 months of daily INH for HIV-positive adolescents and adults with a positive or unknown tuberculin skin

test (TST) result. For some time, WHO has recommended preventive treatment for HIV-negative children younger than five years who are household or close contacts of people with TB but, importantly, in the 2018 guidelines, this has been extended to all household contacts of people with TB in high TB incidence countries. In addition to daily isoniazid, the 2018 guidelines also list 3 months of rifampicin and isoniazid (3RH) (in individuals aged <15years) and 3 months of rifapentine and isoniazid (in adults and children) as suitable regimens for use in countries with high TB incidence.

For countries with a low TB burden, the WHO guidelines recommend the "systematic testing and treatment of LTBI "for people living with HIV, adult and child contacts of TB cases, people initiating anti-tumor necrosis factor-alpha (TNF-) treatment, receiving dialysis, preparing for organ or hematological transplantation, or with silicosis, as well as consideration of the same strategy in prisoners, healthcare workers (HCW), immigrants from high burden countries, homeless persons, and illicit drug users. For treatment, these same guidelines recommend that countries use either six months of daily INH (6H); nine months of daily INH (9H); three months of daily rifampicin and INH (3RH); or three months of once-weekly rifapentine (RPT) and INH (3HP). One month of daily rifapentine and INH (1HP) or four months of daily rifampicin are also listed as alternatives[11].

In September 2018, the United Nations convened a high-level meeting on Tuberculosis (UNHLM-TB), where a renewed commitment was made to the goal of eliminating tuberculosis. Central to this promise was the commitment to prevent tuberculosis so that at least 30 million people (4 million children under 5 and 20 million household contacts, and 6 million persons living with HIV)[1] would receive preventive treatment by 2022. This translates into country-specific goals, and Rwanda's target for TB prevention by 2022 is 85 560 persons, of which 11 610 are children under 5, 14 352 are household contacts over 5, and 59 593 are persons living with HIV[5].

Rwanda has a relatively low TB burden when compared to its immediate neighbors, with an incidence of 57 per 100 000 population, which has been steadily decreasing. The total case notifications of 2019 were 5766. However, Rwanda has a generalized

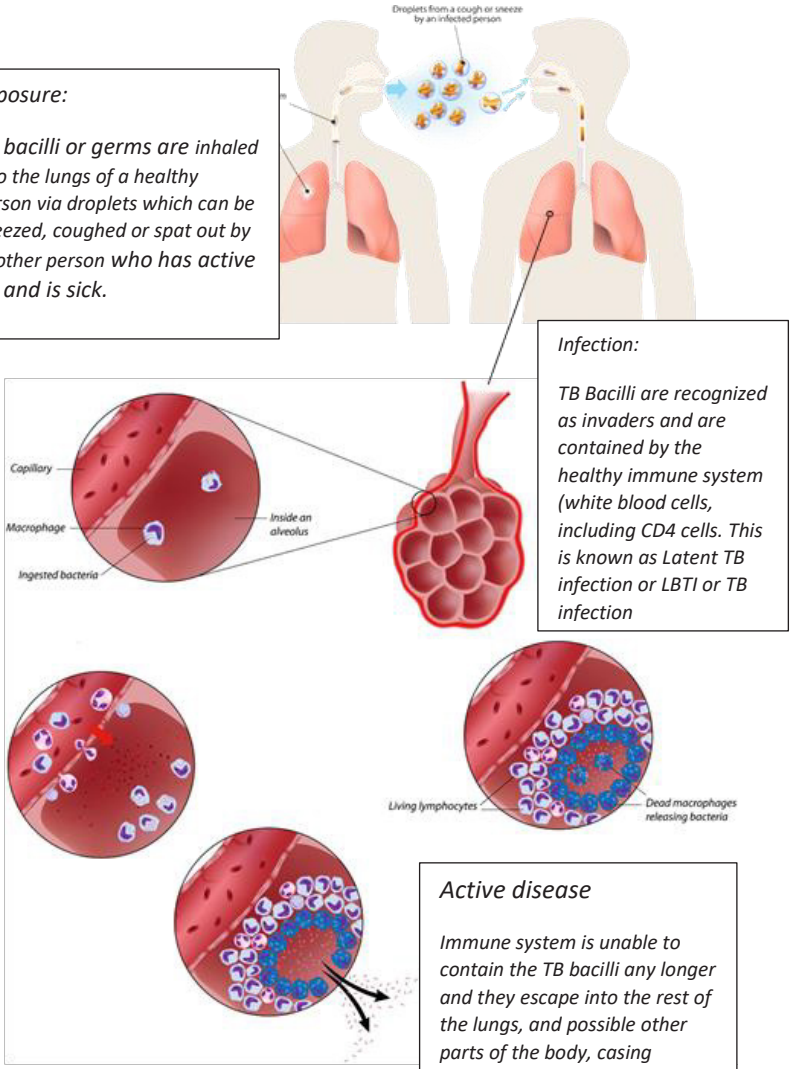
HIV epidemic with a prevalence of 3%, and a higher concentration in key populations. The PLHIV population is estimated at 229,245 in 2018[12,4], of which 190,477 were on ART by 2018. Rwanda has been providing TB preventive treatment to children under 5 and PLHIV. In 2018, 61% of household contacts <5 years of age were estimated to have received treatment.

The Tuberculosis and Lung national strategic plan 2019-2024 has identified TB preventive treatment as a priority gap, highlighting the need to include all household contacts regardless of age, introduce new treatment regimens, and reach the UNHLM and the ministry of health targets set out for the country in terms of prevention.

The purpose of these guidelines is to provide evidence-based recommendations for the management of persons with latent TB infection, based on WHO's most recent guidelines[13], the tuberculosis and lung diseases national strategic plan[14], HIV and adapted to the local epidemiology and context, availability of resources and health infrastructure.

# 2. PATHOGENESIS AND POPULATION AT RISK

Figure 1 Pathogenesis of latent TB[Adapted from Churchyard et al, 2017]




*Exposure:*

*TB bacilli or germs are inhaled into the lungs of a healthy person via droplets which can be sneezed, coughed or spat out by another person who has active TB and is sick.*

*Infection:*

*TB Bacilli are recognized as invaders and are contained by the healthy immune system (white blood cells, including CD4 cells. This is known as Latent TB infection or LBTI or TB infection*

*Active disease*

*Immune system is unable to contain the TB bacilli any longer and they escape into the rest of the lungs, and possible other parts of the body, casing disease. This is known as Active TB disease*

Latent TB infection develops in persons who have been exposed to TB bacilli (germs) from another person, but their immune system is able to contain the infection, so it does not spread. This containment can be lifelong. But more often, persons with this type of TB infection can develop active TB, whereby the immune system is weakened (through increasing age, a concomitant disease for example HIV) and the TB bacilli start multiplying again and are released into the lungs, causing disease. At this point, the person will develop symptoms and be sick.

Latent TB infection, therefore, needs to be treated, so that all the TB bacilli in an exposed/infected individual are killed. This will prevent TB disease from developing in the future.

**Differences between active disease and latent TB infection**

There are many differences between active TB disease and latent TB as summarized in the below table:

| TB disease | Latent TB infection |
|---|---|
| Causes symptoms such as fever, weight loss, cough and night sweats | Does not cause any symptoms |
| Can be diagnosed by finding TB germs in sputum or other tissue | TB germs themselves cannot be found in sputum |
| Treated with four drugs for 6months | Treated with 1-2 drugs for 3-6 months |
| Drug resistance can be detected with a laboratory test once TB bacilli are recovered from the patient | Drug resistance cannot be detected because there are no readily available TB bacilli to test for resistance |
| More likely to occur in persons with decreased immune systems | Can occur in anyone, but progresses to active disease in persons with weakened immune systems |
| Can be seen on an X-ray | Cannot be seen on an X-ray |
| The TST test can be positive when | The TST which tests for |

| | |
|---|---|
| present | previous exposure to TB, can be positive when present |
| The IGRA test can be positive when present | The IGRA test, which tests for previous exposure to TB, can be positive when present |
| TB bacilli can be found in other organs in the body | There are very few TB bacilli, contained only in the lungs and not visible |

**Table 1: Differences between active TB disease and latent TB infection**

## Population at risk for progression from latent TB to active disease

***People with an elevated risk of progression from infection to TB disease*** *such as people living with HIV and patients who have underlying lung disease such as silicosis should receive TB preventive treatment. Additionally, persons preparing for anti-TNF treatment, those receiving dialysis and those preparing for transplantation should receive treatment if they have latent TB infection*

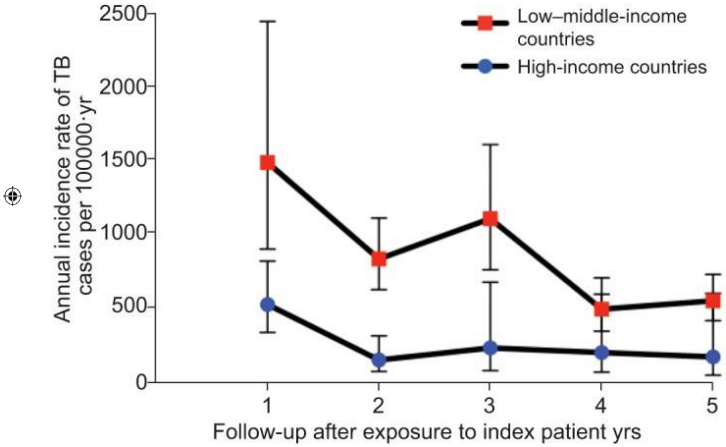
***People with an increased likelihood of exposure to TB disease*** *such as household contacts of people with confirmed TB, persons who work in institutional or crowded settings, such as prisoners, health workers, recent immigrants from countries with a high TB burden, homeless people and people who use drugs should also be considered for TB preventive treatment.*

*Other populations may be considered for TPT to reduce the risk of developing TB, especially if they have a heightened likelihood of unfavourable outcome should disease develop or if the person has multiple risk factors for TB.*

HIV is the strongest risk factor for developing TB disease in those with latent or new TB infection[15]; between 11 and 19% of all HIV-positive people are likely to have Latent TB infection, though it is probably

that this figure is much higher in high-burden settings, as diagnosis of TB infection and TB disease is difficult in people who are living with HIV. Despite greatly increased availability of ART, TB remains a leading cause of morbidity and mortality among HIV-positive people[16]

Contacts of people with TB are also at high risk for developing LTBI and active disease. A 2013 systematic review[17] of 95 studies estimated that the prevalence of active disease in contacts was 3.1% (95% confidence interval (CI) 2–4) and the prevalence of TB infection was 51.5% (95% CI 47–56). This review also found that TB incidence in household contacts of cases varied according to country income (Figure 2).




Annual incidence rate of tuberculosis in contacts by year of follow-up, according to country income(from Fox et al. 201315)
TB: tuberculosis; yr: year

**Figure 2: Annual incidence rate of tuberculosis in contacts**

A recent (2017) systematic review and meta-analysis of the literature, commissioned by WHO[18] for the guideline update found that children in high-burden settings who were household contacts of people with active TB faced an increasing risk of developing LTBI with increasing age. Compared with children aged 0–5 years, risk of infection was

increased in children aged 5–10 years (pooled risk ratio [RR] 1.62 [95% CI 1.25–2.11]; n = 14 studies), was highest in children aged 10–15 years (pooled RR 2.33 [95% CI 1.55–3.50]; n = 11 studies), and was maintained in those aged ≥15 years (pooled RR 2.05 [95% CI 1.53–2.63]; n = 19 studies). In intermediate and low-burden settings, fewer data were available and the risk was less severe, although similar patterns were observed (for children aged 5–15 years vs. 0–5 years, pooled RR 1.18 [95% CI 1.01–1.38] in intermediate-burden settings [n = 4 studies] and pooled RR 1.50 [95% CI 1.14–1.98] in low-burden settings [n = 5 studies]).

This systematic review also examined the risk of progression to active disease among household contacts with latent TB infection. In high-burden settings, the risk was highest in child contacts aged 0–5 years (73 cases among 630 contacts [11.6%; n = 4 studies]), lower in child contacts aged 5–15 years (54 cases among 1,329 contacts [4.1%; n = 4 studies]), and lowest in contacts aged ≥15 years (pooled RR 0.22 [95% CI 0.08–0.60] compared with 0–5 years; n = 3 studies).

# 3. POPULATIONS ELIGIBLE FOR TB PREVENTIVE TREATMENT

## 3.1 Persons living with HIV

### 3.1.1 Adults and adolescents living with HIV

**Recommendation**

*Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if LTBI testing is unavailable. TB preventive treatment should be provided for persons who have completed a course of TB treatment if they are exposed to TB again.*

**Rationale**

TB caused about 251,000 deaths among PLHIV globally in 2018, representing about one-third of all HIV deaths. In Rwanda, the number of TB related deaths amongst PLHIV is estimated to be 320 (Range: 220-340)PLHIV are about 20 times more likely to develop active TB than those without HIV infection. A systematic review of 12 randomized controlled trials (RCTs) found that preventive treatment reduced the overall risk for TB by 33% (relative risk [RR] 0.67, 95% confidence interval [CI] 0.51; 0.87) among the 8,578 PLHIV included[19]. For those who were TST positive, the reduction increased to 64% (RR 0.36, 95% CI 0.22; 0.61). While these studies pre-dated ART for all policies, there is evidence that even in the era of test and treat, TPT confers additional protection for PLHIV and TB incidence remains high even in PLHIV who are on ART and with high CD4 counts. The TEMPRANO trial, a randomized control trial of 2,056 PLHIV showed additional protection from TB preventive treatment in addition to ART in reducing both TB incidence and overall mortality[20], which lasted for more than 5 years[21]. Studies conducted before ART became available showed the value of providing preventive treatment immediately after successful

completion of TB treatment among PLHIV in countries with a TB incidence >100/100,000 population[22] Therefore, preventive treatment is recommended for people who were previously treated for TB.

### 3.1.2 Children and infants living with HIV

**Recommendation**

- *Infants aged < 12 months living with HIV who are in contact with a person with TB and who are unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment.*

- *Children aged ≥ 12 months living with HIV who are considered unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB.*

- *All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment.*

**Rationale**

There are conflicting studies on infants living with HIV. In several studies from South Africa, Madhi et al. showed that primary prevention in children had no benefit in HIV-infected infants identified in the first 3–4 months of life in whom there was no known exposure to active TB[23] but another trial by Zar et al. suggested a considerable reduction in mortality and protection against TB among HIV-infected children who received isoniazid for 6 months[24] Few RCTs included children on ART. Frigati et al did a cohort study that showed a protective effect of TPT in children receiving ART[25].

### 3.1.3 Pregnant and breastfeeding women living with HIV

**Recommendation**

*Pregnancy should not disqualify women living with HIV from receiving preventive treatment with medicines commonly used to treat active TB that are generally considered safe for use in pregnancy, such as isoniazid and rifampicin. Pregnant and breastfeeding women who are unlikely to have TB should be offered TB preventive therapy*

**Rationale**

Pregnant women living with HIV are vulnerable to developing TB during pregnancy or in the first few post-partum months, which can have adverse consequences for both the mother and the foetus, including increased risk of maternal and infant death[26]. Three non-randomized observational studies of TPT in pregnant women reported an overall Odds Ratio of < 1, and were not associated with individual adverse outcomes[27, 28,29]. However, one randomized controlled trial[30] showed a higher risk of adverse outcomes in women who received IPT during pregnancy. None of these studies reported significant risks for maternal hepatotoxicity when receiving IPT. Therefore, it is recommended to not deprive pregnant women of potentially life-saving TB preventive treatment when taking into account the overall risk-benefit assessment. However, there is currently limited information on the safety of rifapentine in pregnancy and regimens which do not include rifapentine should be preferred. Supplemental pyridoxine (vitamin B6) should be given to the infant whose breastfeeding mother is taking isoniazid. Similar to pregnant women living with HIV, the triple pill combination of isoniazid + cotrimoxazole + B6 may be used among breastfeeding women with HIV

## 3.2 Household contacts of persons with tuberculosis

**Recommendation**

- *Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB should be given TB preventive treatment even if LTBI testing is unavailable.*

- *Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation may be given TB preventive treatment if they are within a high burden district, and if they have other risk factors such as low body mass index, and any other risk factor for progression to TB disease*

**Rationale**

A systematic review conducted by the WHO, focusing on household contacts in countries with a TB incidence >100 / 100,00 population, looked at the prevalence of LTBI, progression to active TB disease, and the cumulative prevalence of active TB among household contacts, stratified by age. The prevalence of LTBI was higher among children and adolescents aged > 15 years and adults than in children 15 years. However, all household contacts, regardless of their age or LTBI status, had a higher risk for progression to active TB than the general population. Therefore, preventive treatment is also conditionally recommended for household contacts in other age groups, based on the balance between harm and benefit for individuals and special consideration of ongoing transmission of TB. This recommendation for household contacts stands regardless of the HIV status of the contact.
In the specific context of Rwanda, with a relatively low burden of TB, it is unclear which populations would benefit most from TPT. Testing is available but adds a dimension of cost and practicality. Therefore, the current recommendations will be implemented first in high risk individuals (persons with a BMI <18.5 and those who happen to have a positive test of infection) In the first few years of implementation, operational research will be undertaken to better understand which populations will be able to benefit the most from the intervention.

## 3.3 Other at-risk groups

### 3.3.1 Household contacts of persons who have multi-drug resistant (MDR) TB

**Recommendation**

*In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment can be given when the sensitivity of the index case is known, so that the appropriate preventive regimen can be proposed.*

**Rationale**

The WHO reviewed 4 studies(with more than 20 participants enrolled) that compared participants who received preventive treatment for MDR-TB and those who did not. The first two studies reported either no active TB cases reported in either arm or one case of DS-TB with a different strain[31],[32]. In the third study, 3 of 15 (20%) contacts who refused treatment developed MDR-TB while none of the ones who completed fluoroquinolone-based preventive treatment did[33]. In the last study confirmed or probable TB developed in 2 of 41 (4.9%) children receiving tailored preventive treatment and in 13 of 64 (20.3%) children who did not receive proper preventive treatment[34]. The WHO guidelines recommend that the potential benefits of targeted preventive treatment for contacts of persons who have MDR-TB likely outweigh the harm even though there is a lack of RCT evidence. Therefore, it is recommended that only high-risk individuals be considered for MDR TB preventive treatment, and that confirmation by LTBI testing is obtained prior to treatment. Levofloxacin for 6 months is the regimen of choice, and all contacts of patients with MDR-TB treatment should be followed up at 2 years and investigated for TB. Contacts of RR-resistant TB may also receive MDR- TB preventive therapy unless susceptibility to INH is known, at which point they should receive INH for 6 months. Contacts of INH resistant patients can receive an INH-based regimen based on limited evidence or could benefit from a rifampicin only regimen for 4 months.

### 3.3.2 Other groups at higher risk of developing TB

**Recommendation**

*Other categories who should be systematically tested and treated for latent TB infection if present are:*

- *People who are initiating anti-TNF treatment*
- *People who are receiving chronic dialysis*
- *People who are preparing for an organ or bone marrow transplant*
- *Persons with silicosis*

*Systematic LTBI testing and treatment may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use drugs. This might be implemented in high burden areas and in high risk populations first to assess the risk specific to Rwanda*

*However, TPT testing and treatment is not recommended for people with diabetes, people who engage in the harmful use of alcohol, smokers and underweight/malnourished people unless they also belong to other risk groups. If any of these categories are also household contacts of persons with TB, then they should be prioritized for TPT.*

**Rationale**

There have been studies about the risk of progression to active disease for most of the groups mentioned above. However, an increased risk for progression to active TB was reported for only 4 specific groups; adult and child TB contacts; patients on dialysis and underweight people. On the other hand, patients initiating anti-TNF treatment, patients on dialysis, patients preparing for organ or hematological transplant and patients with silicosis, would benefit most from testing for and treatment of LTBI. The benefits of systematic LTBI testing and TB preventive treatment may not always outweigh the harm to healthcare workers and students, immigrants from countries with a high TB burden, prisoners, homeless people and people who use drugs, mostly due to the high risk of reinfection. If the risk of re-infection is minimized, then the benefits may outweigh the risks. However, the most benefit will be expected from recent infections, and therefore a test of infection should be recommended before treatment. There is insufficient data to recommend TPT in persons with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people without other risk factors such as contact with a person who has active TB disease.

# 4. RULING OUT ACTIVE TB DISEASE

TB preventive treatment is based on the premise that the recipient does not currently have active TB disease. Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm:

- No current cough, fever, weight loss, or night sweats are unlikely to have active TB and should be offered preventive treatment, regardless of their ART status.

- Any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases and offered preventive treatment if active TB is excluded.

- Chest radiography is not a requirement for starting TPT but may be offered to people living with HIV on ART and preventive treatment given to those with no abnormal radiographic findings.

- Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation, these children should be offered TB preventive treatment, regardless of their age.

- For HIV negative household contacts aged >5 years, a chest x-ray can be used to rule out active TB disease

# 5. ALGORITHM FOR TUBERCULOSIS PREVENTIVE TREATMENT (TPT)

## 5.1 Persons living with HIV

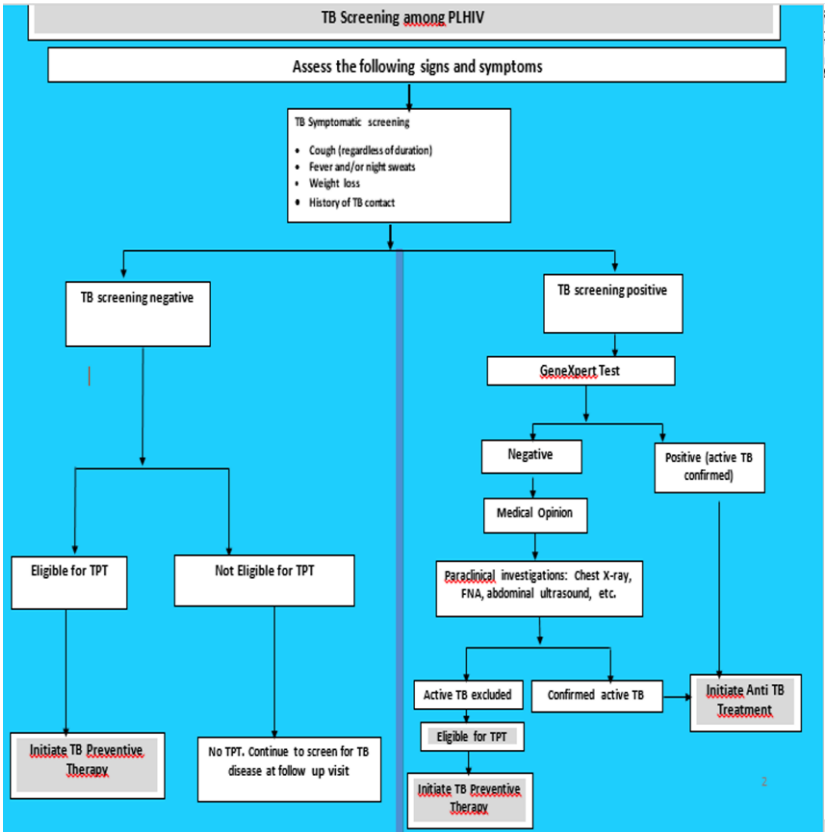



**Figure 3: Algorithm for the provision of TPT in persons living with HIV**

## 5.2 Household contacts of persons with TB

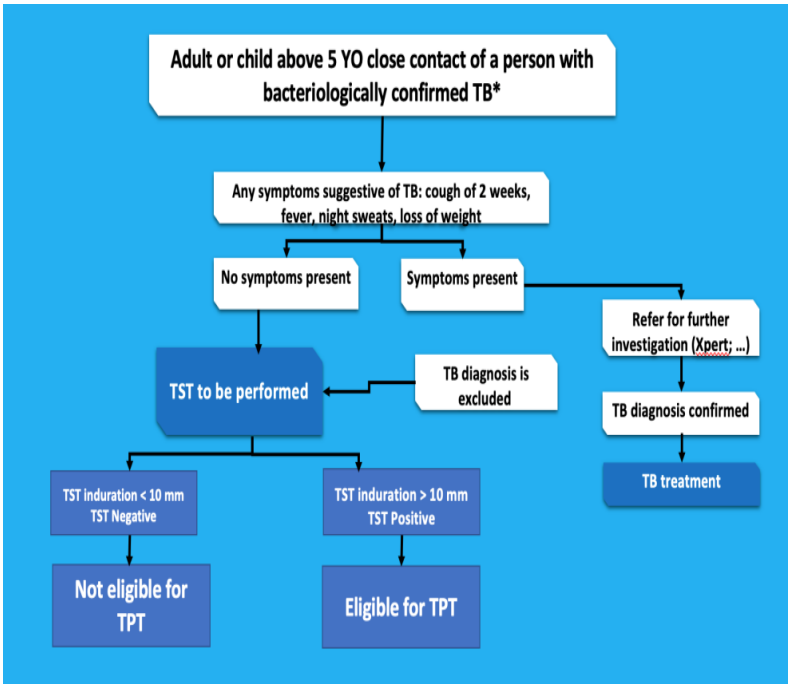



**Figure 4: Algorithm for the provision of TPT to household contacts of persons with TB**

# 6. TESTING FOR LATENT TB INFECTION

**Recommendation**

*Testing for latent TB infection can be carried out through a Tuberculin skin test (TST) or an interferon-gamma release assay (IGRA). Testing is recommended where it is unclear if the benefit for treatment outweighs the risks. In PLHIV and children <5, the risk does not outweigh the benefit, therefore TPT can be started without a test of infection. In household contacts over 5 years of age, a test of infection would be ideal given the low burden setting. However, due to operational concerns with implementation, tests of infection are not required to start in high burden districts and towns until such time as the specific groups where the benefit outweighs risk can be determined through operational research.*

**Rationale**

The WHO reviewed five prospective cohort studies, with a total of 7,769 participants. Three of the studies were conducted in South Africa[35,36,37] and two in India[38,39] and the review concluded that the comparison of TST and IGRA in the same population does not provide strong evidence that one test should be preferred over the other for predicting progression to active TB disease. TST is easier to implement than the IGRA in resource-constrained settings and costs less. However, there is a global shortage of TST that makes this test difficult to access.

Imperfect performance of these tests can lead to false-negative results, particularly for young children and immunocompromised individuals such as PLHIV with low CD4 counts. While it is important to use LTBI testing to ascertain the benefit of TPT, conversions from negative to positive and reversions from positive to negative are more commonly identified with IGRA than with TST[40]

PLHIV who have a positive test for LTBI benefit more from TB preventive treatment than those who have a negative LTBI test. LTBI testing can be used, where feasible, to identify such individuals but should not be a prerequisite to start TB preventive treatment in PLHIV and household contacts aged < 5 years, particularly in settings with a high TB incidence, given that benefits outweigh the risks.

**Table 2: Differences between the TST/Mantoux[41] test and the IGRA test**

| **Mantoux test (Tuberculin skin test, TST)** | **IGRA (interferon-gamma release assay)** |
|---|---|
| Detects old exposure to TB bacilli through an immune reaction | Detects old exposure to TB bacilli through an immune reaction |
| Skin test (needs intra-dermal injection) | Blood test (needs phlebotomy) |
| Results are read by a health care worker | Results are read in the laboratory |
| Does not require laboratory infrastructure | Currently requires sophisticated laboratory infrastructure but might be made a point of care test soon |
| BCG vaccine can make this test positive in the absence of TB infection | Test is not affected by having received BCG in the past |
| Previous TB disease and infection with non-tuberculous mycobacteria can make this test positive | Interpretation of serial IGRAs can be difficult due to a lack of consensus on optimal thresholds for conversion and reconversion |

## Recommendations for testing

Table 3: Recommendations for use of latent TB testing in Rwanda

| Group | Preferable | Alternate |
|---|---|---|
| PLHIV | None/either* | None/either* |
| Children <12 months | None/either* | None/either* |
| Children > 12 months | None/either* | None/either* |
| Pregnant women | None/either* | None/either* |
| Household contacts | | |
| Adults | TST‡ | IGRA |
| Pregnant women | TST‡ | IGRA |
| Children <5 | TST‡ | IGRA |
| Children >5 -15 | TST‡ | IGRA |
| Other | | |
| Immunocompromised | IGRA | TST |
| Receiving anti-TNF therapy | IGRA | TST |

‡

For household contacts in high burden countries, there will be no requirement for testing until the risk/benefit ratio can be established through research or pilots

# 7. TPT REGIMEN RECOMMENDATIONS

**Recommendation**

*Treatment for latent TB infection can be one of the following regimens:*

- *Isoniazid monotherapy for 6 months (or Isoniazid+cotrim+B6 for PLHIV)*
- *Rifampicin and Isoniazid daily for 3 months*
- *Rifapentine and isoniazid weekly for 3 months*
- *Rifapentine and Isoniazid daily for 1 month*

*The choice of regimen depends on the age of the patient, co-morbidities, anticipated drug-drug interactions, availability and patient and clinician preference.*

**Rationale**

**Isoniazid monotherapy for 6 months (6H):** Several studies have shown that isoniazid (INH) for 6 months reduces the overall risk of tuberculosis by 33%, and 64% in those who had a positive TST[17] While there was a trial that showed that continuous INH (approximated by 36 months of INH in PLHIV, not on ART) was more beneficial than 6H by 38%, this was more pronounced in those with a positive TST, and the studies were done at the time when ART was not routinely used or coverage was low. Isoniazid is the preferred regimen among HIV-infected children on protease inhibitor-based regimen (lopinavir-ritonavir), nevirapine, or integrase inhibitors (dolutegravir) due to potential drug-drug interactions. Isoniazid monotherapy should also be protective in contacts of TB patients with laboratory-confirmed isoniazid-susceptible, rifampicin-resistant disease (mono rifampicin-resistant TB).

***Isoniazid + cotrimoxazole + pyridoxine combination****: is an FDC that may be considered as an alternative for PLHIV who need also cotrimoxazole when: shorter rifamycin-containing regimens are not available, drug-drug interactions occur, or during gradual scale-up. These are single scored tablets, therefore, if the required dose is one-third of the adult formulation, this FDC cannot be used for children below five years of age living with HIV*

**Isoniazid and Rifampicin daily for 3 months (3HR):**For TPT among children, the 3HR regimen provides a better tolerated and child-friendly

option compared to isoniazid since dispersible fixed-dose combinations (FDC) are now available for young children. As data on rifapentine dosage for younger children are lacking, in the short term national programmes could consider scale-up of 3HR for TB prevention among children of all age groups. Those weighing under 25 kg may receive (including children < 2 years of age) the same RH formulation used for the continuation phase of TB treatment (R/H, 75/50 mg). Child-friendly FDCs of HR has the added benefit of already being in the national supply chain for the treatment of children < 25 kg.

**Isoniazid and rifapentine once weekly for three months (3HP**): Several studies have shown the efficacy and safety of 3HP when compared to 6H or 9H[42, 434445]. Two of the RCTs involved adults with HIV from South Africa, Peru and a number of countries with a TB incidence of <100/100 000 persons. No significant difference was found in the incidence of active TB between participants given a 3HP and 6H or 9H, the risk for hepatotoxicity was significantly lower and the 3HP regimen was also associated with a higher completion rate in all subgroups. The rates of spontaneous abortion and birth defects were similar to those in the general US population. A per-protocol analysis in another study showed a lower rate of TB infection or death in participants given continuous isoniazid. In all the studies, 3HP was given under direct observation.

**Isoniazid and rifapentine daily for one month (1HP):** One open-label study[46] on the use of 1HP vs 9 months of isoniazid has been published. The Non-inferiority of 1HP as an option for TPT, as defined by the study protocol, was shown in the modified intention to treat (mITT) population. Non-inferiority was also shown for the sub-group with confirmed infection (incidence rate difference per 100 person-years = 0.069 [-0.830 to 0.690]), as well as in males and females, and among those on or without ART at start of the study. Therefore, 1HP remains a viable option as a TPT regimen. Like 3HP, there is insufficient data to recommend it in pregnant women.

**Rifampicin daily for four months**: Rifampicin has an excellent safety profile and is lower in cost. A systematic review showed that 3–4 months' daily rifampicin and 6H have similar efficacy individuals given rifampicin daily for 3–4 months had a lower risk for

hepatotoxicity than those treated with isoniazid monotherapy[47]. However, one of the main challenges with its use is that there is a perception that it might increase the levels of rifampicin resistance in the community. There is no evidence to date demonstrating this phenomenon. However, drug-drug interactions do limit its use in PLHIV, child-friendly formulations are not available, and single-dose rifampicin might be difficult to access where most first-line TB drugs are delivered as FDCs.

**Levofloxacin:** Levofloxacin can be used to prevent MDR TB in contacts of persons who have levofloxacin-sensitive MRD TB as evidenced by a drug susceptibility test. The household contacts should also have proof of latent infection before starting TPT. The regimen is given for 6 months.

**Table 4: Options for TPT treatment in Rwanda**

| Group | 1st line option | 2nd line option |
|---|---|---|
| Persons living with HIV | | |
| Adults | 3HP | 6H* |
| Children <24 months | 3HR‡ | 6H |
| Children > 24months | 3HR | 6H |
| Pregnant women | 6H | 4R |
| Household contacts | | |
| Adults | 3HP | 6H |
| Pregnant women | 6H | 4R |
| Children <24 months | 3HR | 6H |
| Children > 24 months to 15 years | 3HP | 6H |
| Other | | |
| Immunocompromised | 3HP | 6H |

| | | |
|---|---|---|
| Receiving anti-TNF therapy | 3HP | 6H |
| Multi-drug resistant TB | Levofloxacin or High dose of INH(index case with resistance to fluoroquinolone) | Based on susceptibility testing of index patient |

**Isoniazid+Cotrimoxazole+B6 fixed-dose combination can be used instead of 6H in PLHIV*

*ǂ 3HR is available as the continuation phase of TB treatment in dispersible, fixed dose combination format for children under the age of 2.*

## Recommended dosages of TPT medication

Table 5 Dosages for TPT regimens

| Regimen | Children <10 years | Children > 10 years | Adults |
|---|---|---|---|
| 6H | 10mg/kg/day | 5mg/kg/day | 300mg daily |
| 3HR | 15mg/kg/day | 10mg/kg/day | - |
| 3HP | <15kg: H300mg/R300mg<br>15-23kg: H500mg/R450mg<br>24-30kg: H600mg/R600mg<br>>30kg H700mg/R750mg | <15kg: H300mg/R300mg<br>15-23kg: H500mg/R450mg<br>24-30kg: H600mg/R600mg<br>>30kg H700mg/R750mg | 900mg INH/900mg Rifapentine |
| Levofloxacin (MDR) | 15-20mg/kg/day (150-750mg depending on weight) | 15-20mg/kg/day (150-750mg depending on weight) | 750mg for <45kg<br>1gm for >45kg |

**Isoniazid formulation in children(100 mg) and in adults(300mg)**

**Table 6 Isoniazid dosages per tablet**

| | | | | | | |
|---|---|---|---|---|---|---|
| **6H/ daily dose** | **Children** | | | | | |
| | Isoniazid 100 mg | **≤ 5 kg** | **5-9,9 kg** | **10-13,9 kg** | **14-19,9 kg** | **> 25 kg** |
| | | ½ tab | 1 tab | 1 ½ tabs | 2 tabs | 3 tabs |
| | **Adults** | | | | | |
| | Isoniazid 300 mg | **1 tab** | | | | |

**Isoniazid + Rifapentine / FDC in children and in adults**

**Table 7. 3HP dosages per tablet**

| | | | | | | |
|---|---|---|---|---|---|---|
| **3HP/ weekly dose** | **Age 2–14 years** | | | | | |
| | | 10–15 kg | 16-23 kg | 24-30 kg | 31-34 kg | >34 kg |
| | Isoniazid 300 mg + Rifapentine 300 mg* | 1 tab | 1 tab + 1/2 | 2 tabs | 2 tabs + 1/2 | 2 tabs + 1/2 |
| | **Age >14 years** | | | | | |
| | | >30 kg | | | | |
| | Isoniazid 300 mg + Rifapentine 300 mg* | 3 tabs | | | | |

*Fixed Dose Combination (FDC) of Isoniazid + Rifapentine

**Pyridoxine (B6):** Long-term treatment with INH can result in peripheral neuropathy due to Vitamin B6 deficiency. Individuals at risk for peripheral neuropathy, (malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes, pregnant or breastfeeding mothers and their infants) should receive vitamin B6 supplements when taking isoniazid- The standard dose of pyridoxine when used prophylactically for prevention of neuropathy among patients taking isoniazid is 10–25 mg/day.

If peripheral neuropathy occurs (symmetrical numbness and tingling of the extremities) it is usually reversible once INH is stopped and high-dose pyridoxine therapy (100–200 mg/day) is given. Therefore, routine pyridoxine supplementation with isoniazid is probably not necessary and **its absence should not become a barrier to TPT initiation.**

# 8. DRUG-DRUG INTERACTIONS[1]

When two drugs are given together, there can be a change in either of the drug's effects on the body. A drug-drug interaction (DDI) can increase or decrease the action of either or both drugs or can be the cause of adverse events. A DDI can therefore delay, enhance or decrease the absorption of either of the drugs taken together. Many DDI is caused by an enzyme system in the liver called the cytochrome P450. These enzymes can either be induced, and hence more active, or inhibited and hence less active. When more active, they increase the metabolism of other drugs that are passed through the same system and reduce the concentration of these drugs. This can render the second drug ineffective. When the enzyme complex is made less active, then the drugs administered will have reduced metabolism, and their concentration will be increased in the body. They can then lead to more adverse events and side effects.

Both daily Rifapentine (RPT) and daily Rifampicin (RIF) are known to strongly induce the cytochrome P450 enzyme system. Weekly RPT dosing also induces this system, although the duration of the induction is not clear when given weekly, and caution is needed when prescribing RPT with some drugs. The induction and increase in activity of the enzyme mean that the levels of these drugs are reduced, and can therefore be ineffective.
Isoniazid is also a known inhibitor of the cytochrome system and therefore can slow the elimination of co-administered drugs. This can lead to an increase in side-effects. Some people are also slow acetylators of INH, meaning that they eliminate INH more slowly. This can lead to increased INH concentrations and can potentiate the effect on the cytochrome enzymes[48].

As both drugs have opposing effects on the cytochrome system in some instances, the degree of inhibition or induction by each will

[1]Adapted from [IMPAACT4TB 3HP Drug-Drug Interactions, Including ART, ISBN 978-1-990940-34-7, Version 1, September 2019]

determine the direction of the effect. Mostly, rifapentine is thought to be a more potent inducer than INH is an inhibitor if they are both administered.

Likewise, a drug-drug interaction does not necessarily mean that the dosage needs to be adjusted or that concomitant administration needs to be completely avoided. Where available, pharmacokinetic studies can be referenced to understand the magnitude of the interaction and the effect, and whether dose adjustment is necessary.

Both INH and RPT can lead to side-effects. Notably, INH can lead to liver damage especially when administered daily. Therefore, caution should be exercised when using with other drugs that have similar side effects, in order not to potentiate the occurrence of an adverse event. Common drugs where caution should be exercised are acetaminophen/paracetamol, alcohol, amoxicillin, terbinafine, phenothiazines, anabolic steroids should be avoided during treatment with 3HP

If in doubt about any drug interaction, please consult a pharmacologist.

**Table 8: Common drug interactions with Rifapentine and INH**

| **Medication Class** | **RPT *decreases* blood levels** | **INH *increases* blood levels** |
|---|---|---|
| Antiarrhythmics | Disopyramide/Mexiletine/Quinidine/Tocainide | |
| Antibiotics | Chloramphenicol/Clarithromycin/Dapsone/Doxycycline/Fluoroquinolones | |
| Anticoagulants | Warfarin | Warfarin |
| Anticonvulsants | Phenytoin | Phenytoin, carbamazepine |
| Antidepressants | Amitriptyline/Nortriptyline | Some SSRIs |
| Antimalarials | Quinine, Artemisinin | Halofantrine |
| Antipsychotics | Haloperidol | Haloperidol, |

| | | |
|---|---|---|
| | | Pimozide |
| Antivirals | Antiretrovirals (Ritonavir) | |
| Azole Antifungals | Fluconazole, Itraconazole, Ketoconazole | Fluconazole, Itraconazole, Ketoconazole |
| Barbiturates | Phenobarbital | |
| Benzodiazepines | Diazepam | Diazepam, Triazolam |
| Beta-Blockers | Propranolol | |
| Calcium Channel Blockers | Diltiazem/Nifedipine/Verapamil | |
| Cardiac Glycoside Preparations | Digoxin | |
| Corticosteroids | Prednisone | |
| Fibrates | Clofibrate | |
| Oral hypo glycaemic agents | Sulfonylureas | |
| Hormonal Contraceptives | Ethinyl oestradiol/Levonorgestrel | |
| Immunosuppressants | Cyclosporine/Tacrolimus | |
| Methylxanthines | Theophylline | Theophylline |
| Narcotic analgesics | Methadone | Levomethyldate acetate |
| Phosphodiesterase-5(PDE-5)Inhibitors | Sildenafil | |
| Thyroid Medications | Levothyroxine | |

## 8.1 Interactions with antiretrovirals

TB preventive treatment is crucial in persons living with HIV. Therefore, special consideration needs to be taken to elaborate on the potential drug-drug interactions with this class of drugs. Isoniazid does not have any known clinically significant interactions with antiretroviral drugs. Rifapentine, as an active ingredient in 3HP, has the following interactions and contra-indications with antiretrovirals:

- Efavirenz: 3HP can be co-administered with efavirenz without clinically meaningful reductions in efavirenz mid-dosing concentrations or virologic suppression49 supporting the use of Rifapentine with EFV, without dose adjustment.50

- Dolutegravir:Co-administrationofDTGand3HPwaswell-tolerated, safe,anddidnotappeartorequireanydose-adjustmentforDTG in a recent study. However, this study looked at patients who were already suppressed.51 Studies of the effect of co-administration on newly initiated PLHIV with both drugs at the same time are pending.

- Atripla (fixed-dose combination of Efavirenz, emtricitabine and Tenofovir): Among 12 HIV-positive patients on a fixed-dose combination antiretroviral treatment with emtricitabine, tenofovir disoproxil-fumarate and efavirenz (Atripla), weekly RPT at a dose of 900mg resulted in minimal (Cmin) reductions in efavirenz and tenofovir and did not modify HIV viral load or CD4 counts.52

- Raltegravir and 3HP administration of rifapentine with raltegravir (RAL) were found to be safe and well-tolerated53; supporting the use of Rifapentine with RAL.[54]

### 8.1.1Antiretrovirals that cannot be used with 3HP

As potent enzyme inducers, the rifamycins can accelerate drug metabolism, resulting in a significant reduction in ARV drug exposure. The common ARV drugs most affected by CYP induction include ***all protease inhibitors (PIs ) including Kaletra (LPV/r),*** and some ***non-nucleoside reverse transcriptase inhibitors (NNRTIs), including Nevirapine***.[55]

### 8.1.2 Interactions with anti-malarial drugs[2]

Isoniazid does not have any known significant interaction with anti-malarial drugs currently being recommended by WHO. Rifapentine, by virtue of its effect on metabolism, could potentially have interactions with Artemisinin-based combination therapies (ACTs) recommended by WHO as the first-line treatment for uncomplicated P. falciparum malaria in all adults and children. This interaction has not been studied and the following guidance is based on extrapolation from studies with rifampicin, which has similar effects.

The **latest WHO Malaria Guidelines**, published in 2015[56] acknowledge the significant interactions between antimalarials and ***rifampicin*** insection 5.5(pg.56):

*"Concomitant administration of rifampicin during **quinine** treatment of adults with malaria was associated with a significant decrease in exposure to quinine and a **five-fold recrudescence rate**. Similarly, concomitant rifampicin with **mefloquine** in healthy adults was associated with **a three-fold decrease in exposure to mefloquine**". In adults co-infected with HIV and TB who were being treated with Rifampicin, administration of **artemether + lumefantrine** resulted in lower exposures to a 9-fold decrease in exposure to artemether, a 6-*

[2] Adapted from [IMPAACT4TB Clinical Information: Malaria & 3HP, ISBN 978-1-990940-28-6, Version 1, September 2019]

*fold decrease in dihydro artemisinin, and 3-fold decrease in lumefantrine"*

*In 2015, the WHO concluded that "there is insufficient evidence at this time to change the current mg/kg body weight dosing recommendations; however, as these patients are at high risk of recrudescent infections, they should be monitored closely"*

Referring to malaria treatment in special risk groups, the guidelines note that rates of treatment failure are higher with hyper parasitaemia and in areas, with artemisinin-resistant falciparum malaria and malaria patients require greater exposure to antimalarial drugs (longer duration of therapeutic concentrations):

WHO recognises that the acceptability, tolerability, safety and effectiveness of augmented ACT regimens in special circumstances, including concomitant rifampicin therapy, requires urgent evaluation.[57]

***Induction of P450 cytochrome*** by intermittent doses of RPT is approximately 75-80% the magnitude of that caused by RIF. The daily dosing of RPT in the TB TC Study 29B resulted in greater induction of cytochromes than with RIF[58], however, RPT is a less potent inducer when given weekly; this will likely wax and wane over the week and will be difficult to predict.

In the absence of information regarding 3HP and antimalarial, the only guidance that can be offered currently is:

1. **If a patient is diagnosed with malaria but is not yet on TPT, decisions regarding any TPT initiation should be delayed until the episode of malaria has resolved**.

   ***Rationale****: if a patient is symptomatic /febrile due to malaria, then active TB cannot be effectively ruled out, and therefore a course of TPT should not be commenced*

2. **If a patient is diagnosed with malaria while on 3HP, the patient should be treated for malaria and clinically monitored according to national guidelines to ensure that malaria is cured. At this stage, the available evidence is insufficient to indicate that the dosage of adjustment is required.**

   ***Rationale:*** *advice from the WHO malaria section as stated in the WHO Malaria Treatment Guidelines that although there is a well-understood DDI for TB treatment only (and not prevention and intermittent dosing), malaria treatment can proceed without and without dose adjustment.*

3. **If a patient has malaria recrudescence while on 3HP, and the patient should be retreated for malaria according to national guidelines. The 3HP regimen should be withheld only if the new treatment also includes a drug with known interactions with rifamycins. In that case, 3HP should be recommended once the episode of malaria is resolved.**

   ***Rationale:*** *if a clinically significant DDI is already suspected in a particular patient due to malaria treatment failure, then retreatment should consider that by withholding 3HP for the duration of malaria retreatment if using drugs that have a known interaction with rifamycins*

4. **If a patient meets diagnostic criteria for severe malaria (impaired consciousness, low blood glucose, high bilirubin/jaundice, bleeding, anaemia, kidney failure, and parasitaemia>10%) while on 3HP, the 3HP regimen should be withheld and the patient should be urgently treated according to national guidelines. 3HP should be recommenced only once the episode of malaria is fully resolved.**

***Rationale:*** *severe malaria is associated with mortality approaching 100%, therefore all efforts should be made to ensure that treatment is successful, and any other drugs should be withheld.*

# 9. CLINICAL MONITORING[3]

## 9.1 . Baseline evaluation

**Rule out active TB**

All patients should first be evaluated for signs and symptoms of active TB (before commencing a course of TPT. Once active TB has been ruled out, eligible patients should be evaluated to assess their risk of side-effects, and determining which regimen they should be started on.

### Baseline liver function testing

Providers should consider at least baseline AST (aspartate aminotransferase), and other liver function tests according to their clinical judgement, in the following patient groups:

- HIV infection (these are typically obtained when starting ART)
- Daily alcohol consumption
- Liver disorders including viral hepatitis
- Postpartum period (≤3 months after delivery)
- Concomitant use of other hepatotoxic medicines

For individuals with abnormal baseline test results, sound clinical judgement is required to ensure that the benefit of TB preventive treatment outweighs the risks and that regular monitoring can be ensured.

Otherwise, **healthy household child contacts do not require baseline liver function testing**. Providers can consider measuring baseline liver function tests in children and adolescents living with HIV, having other liver disorders, or taking other hepatotoxic medications. For children and adolescents with abnormal baseline liver function tests, the risks and benefits of 3HP should be weighed.

[3]Adapted from [IMPAACT4TB 3HP Adverse Events And Monitoring Schedule, ISBN 978-1-990940-24-8, Version 1, September 2019]

## 9.2. Routine monitoring for adults and children

Patients taking TPT should be monitored at monthly visits. The purpose of monthly visits is to screen for side-effects of the drugs, assess adherence and provide support as appropriate to safely retain the patient in care until treatment completion.

### Screen for active TB

Even if active TB has been ruled out prior to commencing treatment, a patient may develop active TB during TPT. Therefore, patients should be screened for the signs and symptoms of active TB at each monthly visit.

### Screen for symptoms of drug reactions/interactions

Patients should be systematically evaluated for symptoms of the drug reactions frequently associated with TPT:

- Hepatotoxicity (table 1, with an emphasis on early symptoms)
- Flu-like or systemic hypersensitivity reactions (table 2 above)
- Peripheral neuropathy (burning, stinging, or numbness in hands or feet)

### Routine monitoring of liver enzymes

For most patients, routine liver function testing is not recommended. Patients at higher risk for hepatotoxicity (as described above) should receive a baseline AST. If this test is within normal limits, no further routine monitoring is needed.
Patients with raised baseline AST should have a repeat AST if deemed clinically necessary (symptoms and signs of liver toxicity and/or clinical suspicion.

Additional monitoring tests can be conducted for patients at higher risk of hepatotoxicity but with normal baseline AST on an individual basis and at the discretion of the treating clinician.

**Assess adherence**

Adherence should be assessed at every monthly monitoring visit. If appropriate, further support should be offered to assist the patient to remain safely in care until the end of treatment. Detailed guidance on this topic is provided in the IMPAACT4TB Technical Brief entitle Adherence.

## 9.1 Schedule of visits

Table 9: Schedule of Visits for patients taking a 6 month regimen of TPT

| Visit number | Initial | | Month 1 | | Month 2 | | Month 3 | | Month 4 | | Month 5 | | Month 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug used | 3HP 3HR | 6H | 3HP 3HR | 6H | 3HP 3HR | 6H | 3HP 3HR | 6H | 3HP 3HR | 6H | 3HP 3HR | 6H | 3HP 3HR | 6H |
| Assess for Eligibility | X | X | | | | | | | | | | | | |
| Weight | X | X | X | X | X | X | X | X | | X | | X | | X |
| Temperature | X | X | X | X | X | X | X | X | | X | | X | | X |
| R/o active TB (symptom screen) | X | X | X | X | X | X | X | X | | X | | X | | X |
| Pregnancy test in women of childbearing age | X | | | | | | | | | | | | | |
| Physical exam –check for signs of liver toxicity | X | X | X | X | X | X | X | X | | X | | X | | X |
| Review adherence | | | X | X | X | X | X | X | | X | | X | | |

## 9.2 Side-effects/adverse drug reactions associated with TPT

### Hepatotoxicity

Liver injury, also known as hepatotoxicity is more commonly due to isoniazid than rifapentine

10-20% of adult patients taking daily isoniazid either alone or in combination develop an asymptomatic rise in hepatic enzymes followed by a return to normal levels despite the continuation of treatment. This is sometimes known as hepatic adaptation. It is a normal physiological response and is not dangerous.

Clinically significant hepatotoxicity, defined as a rise in transaminase enzymes to more than three times the upper limit of normal with symptoms, or more than five times without symptoms, occurred in 0.4% (4 in 1000) of patients taking 3HP and 1.8% (18 in 1000) of patients taking 9H in one study.

Risk factors for TPT-related hepatotoxicity include:[59]

- older age
- raised liver enzymes at baseline
- pregnancy
- daily alcohol consumption
- comorbid liver disease
- concurrent use of other hepatotoxic medications.

Hepatitis usually develops over a period of days to weeks. The first symptoms to develop are mild, persistent, insidious, and somewhat non-specific. Later, symptoms more typically associated with hepatitis develop as a result of liver injury and cholestasis.[60]

**Table 10: Symptoms of liver damage in adults and children**

| Early symptoms | Later symptoms |
|---|---|
| • Weakness<br>• Fatigue and/or somnolence<br>• Anorexia/loss of appetite<br>• Fever<br>• Nausea or vomiting | • Abdominal pain<br>• Jaundice (yellow skin and/or eyes)<br>• Itchy skin<br>• Dark, brown, or tan colored urine (darker or additional discoloration than due to rifapentine)<br>• Pale stools<br>• Easy bruising or bleeding |

**Table 11 Management of liver toxicity according to liver function tests**

| Grade | AST IU/L | ALT IU/L | Management |
|---|---|---|---|
| Normal values | 5-35 | 5-40 | Can take INH if not other contra-indication |
| Grade 1 | >44 | >50 | Continue INH, reassure the patient and monitor AST/ALT |
| Grade 2 | >88 | >100 | Continue INH, reassure the patient and monitor AST/ALT |
| Grade 3 | >175 | >200 | Stop INH, evaluate all possible causes and re-initiate if INH if <200 IU/l |
| Grade 4 | >350 | >400 | Stop INH, evaluate all possible causes and re-initiate if INH if <200 IU/l |

**Flu-like syndrome and other systemic hypersensitivity reactions**

A flu-like syndrome consisting of fever or chills, in combination with weakness, fatigue, muscle or bone aches, tachycardia or palpitations, flushing, syncope, dizziness, headaches, conjunctivitis, sweats, or other similar symptoms, has been associated with intermittent Rifamycin administration[61] [62] [63]. *This is a rare drug reaction, is usually mild and self-resolving, and most patients will be able to continue 3HP to complete the preventive treatment.*

Symptoms consistent with this flu-like syndrome were reported in approximately 3-4% of patients taking 3HP in randomized and non-randomized studies[64]. Other systemic hypersensitivity syndromes were reported in approximately 1% of patients in one study, including cutaneous (rash, itching or swelling of lips or face – the most common), respiratory (cough, chest pain), gastrointestinal, or other miscellaneous symptoms. In other studies of 3HP, no such reactions were reported. Flu-like and other hypersensitivity reactions are usually mild, self-limiting within 24 hours, and do not reliably recur on re-challenge with 3HP. These reactions occurred most commonly after 3-4 doses of 3HP, and are associated with the white race, female sex, age> 35and lower BMI.[65]

Rarely, these reactions can be more severe, involving hypotension or syncope, and in very rare cases requiring hospitalization. In one study including patients taking 3HP, severe reactions were reported for 0.3% of participants (3 in 1000).[3]

**Table 12 Symptoms of flu-like or hypersensitivity reactions**

| Syndrome | Features | Frequency |
|---|---|---|
| Flu-like | Fevers or chills<br>PLUS<br>Weakness, fatigue, muscle or bone aches, tachycardia or palpitations, flushing, syncope, dizziness, headaches, conjunctivitis, sweats, other similar symptoms. | 3-4% |
| Cutaneous | Rash, itching, swelling of face or lips (angioedema), anaphylaxis. | <1% |
| Gastrointestinal | Nausea, vomiting, abdominal pain. | Rare |
| Respiratory | Shortness of breath, bronchospasm. | Rare |
| Severe hypersensitivity | Hypotension, tachycardia, syncope, bronchospasm, anaphylaxis. | Very rare (<0.3%) |

## Peripheral Neuropathy

Neuropathy is associated with the use of daily isoniazid, it has not been reported as a specific AE in studies of 3HP. Pyridoxine (B6), if available, can be administered to minimize the risk of peripheral neuropathy amongst those at higher risk.

**Table 13 Suggested management of peripheral neuropathy and arthralgia**

| | Peripheral Neuropathy | Arthralgia | Management |
|---|---|---|---|
| Grade 1 | Paresthesia, mild pain | Pain in joints | Continue INH, reassure patient. Start pyridoxine and analgesics |
| Grade 2 | Paresthesia, moderate pain | Pain with moderate functional | Continue INH, reassure patient. Start pyridoxine and |

| | | | |
|---|---|---|---|
| | | impairment | analgesics |
| Grade 3 | Paresthesia, severe pain | Pain with severe functional impairment | Stop INH, reassure the patient and treat with pyridoxine and analgesics. RE-initiate INH if symptoms disappear 2 weeks after stopping. |
| Grade 4 | Unbearable pain disability | | Stop INH, reassure the patient and treat with pyridoxine and analgesics. RE-initiate INH if symptoms disappear |

## Comparison of Adverse Events among TPT Regimens

**Table 14 Comparative rates of adverse events for different TPT regimens.**

| | 3HP | 3-4HR | 6H | 9H |
|---|---|---|---|---|
| Any AE (treatment related or not) | 11.5% | 29.7% | 36.1% | 17.6% |
| Withdrawals due to AEs | 1.7% | 2.2% | 3.8% | 6.4% |
| Flu-like and/or systemic hypersensitivity reactions | 3.8% | n/a | n/a | 0.5% |
| Hepatotoxicity | 1% | 6.8% | 2.7% | 5.6% |

## Adverse drug reactions in children

### Hepatotoxicity

Hepatotoxicity is rarely reported amongst children on TPT, occurring in about 1% of children taking isoniazid preventive therapy. In one randomized study comparing children treated with 3HP and a limited

number of programmatic studies of 3HP in children, there were no cases of hepatotoxicity[66].

Up to 10% of children taking isoniazid alone can have liver enzyme elevations that do not result in clinically significant disease. Routine laboratory monitoring for hepatotoxicity in children is not recommended. Clinically significant disease is by definition symptomatic. Children with hepatotoxicity most commonly present sub acutely with the development of poor appetite, nausea, vomiting and/or abdominal pain that persist and worsen over time. Later, liver tenderness, hepatomegaly and jaundice develop. If identified early and medications are stopped, there are typically not permanent sequelae from the drug-induced hepatotoxicity.

**Flu-Like Syndrome and Other Systemic Hypersensitivity Reactions**

Flu-like and other systemic hypersensitivity reactions were similarly rare amongst children. Symptoms consistent with a flu-like syndrome were reported in approximately 0.6% of patients taking 3HP in one randomized study. Other systemic hypersensitivity syndromes were reported in approximately 1-2% of patients in this study, including cutaneous (rash, itching or oral blisters) or gastrointestinal symptoms. In small programmatic studies of 3HP in children, no such hypersensitivity reactions were reported.

As in adults, hypersensitivity reactions are usually mild, self-limiting (<24 hours' duration), and do not reliably recur with re-challenge of 3HP. More serious reactions are thought to be rare, no hospitalizations, life-threatening events, disability or permanent damage was seen in the pediatric 3HP trial.

**Peripheral Neuropathy**

Children and adolescents living with HIV and those with malnutrition may be at elevated risk of peripheral neuropathy. Breastfeeding mothers, PLHIV, persons with diabetes, renal failure, chronic alcohol dependence and malnutrition are at higher risk for developing

peripheral neuropathy. When available, vitamin B6 should be used to lower this risk. The initiation of TPT should not be delayed if vitamin B6 is not available.

Individuals receiving TPT do not have active disease and therefore their risk for AEs during treatment must be minimized. This can be achieved by careful assessment of the patient prior to commencing 3HP, and routine monitoring during treatment.

## 9.3 . Management of drug reactions due to TPT in adults and children

Severe drug reactions need to be referred to the appropriate level of care immediately. Signs and symptoms of severe drug reactions that may occur while taking TPT are:

- Circulatory impairment (hypotension, tachycardia, syncope)
- Respiratory impairment (bronchospasm, wheeze, chest pain, tachypnea, syncope)
- Type I hypersensitivity (anaphylaxis, angioedema)
- Severe cutaneous reactions (rash with blistering, vesicles, or mucosal involvement)

The table below summarizes management for drug reactions that can occur during treatment with INH or with Rifapentine. If it is unclear what the symptom is or if it is associated with TPT, the patient should be referred immediately to a higher level of care.

**Table 15. Suggested management of selected drug reactions**

| Reaction/symptom | Management |
|---|---|
| *Flu-like or systemic hypersensitivity reactions* | |
| Severe hypersensitivity or cutaneous reactions, including angioedema and anaphylaxis | 1. Discontinue TPT<br>2. Provide urgent supportive care<br>3. Refer for further assessment and management as appropriate |
| Flu-like syndrome (mild/moderate)<br>*OR*<br>Mild cutaneous reactions (rash, itching)<br>*OR*<br>Gastrointestinal reactions<br>*OR*<br>Respiratory reactions | 1. Withhold TPT<br>2. Offer ancillary treatments for symptomatic management as appropriate<br>a. Antihistamines (diphenhydramine, loratadine etc.)<br>b. Antiemetics, antidiarrheals or ORS<br>c. Bronchodilators<br>d. Steroids<br>3. Monitor symptoms<br>4. Re-challenge 3HP at next dose if symptoms resolve |
| *Hepatotoxicity* | |
| Any symptoms of hepatitis develop while taking 3HP | 1. Withhold TPT<br>2. Assess for other causes of symptoms (gastroenteritis, etc)<br>3. Test AST (other liver function tests at provider discretion) |
| AST <3x ULN<br><br>(Test may have been conducted in a patient with symptoms or with raised baseline AST) | 1. Continue TPT<br>2. Monitor symptoms<br>3. Reassess risk factors<br>4. Check AST again if symptoms do not resolve |
| AST ≥3x ULN with any symptoms of hepatitis | 1. Withhold TPT<br>2. Monitor AST and symptoms |

| | |
|---|---|
| *OR*<br>AST ≥5x ULN | 3. Reassess risk factors<br>4. Re-challenge with TPT once symptoms resolved and AST <3x ULN |
| AST ≥10x ULN<br>*OR*<br>Symptoms of severe hepatitis<br>• Jaundice<br>• Dark urine<br>• Abdominal pain | 1. Discontinue 3HP<br>2. Supportive care<br>3. Monitor liver function tests |
| *Other AEs* | |
| Active TB signs or symptoms<br>*OR*<br>Malaria diagnosis and treatment<br>*OR*<br>Diagnosis and treatment of other acute illness | 1. Withhold TPT<br>2. Investigate and treat for active TB, malaria or other acute illness<br>3. Continue TPT only after treatment of the acute illness is completed and symptoms have resolved |
| Pregnancy | 1. Discontinue 3HP if this was the regimen<br>2. Discuss timing and options for completing a course of TPT using isoniazid |

All adverse drug reactions need to be reported through the patient record form. This is done by ticking the appropriate side effect on the patient file, and this is then recorded and analysed centrally.

# 10 DIFFERENTIATED HIV SERVICE DELIVERY

- DSD approaches for PLHIV who are stabilized are expected to reduce overcrowding at ART clinics, enhance the quality of care, improve adherence and viral suppression rates, and increase convenience for people DSD is expected to enable appropriate support and education on potential adverse events, tolerability and importance of treatment completion In principle, all recommended TB services should be incorporated within these models of service delivery and existing mechanisms to review the quality of ART services should be harnessed for monitoring the implementation of intensified TB case finding (ICF) and TPT services The following interventions should be considered for TB care under all DSD programmes

- All recommended TB/HIV services offered to PLHIV – including regular TB screening, referral for diagnosis when TB symptoms are noted, and TPT if TB disease is ruled out – should be done at regular intervals (at least once a quarter)

- TPT may be started during pre-ART evaluation or before starting spaced appointments under DSD, particularly for the shorter regimens (1HP) or at the time of follow-up visit to the health center if longer regimens (6H, 4R, 3HR, 3HP) are implemented as per national guidelines

# 11 ETHICS AND TB PREVENTIVE TREATMENT

TB preventive therapy has been shown to save lives by preventing TB in high-risk populations. However, it should be noted that TB preventive treatment, like most preventive treatment, is offered to persons who are not currently sick. Therefore, the risks and benefits have to be carefully considered to ensure beneficence and to avoid doing harm. This is particularly the case in settings where testing for latent TB infection is not done, and therefore some persons who will be offered TPT may not need it. In high burden settings, TPT can alter the trajectory of the TB epidemic, thereby improving health outcomes for the population at large. This is not necessarily the case in low-burden settings. Lastly, while pregnancy is a special state and carries with it risks for the mother and unborn child, it is important to still offer pregnant women the same treatments and benefits of treatment to protect their health, while at the same time ensuring no harm is done to the foetus.

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