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WORLD HEALTH ORGANIZATION

**TARGET PRODUCT PROFILES FOR
TUBERCULOSIS PREVENTIVE TREATMENT**

DRAFT

1 ABBREVIATIONS

2	1HP	One month of rifapentine plus isoniazid daily
3	3HP	Three months of rifapentine plus isoniazid weekly
4	3HR	Three months of daily rifampicin plus isoniazid
5	4R	Four months of daily rifampicin monotherapy
6	6H	Six months of daily isoniazid monotherapy
7	9H	Nine months of daily isoniazid monotherapy
8	ART	antiretroviral treatment
9	CI	confidence interval
10	FDC	Fixed-dose combination
11	GDG	Guideline Development Group
12	HIV	human immunodeficiency virus
13	Hr-TB	isoniazid-resistant, rifampicin-susceptible TB
14	IGRA	interferon-gamma release assay
15	IPT	isoniazid preventive treatment (or monotherapy)
16	LA/ER	long-acting/extended-release
17	LTBI	latent tuberculosis infection
18	MDR-TB	multidrug-resistant tuberculosis
19	MTb	Mycobacterium tuberculosis
20	OR	odds ratio
21	PLHIV	people living with HIV
22	RCT	randomized controlled trial
23	RR	relative risk
24	TST	tuberculin skin test
25	TB	tuberculosis
26	TBI	tuberculosis infection
27	TPP	Target product profiles
28	TPT	TB preventive treatment

1 DEFINITIONS

2 *Note:* The definitions listed below apply to the terms as used in this document. They may have
3 different meanings in other contexts.

4 **Adolescent:** A person aged 10–19 years

5 **Adult:** A person over 19 years of age

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

8 **Child:** A person under 10 years of age

9 **Contact:** Any person who was exposed to a person with tuberculosis

10 **Contact investigation:** A systematic process for identifying previously undiagnosed people with TB
11 among the contacts of an index case. Contact investigation consists of identification and
12 prioritization and clinical evaluation. In some settings, the goal includes testing for LTBI to identify
13 candidates for preventive treatment.

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

19 **Household contact:** A person who shared the same enclosed living space as the index case for one or
20 more nights or for frequent or extended daytime periods during the 3 months before the start of
21 current treatment.

22 **Incipient disease:** an infection with viable *M. tuberculosis* bacteria that is likely to progress to active
23 disease in the absence of further intervention but has not yet induced clinical symptoms,
24 radiographic abnormalities, or microbiological evidence consistent with active TB disease^a.

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

29 **Infant:** A child under 1 year (12 months) of age

30 **Latent tuberculosis infection (LTBI):** A state of persistent immune response to stimulation by
31 *M. tuberculosis* antigens with no evidence of clinically manifest active TB. There is no gold standard
32 test for direct identification of *M. tuberculosis* infection in humans. Most infected people have no
33 signs or symptoms of TB but are at risk for active TB disease. This state is also referred to, more
34 accurately, as 'TB infection' (TBI). This should NOT be confused with *active TB disease*.

^a Drain PK, Bajema KL, Dowdy D, *et al.* Incipient and subclinical tuberculosis: a clinical review of early stages and progression of infection. *Clinical Microbiology Reviews* 2018; 31(4): e00021-18

1 **Target product profiles (TPP):** outlines the desired 'profile' or characteristics of a product that is
2 aimed at a particular disease or diseases. TPP state intended use, target populations and other
3 desired attributes of products, including safety and efficacy-related characteristics. Such profiles
4 usually guide product research and development.

5 **TB preventive treatment:** Treatment offered to individuals who are considered at risk of TB disease
6 in order to reduce that risk. Also referred to as treatment of TB infection, LTBI treatment or TB
7 preventive therapy.

8 **Tuberculosis (TB):** The disease state due to *M. tuberculosis*. In this document, it is commonly
9 referred to as "active" TB or TB "disease" in order to distinguish it from TB infection

10 **Tuberculosis infection:** refers here to a state of persistent immune response to stimulation by
11 *M. tuberculosis* antigens with no evidence of clinically manifest active TB. This is also commonly
12 referred to as LTBI (see above) but given that infection cannot always be considered "latent" the
13 term TBI reflects better the whole spectrum of infection to which the TPP refer.

14 **Underweight:** in adults usually refers to a body mass index <18.5 and in children < 10 years to a
15 weight-for-age < -2 z-scores

I. INTRODUCTION

Tuberculosis (TB) is a major yet preventable global health problem, with an estimated 10 million new cases worldwide in 2018, resulting in more than 1.5 million deaths, making it the leading infectious disease cause of death worldwide (1).

One quarter of the global population is estimated to be infected with *Mycobacterium tuberculosis* (*Mtb*) (2). Latent TB infection (LTBI) is classically defined as a '*state of persistent immune response to stimulation by Mtb antigens without evidence of clinically manifested active TB disease*'. The vast majority have no signs or symptoms of TB disease and are not infectious, although they are at risk of progressing from infection to active TB disease and becoming infectious. On average, about 5–10% of people who are infected with TB will develop active disease over the course of their lives – the highest risk being in the first year after infection (3). Children <5 years, adolescents ≥10 years of age and people living with HIV (PLHIV) have a high risk of developing active TB disease following infection, including severe life-threatening forms such as TB meningitis (4). As TB infection is more likely to progress rapidly to TB disease in children and adolescents, household contacts of infectious TB cases in these age group are at particular risk (5,6). Untreated HIV infection is the strongest risk factor for progressing from TB infection to disease, with an overall annual risk estimated at 10% (7), particularly in children (8,9). For these reasons, prevention of TB is a crucial component of the WHO End TB Strategy that calls for 90% coverage of TB infection treatment among persons living with HIV (PLHIV) and household contacts of infectious TB cases by 2035 (10). The UN high-level meeting on TB, in September 2018, further emphasized the need to strengthen implementation of TB preventive treatment (TPT) and called for 30 million people, including 4 million children <5 years of age, to receive TPT by 2022 (11).

Despite the fact that TPT has been available for more than 60 years and in spite of strong evidence demonstrating its effectiveness, uptake and scale-up have been slow, mainly due to the limitations of both diagnostic assays and available regimens (long duration, cost, toxicity, adherence issues, and operational aspects). Critical gaps remain in achieving global targets: in the 16 high TB or TB/HIV burden countries that reported providing treatment in PLHIV in 2018, coverage reached 49% only (12). Globally, TPT was initiated in only 27% of the 1.3 million household contact children aged under 5 years estimated to be eligible for treatment. The availability of, and access to, new drugs or regimens that can be administered for a shorter duration and with fewer adverse events than with the current 6-12 months TB preventive strategies is imperative to allow larger-scale implementation.

Even with improved TPT options in the future, it is envisaged that treatment of infection would remain one of a series of articulated actions that programmes need to put in place for effective TB control. Scale-up of TPT would need to be matched with active case finding, better treatment for active TB and other measures to reduce transmission and unfavourable outcome of disease episodes. Parallel improvements in these areas, as well as development of new TB vaccines, will be critical.

II. Tuberculosis Preventive Treatment^b: background and current situation.

The aim of treatment of TB infection (TBI)^c is to prevent progression to active clinical disease through killing of resident bacilli in the host. Isoniazid (H) administered daily for 6 to 12 months (6-12H) has been the mainstay of treatment for more than fifty years, with efficacy ranging from 54% to 88% (13,14). A re-analysis of the U.S. Public Health Service isoniazid trials of the 1950s-1960s showed that the benefit of isoniazid increased progressively when administered for up to 9 or 10 months and stabilized thereafter, leading to the recommendation of the 9-month isoniazid regimen as adequate treatment (15). However, further studies showed similarities between the 6 and 12 months regimens in non-HIV infected persons (16). (**Annex 1**).

Other treatments including rifampicin (R), isoniazid and rifampicin (HR), or isoniazid and rifapentine (HP), have been investigated and proven to be safe and efficacious (16). (**Table 1**). Several randomized studies have compared 3–4 months of daily isoniazid and rifampicin (3-4HR) to daily isoniazid alone for 6–12 months in adults, and a meta-analysis found that 3-4HR was equivalent to 6-12H in terms of efficacy, safety, and mortality (17). A randomized controlled trial in children <15 years found that 3-4HR was at least equivalent to 9H (no child from either group experienced a clinical episode of active TB) (18). Recently, a multicentre clinical trial among 6859 subjects showed that 4-months of daily rifampicin (4R) was non-inferior to 9-months of daily isoniazid (9H) for the prevention of active TB, and was associated with a higher rate of treatment completion and better safety, both in adults and children (19, 20).

A once-weekly, directly observed, regimen combining isoniazid and rifapentine for 3 months (3HP) was shown to be non-inferior to self-administered 9H, and associated with higher treatment-completion rates (82.1% vs. 69.0%) and less hepatotoxicity (0.4% vs. 2.7%) (21). Similar results were observed in the extension of the study in children aged 2 to 17 years, and no hepatotoxic effects attributed to treatment were observed in either study group (22). A follow-up study in HIV infected adults showed that the 3HP regimen was as effective as the 9H regimen and was associated with a higher treatment-completion rate (89% vs. 64%) (23). The weekly 3HP regimen was also evaluated in South African adults who had HIV infection and a positive tuberculin skin test (TST) and were not receiving antiretroviral therapy (ART); the efficacy of that regimen was shown to be similar to a 6-month isoniazid regimen (24). In a large post-marketing evaluation of 3HP use across 16 US TB programmes as well as in routine health care settings, completion of 3HP was greater overall than rates reported from clinical trials, and greater than historically observed using other regimens among reportedly non-adherent populations (25). Further, a systematic review published in 2018 showed that 3HP was *similar* to other TB infection treatment regimens (including 6H, 9H, 3-4HR, 2-3RZ) in terms of effectiveness, risk of adverse events, risk of discontinuation due to adverse events, and risk of death, and had higher completion rate (26).

^b Tuberculosis (or TB) preventive treatment in this document is a shortened manner of referring to the treatment of tuberculosis infection for prevention of TB disease (see also Definition)

^c Given that infection cannot always be considered latent and that the main difference with active TB is the absence of disease, in this document, unless otherwise stated, we use the term *Tuberculosis Infection* (TBI) to represent all stages of infection with *M. tuberculosis* without clinical manifestations of active TB disease.

Recently, a 1-month regimen of daily isoniazid + rifapentine (1HP) delivered to HIV-infected patients aged 13 years and above, living in areas of high TB prevalence or who tested positive for TB infection, was shown to be *non-inferior* to 9 months of isoniazid alone in a Phase III randomized, open-label, controlled trial (27). The 1HP regimen was also found to be non-inferior to 9H in a subset of participants with a positive test for TB infection (tuberculin skin test or IGRA). Serious adverse events occurred in 6% of the patients in the 1HP group and in 7% of those in the 9H group ($P = 0.07$). Treatment completion was higher in the 1HP arm than in the 9H arm (97% vs. 90%, $P < 0.001$). Of note, most of the participants were on ART.

Table 1. Regimens for Tuberculosis Preventive Treatment according to pooled efficacy, risk of hepatotoxicity, and main adverse events.^d

Drug Regimen	Dosage	Efficacy vs. Placebo*	Efficacy vs. 6 Mo of Isoniazid*	Hepatotoxicity vs. 6 Mo of Isoniazid*	Adverse Events
<i>odds ratio (95% confidence interval)</i>					
Isoniazid alone for 6 or 9 months	Adults, 5 mg/kg; children, 10 mg/kg (maximum, 300 mg)	6-month regimen: 0.61 (0.48–0.77); 9-month regimen: 0.39 (0.19–0.83)	Not applicable for 6-mo regimen, and not available for 9-mo regimen	Not applicable for 6-mo regimen, and not available for 9-mo regimen	Drug-induced liver injury, nausea, vomiting, abdominal pain, rash, peripheral neuropathy, dizziness, drowsiness, and seizure
Rifampicin alone for 3 to 4 months	Adults, 10 mg/kg; children, 10 mg/kg (maximum if <45 kg, 450 mg; maximum if ≥45 kg, 600 mg)	0.48 (0.26–0.87)	0.78 (0.41–1.46)	0.03 (0.00–0.48)	Influenza-like syndrome, rash, drug-induced liver injury, anorexia, nausea, abdominal pain, neutropenia, thrombocytopenia, and renal reactions (e.g., acute tubular necrosis and interstitial nephritis)
Isoniazid plus rifampicin for 3 to 4 months	Adults, 10 mg/kg; children, 10 mg/kg (maximum if <45 kg, 450 mg; maximum if ≥45 kg, 600 mg)	0.52 (0.33–0.84)	0.89 (0.65–1.23)	0.89 (0.52–1.55)	Influenza-like syndrome, rash, drug-induced liver injury, anorexia, nausea, abdominal pain, neutropenia, thrombocytopenia, and renal reactions (e.g., acute tubular necrosis and interstitial nephritis)
Weekly rifapentine plus isoniazid for 3 months	Adults and children: rifapentine, 15–30 mg/kg (maximum, 900 mg)†; isoniazid, 15 mg/kg (maximum, 900 mg)	Not available	vs. 9 Mo of Isoniazid 0.44 (0.18–1.07)§	vs. 9 Mo of Isoniazid 0.16 (0.10–0.27)	Hypersensitivity reactions, petechial rash, drug-induced liver injury, anorexia, nausea, abdominal pain, and hypotensive reactions
Daily rifapentine plus isoniazid for 1 month	Adults and adolescents (> 13 y.o): 300 mg daily for a weight of <35 kg, 450 mg daily for a weight of 35 to 45 kg, and 600 mg for a weight of >45 kg) plus isoniazid at a dose of 300 mg daily (1-month group)	Not available	vs. 9 Mo of Isoniazid <i>Risk difference:</i> 0.02 per 100 person-years (–0.30 - 0.34)	vs. 9 Mo of Isoniazid 0.47 (0.30–0.75)	Nausea, vomiting, drug associated fever, anaemia, neutropenia, elevated liver-enzyme levels, peripheral neuropathy

* Data on efficacy and hepatotoxicity are from Stagg et al and Swindells et al

^d **Adapted from:** Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis infection. *N Engl J Med* 2015;372:2127-35.

† The Food and Drug Administration recommends increasing the daily dose of efavirenz to 800 mg when it is co-administered with rifampicin, but clinical outcomes and patient PK data do not support this recommendation.
‡ The following incremental adjustments are required for persons weighing less than 50 kg: 10.0 to 14.0 kg, 300 mg; 14.1 to 25.0 kg, 450 mg; 25.1 to 32.0 kg, 600 mg; and 32.1 to 49.9 kg, 750 mg.
§ The comparison is with 9 months of isoniazid.

III. Target Product Profiles for TB Preventive Treatment

1. The need of new medicines/regimens for the treatment of TB infection:

The development of short, safe, efficacious and easy-to-take regimens for the treatment of TB infection and prevention of TB disease development requires detailed information on the respective safety and toxicity of the regimen's components, their potential for drug-drug interactions (DDIs), their propensity for development of drug resistance while on therapy, and their use in specific patient populations - such as contacts of MDR-TB cases, persons infected with HIV, pregnant women or children (28) (**Annex 2**). For these reasons, target product profiles (TPPs) aim at identifying the key product attributes to be considered for the development of best and most suitable TB prevention treatments (29). Thus, the determination of TPPs for the treatment of TB infection is expected to assist developers in aligning the characteristics of new treatment regimens with programmatic needs at country level. Of note, the target product could be either a combination of medicines or an individual medicine.

2. Objective and Target audience

The target audience comprises the pharmaceutical industry, academia, research institutions, product development partnerships, non-governmental & civil society organizations, and donors.

3. Methods

The WHO/GTB programme followed WHO Standard Procedures for the development of Target Product Profiles, Preferred Product Characteristics, and Target Regimen^e, and used a stepwise approach to identify specific regimen features that could have an impact both at patient and population level. The activities included a series of expert meetings, mathematical modelling, cost-effectiveness analysis and wide web-based interaction with stakeholders.

3.1 Baseline elements:

A scoping group was established by WHO/GTB. This group met in Montreal in September 2019 to review the available evidence and discuss on potential targets for TPT. Ahead of this, a rigorous pipeline analysis was undertaken, coupled with a systematic literature review to assess the need and context for development of TPPs for the treatment of TB infection and to develop the initial draft of the TPP attributes. Baseline elements of the TPPs were discussed at the initial meeting, followed by a number of teleconference calls and consultations with various stakeholders to adjust the various proposed targets, informed by results of the complementary analyses described below.

^e WHO Target Product Profiles, Preferred Product Characteristics, and Target Regimen: Standard Procedures. World Health Organization, Geneva, Switzerland. V1.0 December 2019.

3.2. Mathematical modelling

The major goal of new TPP for tuberculosis preventive treatment is to improve TB control through shorter, simpler, more tolerable and more efficacious regimens that are affordable and accessible, and that can rapidly reduce morbidity and mortality from TB. Individual treatment success rates, disease transmission, antimicrobial resistance, and operational factors may all affect a regimen's ability to fulfil this role. In order to prioritize different characteristics when constructing and evaluating new preventive regimens, a mathematical modelling framework was developed to identify the specific regimen properties that would be most predictive of the impact of a future regimen in different settings. Basic regimen attributes were adopted to identify a minimal set relevant for epidemiological impact:

- (i) Duration of regimen: time of administration of the regimen (months);
- (ii) Trial-based efficacy against DS-TB: reduction in cumulative incidence that would be observed under trial conditions, over a 5-year follow-up, TPT vs. no TPT;
- (iii) DR-Barrier: proportion of treated individuals with DS infection who do not acquire Rifampicin-Resistant infection;^f
- (iv) Forgiveness to regimen non-completion: amongst those not completing regimen, proportion that nonetheless get full benefit of regimen.
- (v) Ease of adherence: proportion completing regimen.

The analysis focused on four different settings, representing different epidemiological conditions: Kenya, South Africa, India and Brazil. In each country, the potential impact was modelled of full adoption of the UN High-level meeting (HLM) targets for preventive therapy amongst PLHIV and all-age household contacts of notified TB cases. Assuming that HLM coverage targets are fully met by 2022 and maintained thereafter, impact was quantified as the percentage reduction in cumulative incidence between 2020 and 2035, relative to a baseline of isoniazid TPT coverage remaining at current levels over the same period.

^f It was assumed that a rifamycin-containing regimen will have half the efficacy against tuberculosis infection with DR-TB, compared to that against infection with drug-susceptible-TB. For simplicity, a non-rifamycin-containing regimen (such as 6H) would be considered as having no capacity to generate DR-TB, thus effectively having a 100% DR-Barrier.

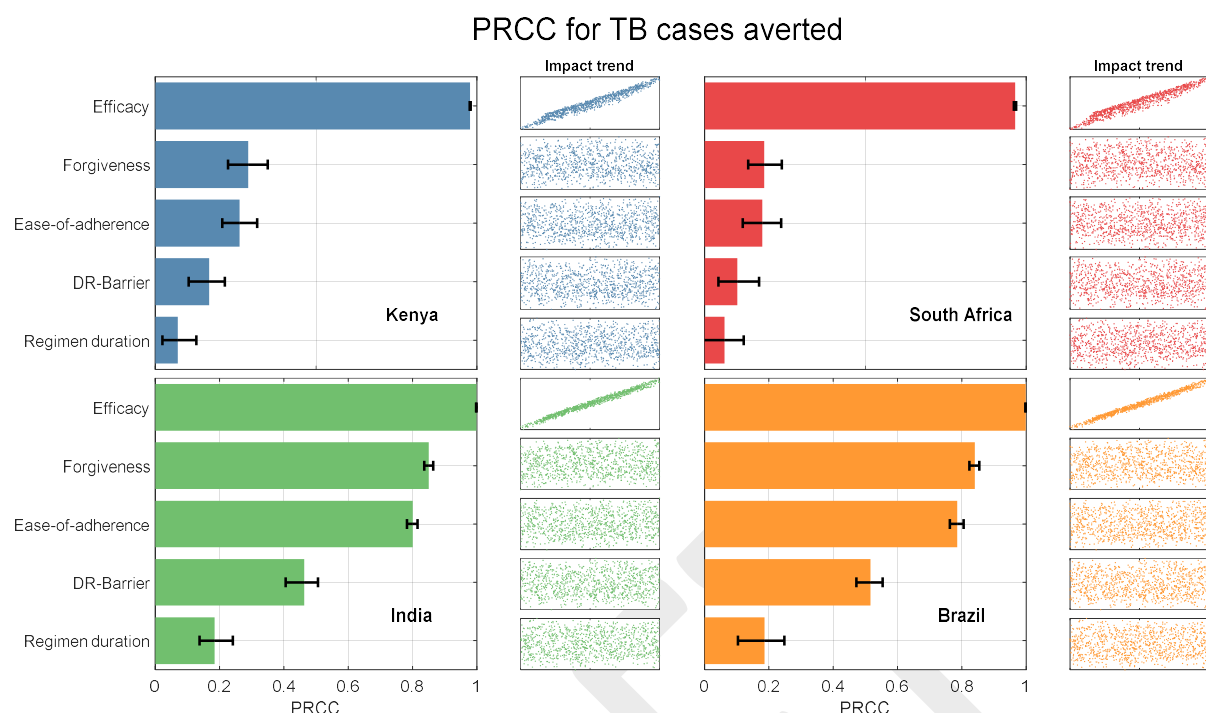


Figure 1. Results for the influence of each attribute on TB incidence impact.

Bars represent partial rank correlation coefficients (PRCC) between individual attributes and impact. Scatter plots show each attribute plotted against impact.

Results for the influence of each attribute on incidence impact are shown on **Figure 1**, which depicts the modelled impact of 1,000 different regimens, representing different combinations of attributes on the continuum between minimal and optimal scenarios. As can be seen, regimen's *efficacy* is the attribute that is most predictive of incidence reduction in all settings. Amongst the remaining 'secondary' attributes, forgiveness and ease-of-adherence play the most prominent roles, as modifiers of the impact of efficacy. Of note, there is a substantial variation in the role of these secondary attributes between South Africa and Kenya vs. India and Brazil, most probably reflecting differences in HIV prevalence.

3.3 Cost-effectiveness analysis

A bottom-up, or micro-costing, approach was used to capture detailed costs related to the current standard of care for TB and LTBI treatment in Brazil and South Africa. This approach estimates personnel and resource use from the health system perspective for a typical or "average" patient seeking care. In the case of TB, it would include cost components such as personnel time to administer clinical care, equipment needed for diagnosis, TB medication and other related supplies, expressed in 2019 US dollars. Within this approach, TPT related costs are assumed to be only those related to treatment, which comprised an initial medical visit, treatment medication (assumed in this analysis to be 6 months of INH administered daily in the base case) and follow up medical visits. Costs of screening for TB infection were not included in this analysis. Costs related to adverse events were considered on a pro-rated basis across the entire cohort.

Active TB related costs were calculated separately for those with DS-TB and DR-TB. Costs related to inpatient stays and outpatient visits were included, as was treatment monitoring. For treatment supervision, two treatment modes were considered, i.e. DOT and a mixed mode of DOT/SAT (self-administered treatment). Component costs for treatment monitoring, inpatient and outpatient visits, and corresponding proportions were obtained from country TB programs and literature.

Cost-effectiveness of TPT was evaluated by calculating the incremental cost-effectiveness per TB case averted by TPT. Overall, it was found that increased costs to scale-up TPT are being largely outweighed by cost savings from averted TB cases: for example, compared to the baseline scenario, implementation of a TPT corresponding to the *minimal* TPP for TPT in South Africa was estimated to cost an additional \$12 million, but resulted in estimated savings of \$273 million from averted TB cases—hence overall savings of \$261 million with 842 thousand TB cases averted. Greater savings were observed with the *optimal* TPP for TPT regimen, as well as with rifamycin-sparing minimal TPP regimens.

3.4 Development of draft target product profiles

Based on the above, a first draft of the TPP document and related TPP tables was written, that underwent a series of revisions from the scoping group, including group discussions through webinars.

4. Description of the TPPs for TB Preventive Treatment:

4.1. Principles

The WHO Standard Procedures for the development of Target Product Profiles, Preferred Product Characteristics, and Target Regimen⁸ highlights the elements that should (obligatory) and could (optional) be part of any target product profile. At a minimum, TPPs usually specify the following characteristics: the clinical indication of the therapeutics/regimen; the goal to be met and the measure of efficacy; the target population that will receive the treatment; the level of implementation in the healthcare system; and the intended users. The selected targets should outline the most important performance and operational characteristics, with the term “minimal” used to refer to the lowest acceptable output for a characteristic, and “optimal” used to refer to its ideal target. The following are indications of the various attributes that can be identified as specific quantifiable targets in TPPs for treatment of TB infection. For the details of these targets and related key issues to be addressed, the **TPP Tables** outline the various regimen attributes with relevant targets and capture the minimum and optimum characteristics of the regimen to be developed (see **pages 15-23**):

- The **minimum** requirements column provides instructions detailing targets that *improve on the current standard of care* and which therefore represent an acceptable minimum for global health impact when developing candidate regimens. These criteria provide context for defining clear minimal “go/no-go” decisions to be used throughout the development process.
- The **optimal** requirements specify performance and use characteristics of an ‘ideal’ product for which the global health impact would be broader, deeper, and potentially quicker.

⁸ WHO Target Product Profiles, Preferred Product Characteristics, and Target Regimen: Standard Procedures. World Health Organization, Geneva, Switzerland. V1.0 December 2019.

For both minimum and optimal categories, an *annotations* column provides elements of the rationale supporting the selected targets for each attribute.

A number of regimen attributes or characteristics were identified and included as proposed targets. Certain attributes appeared as '**priority**' since their minimum targets should be clearly met in order to make a 'go/no go' decision, while some others, less essential, could be considered as potential trade-offs, and are subsequently defined as '**desirable**'. For example, if a new regimen were to be better tolerated or have a greater efficacy, it could justify a trade-off in a desirable area such as the number of drugs in the regimen or its duration. (*Note: for desirable attributes, the 'go/no-go' decision process does not apply.*)

Overall, this document lays out the minimal levels of acceptable performance and use characteristics for novel TPT regimens, as well as what the optimal performance could be, for a number of key priority and desirable attributes. The minimal and optimal characteristics thus define a range: it is therefore expected that the resultant products—regimens that treat TB infection—will meet all of the minimal characteristics for the *priority* attributes and as many of the *desirable* attributes as possible. It is hoped that the formulation of these criteria will provide a baseline for developing candidates well-suited for best prevention of TB disease.

4.2. Priority Attributes

1. Indication

Ideally, a new TB infection treatment should be efficacious against all *Mtb* strains harboured by an individual and be independent of their resistance profile. Considering that (i) contacts of infectious TB cases and people living with HIV are priority populations for TB prevention, and that (ii) the vast majority of infected people harbour bacilli that are susceptible to rifampicin, the 'minimum' target scenario considers these populations mainly. The capacity to treat TB infection in all populations regardless of the resistance profile of the *Mtb* strains harboured by infected individuals defines the 'optimal' scenario – i.e. *the proposed new TPT regimen would have to be efficacious in individuals who are recent contacts of drug-susceptible as well as drug-resistant TB cases*. In any case, however, active TB must be formally excluded and treatment of TB infection should only be given to persons without tuberculosis disease.

2. Efficacy

In clinical trials, the efficacy of TB infection treatment is usually defined as the proportion of participants who remain TB-free for a reasonable period of follow-up after treatment completion – usually between 2 and 5 years. The expected *duration* of protection from a regimen is, however, subject-dependent (since risk of developing TB disease varies with age, sex and host immune response capacity), as well as setting-dependent (i.e. high vs. low TB transmission areas, defining various degrees of reinfection vs. reactivation). Historical observational studies showed long average duration of protection, but in a meta-analysis, treatment was generally more efficacious in low vs. high TB incidence populations (OR 1.58, 95% CI 1.01-2.48) (17).

3. Safety and Tolerability

As the target population is likely to be *healthy*, safety and tolerability are particularly important attributes. The main reported risk so far is hepatotoxicity, but other adverse events should be considered as well (cutaneous reactions, hypersensitivity reactions, gastrointestinal

intolerance, peripheral neuropathy, cardiotoxicity), as these can lead to temporary or permanent treatment cessation. Clearly, the safer the regimen, the easier it will be to roll out - as the need for careful, complex or possibly expensive monitoring will go down. This will also mean that more providers (front line workers) will be able to use it. In the TPP table, targets are provided with reference to the current standards of care treatment.

4. Drug-drug interactions

Targets are provided with reference to most common drug-drug interactions (DDIs) observed to-date with current TB infection treatments given to HIV positive people receiving ART. Other concurrent diseases should be considered as well, especially with regard to reported increase in non-communicable diseases requiring chronic treatment (diabetes, hypertension, post-transplant, rheumatological diseases) as well as infectious/parasitic diseases in the tropics (malaria, etc.). It might not be possible to avoid all DDIs - but the DDI should be manageable through simple clinical algorithms.

5. Barrier to emergence of drug resistance / risk of drug resistance following treatment

Likelihood of emergence of resistance to isoniazid has long been an argument against provision of TB infection treatment in programme conditions, especially at the time isoniazid was provided as monotherapy for long periods of time (6-12 months). However, there is no evidence that monotherapy of TB infection creates resistance. Ideally, the newly proposed regimen should not lead to emergence of resistance. The barrier to resistance should however be considered in case of repeated dosing, for instance in HIV infected persons.

6. Target population

Target populations include people with HIV infection, household (and other close) recent contacts of confirmed infectious TB cases including neonates and young children, as well as specific at-risk populations - i.e. patients with immunosuppressive conditions such as poorly controlled diabetes mellitus, initiation of anti-TNF treatment, chronic renal failure receiving dialysis, preparation for organ or haematological transplant, and silicosis.

7. Formulation, dosage, frequency and route of administration

The following aspects should be considered: (i) the availability of single tablet regimens; (ii) the availability of scored or dispersible and palatable tablets for ease of treatment in children; and (iii) the dosing frequency (daily vs. weekly). If a regimen is to be intermittent, it is essential that it retains priority attributes while being administered intermittently (e.g. once weekly). More frequent dosing (e.g. more than once a day) can be considered if it allows significant reduction in total duration of treatment, as well as improvement in safety and tolerability - or other substantial improvement that would offset the challenges associated with longer duration (e.g. treatment adherence and completion).

8. Stability / Shelf life

Current therapies have at least 24 months of stability. Since TPT would have to be provided in high TB burden countries that are more likely to experience heat and humidity, it is essential that the medicine(s) are stable across all climate zones and, preferably, have no cold chain requirements.

4.3. Desirable attributes:

1. Cost

Projected treatment costs should be compatible with wide access and scale-up. An improved regimen may provide advantages in other costs to programmes and/or patients by being shorter, better tolerated, requiring minimal to no monitoring, etc. This would reduce non-drug costs due to monitoring, clinical visits, management of adverse events/toxicity, etc. The cost and associated resource demands to implement the regimen at the scale needed to impact upon global TB incidence should not upset health equity to the disadvantage of any subpopulation in both low and high resource settings.

2. Pregnancy and breast-feeding

Formulations are needed that are safe for pregnant women and women of reproductive age. Appropriate care during the antenatal and postnatal periods and during delivery is necessary to reduce risk of adverse pregnancy outcome.

3. Treatment adherence and completion

To maximize adherence to therapy, current guidelines recommend the use of a broad range of patient-centred care and case management strategies, including directly observed therapy (DOT) or virtually-observed therapy (VOT) using electronic or mobile health devices, education, incentives and enablers, that can assist with compliance to long regimens. Studies have shown that the shorter treatments (4R, 3HP, 1HP) were associated with higher completion rates compared to longer control regimens (18,22,27). For the *minimum* target, the majority of patients in a new regimen should be able to complete self-administered therapy, with only selected populations requiring DOT or VOT among other labour- or cost-intensive activities, while for the *optimal* target, self-administration of therapy should be the standard in all populations. Clinical follow-up and monitoring should take place to assess potential adverse events.

4. Need for Drug Susceptibility Testing in Index TB cases

Where molecular diagnostic tests are available, a single, rapid, molecular rifampicin-susceptibility test will suffice to assess the drug susceptibility profile of the bacilli population in the index case and confirm the suitability of using the new regimen. In an optimal scenario, the new treatment regimen should be usable in all conditions and settings, whatever the drug-susceptibility profile of the index case, and in particular, irrespective of the likelihood of rifampicin-resistant TB transmission.

Summary tables of proposed attributes for Preventive TB Treatment

1. Priority attributes

Variable	Minimum <i>The minimal target should be considered as a potential go/no go decision point – for the given “priority attributes”</i>	Optimal <i>The optimistic target should reflect what is needed to achieve broader, deeper and quicker global health impact</i>	Annotations <i>For all parameters, included here is the rationale for why this feature is important and/or for the target value</i>
<i>Indication</i>	The regimen is indicated for the treatment of TB infection to prevent development of TB disease in at risk individuals as defined in current WHO guidelines (Annex 3).	The regimen is indicated for the treatment of TB infection to prevent TB disease in <u>all</u> individuals recognized at risk for developing TB, regardless of the drug susceptibility profile of the harboured bacilli population.	According to the latest WHO recommendations on TB preventive treatment (Annex 3) , ^h the most at-risk populations for LTBI testing and treatment are as follows: 1. 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. 2. 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. 3. 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. 4. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if LTBI testing is unavailable.
<i>Efficacy</i>	A regimen with efficacy <i>not inferior</i> to the current standard of care for treatment of TB infection (e.g. 6months INH or 3HP).	A regimen with efficacy <i>superior</i> to the current standard of care regimen for treatment of TB infection, leading to life-time protection in areas of low risk of re-infection.	To be effective, TPT regimens must be able to kill bacteria that have low growth rates and those that undergo occasional growth spurts (sterilizing), in addition to killing those with high growth rates (bactericidal), otherwise the risk of reactivation will persist after prophylactic treatment has been completed.

^h WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment. Geneva: World Health Organization; 2020.

			<p>Efficacy in TB prevention is currently defined in clinical trials as occurrence free (defined as a combination of breakthrough TB + TB deaths) 2 to 5 years after treatment completion. The targets provided take into consideration the odds of efficacy of the current six-month INH and 3HP regimens for TB infection treatment vs. placebo, respectively: 0.65 (0.50, 0.83) and 0.58 (0.30, 1.12).ⁱ</p> <p>Notes:</p> <ul style="list-style-type: none"> - The term “not inferior” refers to the results of investigational trials using the non-inferiority design. Non-inferiority trials investigating new TPT regimens would need to be designed and conducted under most rigorous conditions so as to generate reliable results (including the careful selection of the control regimen and appropriate choice of the margins of non-inferiority (delta)).^{j,k} - The expected efficacy and duration of imparted protection is population-dependent (e.g. PLHIV; children) as well as setting-dependent (i.e. high vs. low TB transmission areas). Historical observational studies showed long average duration of protection.^l However, in a meta-analysis, treatment was generally less efficacious in high vs. low incidence populations (ROR 1.58, 95% CI 1.01-2.48).^e
Duration of treatment administration	3 months or less	Two weeks or less	<p>This attribute refers to the <i>total duration of administration of treatment</i>, whatever the frequency of administration (e.g.: one month daily or 3 months weekly).</p> <p>This duration should be independent from the resistance profile of the strains harboured by the individual (i.e.: fully susceptible or resistant TB bacilli strains).</p>

ⁱ Zenner, D, Beer, N, Harris, RJ, Lipman, MCI, Stagg, HR & van der Werf, MJ. Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis. Annals of Internal Medicine, 2017; 167;4: pp. 248-255. DOI: 10.7326/M17-0609

^j Phillips PPJ, Mitnick CD, Neaton JD, Nahid P, Lienhardt C, Nunn AJ. Keeping phase III tuberculosis trials relevant: Adapting to a rapidly changing landscape. PLoS Med. 2019; 16(3): e1002767. <https://doi.org/10.1371/journal.pmed.1002767> PMID: 30901331

^k Olliaro PL, Vaillant M (2019) Designing noninferiority tuberculosis treatment trials: Identifying practical advantages for drug regimens with acceptable effectiveness. PLoS Med 16(7):e1002850. <https://doi.org/10.1371/journal.pmed.1002850>

^l Comstock GW, Baum C, Snider DE. Isoniazid prophylaxis among Alaskan Eskimos: a final report of the bethel isoniazid studies. Am Rev Respir Dis. 1979;119:827–30

<i>Safety and Tolerability</i>	<p><i>Safety:</i> Incidence and severity of adverse events <i>better</i> than current standard of care treatment.</p> <p>Requirement of no more than monthly clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing kidney or liver disease, diabetes etc.).</p> <p><i>Tolerability:</i> frequency of adverse events leading to treatment cessation <i>lower</i> than with current INH-based standard of care treatment.</p>	<p><i>Safety:</i> Incidence and severity of adverse events <i>better</i> than the current <u>safest</u> treatment (ie: 4Rif and 3HP regimens)</p> <p><u>No</u> requirement of active clinical monitoring and no laboratory monitoring for drug toxicity needed, preferably not requiring additional monitoring or encounters in special populations (pre-existing liver disease, diabetes, etc.).</p> <p>The target product should not require any additional medication to allay toxicity (e.g. pyridoxine in INH)</p> <p><i>Tolerability:</i> No AE leading to treatment cessation</p>	<p>Hepatotoxicity and clinical hepatitis are serious adverse events associated with drugs that are currently used for the treatment or prevention of tuberculosis, being used either alone or in combination. Neuropathy is a frequent accompaniment of INH.</p> <p>Results from a standard meta-analysis indicate OR for hepatotoxicity with 6 months and 9 months isoniazid monotherapy <i>vs.</i> no treatment of 1.10 (95% CI: 0.40; 3.17) and 1.70 (95% CI 0.35;8.05), respectively. Rifampicin-only and HP regimens had lower rates of hepatotoxicity than isoniazid monotherapy regimens of 6 or 9 months duration. Regimens containing pyrazinamide had higher hepatotoxicity than 6 months of isoniazid or 12 weeks of HP.</p>
<i>Drug-drug interaction (DDI) and metabolism</i>	<p>Ability to use safely with any other medications with minimal dose adjustment, particularly with current first and second line ART.</p>	<p><u>No</u> dose adjustment with any other medications <i>and</i> ability to use safely with any other drug</p>	<p>ART regimens may include drugs that are substrates of P450 or other metabolizing enzymes or that inhibit or induce P450 enzymes. As a benchmark, the target regimen should be <i>free</i> of the problems currently encountered when using rifamycins with ARVs that may complicate their use in PWHIV.</p> <p>For the <i>minimum</i> target, dose adjustment of component drug(s) <u>may</u> be needed to manage DDI. Such adjustments would require that dose size/formulations are readily available.</p> <p>For the <i>optimistic</i> target, <u>no</u> dose adjustments should be needed, including for HIV therapies, allowing for regimen to be used easily and in a standardized way across populations.</p>
<i>Barrier to emergence of drug resistance</i>	<p>Potential for acquisition of resistance is <i>no worse</i> than with current regimens, using current methods of excluding active TB.</p>	<p>In vitro rate of mutation conferring resistance is <i>lower</i> than rifampicin. Limited number of gene targets (<2) linked to resistance development</p>	<p>There is no evidence so far of a significant association between generation of resistance to TB drugs and the use of isoniazid or</p>

<i>(propensity to develop resistance, generation of cross-resistance)</i>		Lack of cross-resistance with existing drugs.	<p>rifamycins for treatment of TB infection in the absence of active TB.^{m,n}</p> <p>Ideally, drugs included in the preventive treatment should protect each other against emergence of resistance. Initial resistance to the drugs included in the regimen should be non-existent, and mutants with resistance against these drugs should not be cross-resistant to drugs used in first or second line TB regimens. This last attribute is extremely important in order not to compromise the use of potential new drugs. Lastly, it would be desirable that the target preventive treatment regimen does not generate resistance when used in people infected with strains resistant to other commonly used TB treatments.</p> <p>As a reference,^o frequency of resistance to rifampicin is 2.25×10^{-12}</p>
<i>Target Population</i>	<p>Populations with <i>established high-risk of progression to TB disease</i> e.g.:</p> <ul style="list-style-type: none"> - HIV infected adults, adolescents and children aged ≥ 12 months (with unknown or a positive tuberculin skin test) regardless of ART use; - HIV-negative children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB; - Patients with immunosuppressive conditions such as initiation of anti-TNF treatment, patients with chronic renal failure receiving dialysis, 	<u>All</u> individuals at risk of TB development from all age groups, irrespective of HIV status, whether living in countries with high, medium or low TB incidence, regardless of the drug susceptibility profile of the harboured bacilli population, in whom active TB has been formally ruled out.	<p><i>Minimum</i> criteria concentrate on currently recommended target groups in high TB burden countries.^p</p> <p><i>Optimistic</i> criteria consider <u>all</u> TB infected population who may in theory be screened and in whom active TB has been formally ruled out.</p> <p>Note:</p> <ul style="list-style-type: none"> - <i>In children, PK and safety studies will be needed in <u>both</u> minimum and optimistic scenarios, but efficacy trials in this population are not necessarily required. TB regimen developers should consider initiating PK and safety paediatric studies across all paediatric age groups when a drug shows promising efficacy and safety in phase 2A adult trials.^q</i> - <i>End-stage renal and liver disease may require significant adjustments in dose and frequency of administration, and may increase the need for clinical and laboratory monitoring. It would</i>

^m Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. Emerg Infect Dis. 2006;12(5):744–51;

ⁿ den Boon S, Matteelli A, Getahun H. Rifampicin resistance after treatment for latent tuberculous infection: a systematic review and meta-analysis. Int J Tuberc Lung Dis. 2016;20(8):1065–71.

^o David HL. Probability distribution of drug-resistant mutants in unselected populations of Mycobacterium tuberculosis. Appl Microbiol. 1970;20(5):810-4.

^p WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment. Geneva: World Health Organization; 2020. (WHO/CDS/TB/2018.4).

^q Nachman S, Ahmed A, Amanullah F, Becerra MC, Botgros R, Brigden G, et al. Towards early inclusion of children in tuberculosis drugs trials: a consensus statement. The Lancet Infectious Diseases. 2015;15(6):711-20.

	<p>patients preparing for organ or haematological transplant, and patients with silicosis.</p> <p><i>In all these situations, active TB is formally ruled out</i></p>		<p><i>be desirable, however, for the optimal TPT regimen to be usable in patients with severe renal or hepatic disease.</i></p>
<p><i>Formulation, Dosage, Frequency and Route of Administration</i></p>	<p>Formulation to be oral, with a daily intake as a maximum for all drugs in regimen, including paediatric forms (dispersible, scored tablets, palatability).</p> <p>If long acting formulation (LAF): injection with or without oral lead-in with injection no more than 1x/per month (Annex 4).</p> <p>Single dissolvable implant use for complete course of therapy.</p>	<p>Formulation to be oral, without a need for weight adjustment, including paediatrics forms (dispersible, scored tablets). Ideally, 1 single pill per day or week for the duration of treatment (depending on daily or weekly formulation). No specific food requirements.</p> <p>Single LAF injection without oral lead-in to be given once or twice or a single dissolvable implant with long lasting protection.</p>	<p>If ≥ 2 drugs orally, FDC with proven bioavailability and bioequivalence for all components is optimal to facilitate implementation across all targeted recipients of TB preventive therapy.</p> <p>Dosing frequency: daily intake is advantageous in PLHIVs as ingestible together with daily ART. Weekly intake might be more advantageous but under strict conditions of treatment adherence.</p> <p>No special requirement regarding food or companion drugs; ideally no restriction with alcohol. Long acting injection or implant formulations have strong practical and operational advantages as they cancel the need of directly observed therapy. In addition, avoiding oral delivery and associated first pass metabolism through the liver may bring additional benefits in terms of drug-drug interactions.^r</p>
<p><i>Stability / Shelf Life</i></p>	<p>Oral regimen: Heat, humidity and light stable, with shelf life for all drugs greater than or equal to two years. No cold chain needed.</p> <p>Injectable: stable across all climate zones. If cold chain required, to be compatible with current vaccine cold chain requirements (between 2°C and 8°C).</p>	<p>Oral regimen: Heat, humidity and light stable, with shelf life for all drugs greater than or equal to five years. No cold chain needed.</p> <p>Injectable: stable across all climate zones and no cold chain required.</p>	<p>Current therapies have at least 24 months of stability.</p> <p>Climatic zones are Zone I : temperate Zone II : subtropical, with possible humidity Zone III : hot/dry Zone IV : hot/humid</p>

^r Swindells S, Siccardi M, Barrett SE, Olsen DB, Grobler JA. Long-acting formulation for the treatment of latent TB infection: opportunities and challenges. Int J Tuberc Lung Dis. 2018 February 01; 22(2): 125–132. doi:10.5588/ijtld.17.0486.

2. Desirable attributes

Variable	Minimum	Optimal	Annotations
<i>Cost of regimen</i>	Projected cost of the drug(s) or treatment courses should be compatible with wide access.	Projected cost of the drug(s) or treatment course should be compatible with wide access and scale-up.	<p>Access to essential medicines is part of the right to the highest attainable standard of health ("the right to health") and is well founded in international law. Economic factors affecting price, demand and availability of the regimens will depend on many factors, including -but not limited to- how well the new regimens meet or surpass the attributes as described herein (efficacy, safety, adherence etc.).</p> <p>An improved regimen may provide advantages in other costs to programmes/patients by being shorter in duration, and/or better tolerated, and/or requiring minimal to no monitoring, etc, thus reducing non-drug costs. The cost and associated resource demands to implement the regimen at the scale needed to impact upon global TB incidence should not upset health equity to the disadvantage of any subpopulation in both low and high resource settings.</p>
<i>Special Populations</i>	<p>For women of reproductive age, PK and safety studies support the use of the regimen with <i>minimal</i> dose adjustment.</p> <p>There must be no foetal risk profile, based on preclinical data.</p> <p>The drugs are safe with breastfeeding.</p> <p>Safe and tolerable for patients with co-morbidities.</p>	<p>For women of reproductive age and pregnant women, PK and safety studies support the use of the regimen <i>without</i> dose adjustment.</p> <p>There must be no foetal risk profile, based on preclinical data.</p> <p>The drugs are safe with breastfeeding.</p> <p>Safe and tolerable for patients with co-morbidities.</p>	<p>Formulations are needed that are safe for pregnant women and women of reproductive age. Results from a recent study of 6-month duration IPT in HIV infected pregnant and post-partum women showed that the risk of an adverse pregnancy outcome (stillbirth or spontaneous abortion, low birth weight in an infant, preterm delivery, or congenital anomalies in an infant) was greater when IPT was initiated during pregnancy than during the postpartum period.⁵ This is in contrast with finding from three observational studies that suggested no higher risk of adverse pregnancy outcomes in women who initiated IPT</p>

⁵ Gupta A, Montepiedra G, Aaron L, Theron G, McCarthy K, Bradford S, et al. Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women. N Engl J Med 2019;381:1333-46.

			during pregnancy. ^{t,u,v} According to latest WHO guidelines, there is insufficient grounds to change previous guidance, and systematic deferral of IPT to the postpartum would deprive women from its protective effect at a point when they are more vulnerable to TB. ^b In any case, appropriate care during the antenatal and postnatal periods and during delivery is recommended to reduce risk of adverse pregnancy outcome. <i>Note: given malformations and fetal loss noted in animal studies, use of alternate drugs to rifapentine for tuberculosis treatment and prophylaxis in pregnancy is recommended.</i>
<i>Treatment adherence and completion</i>	At least as good adherence and chance of treatment completion as with existing short-course recommended regimens (4R; 3HP). Suitable for self-administration in all populations (not for LAF).	Better adherence and chance of completion than with existing short-course recommended regimens. Suitable for self-administration in all populations (not for LAF).	To maximize adherence to therapy, current guidelines recommend the use of a broad range of patient-centred care and case management strategies, including DOT, VOT using e/m-health devices, education, incentives, and enablers. For the <i>minimum</i> target, the majority of patients in this new regimen should be able to complete therapy with minimum support, with only selected populations requiring DOT/VOT among other labour- or cost-intensive activities. For the <i>optimal</i> target, all populations should be able to complete therapy via self-administration, without need for DOT or other interventions.
<i>Need for DST</i>	DST test available for the index TB case when required.	No need for testing index TB case.	Where molecular diagnostic tests are available, a single, rapid molecular rifampicin-susceptibility test will suffice. In optimal conditions, the new TPT regimen should be usable in all conditions and settings, particularly in settings in which there is moderate to high likelihood of rifampicin-resistant TB transmission.

^t Taylor AW, Mosimaneotsile B, Mathebula U, Mathoma A, Moathlodi R, Theebetsile I, et al. Pregnancy Outcomes in HIV-Infected Women Receiving Long-Term Isoniazid Prophylaxis for Tuberculosis and Antiretroviral Therapy. *Infectious Diseases in Obstetrics and Gynecology*. 2013;2013:1–5.

^u Salazar-Austin N, Cohn S, Lala S, Waja Z, Dooley KE, Hoffmann CJ, et al. Isoniazid Preventive Therapy and Pregnancy Outcomes In HIV-Infected Women in the Tshepiso Cohort. *Clinical Infectious Diseases*. 2019 Oct 21;ciz1024.

^v Kalk EK, Heekes A, Mehta U, de Waal R, Jacob N, Cohen K, et al. Programmatic review of safety and effectiveness of isoniazid preventive therapy in HIV-infected pregnant women on ART in routine care. *Reproductive Toxicology*. 2018 Sep;80:155.

V. CROSS-CUTTING ASPECTS:

Whatever priority and/or desirable targets are being met, the following aspects are to be considered carefully before, or during, regimen development:

1. *Safety*: It is essential to keep in mind that – apart from HIV-infected or other immune-suppressed persons – treatment of TB infection is being offered to individuals *who are otherwise healthy and do not consider themselves affected by any specific illness*. Therefore, preventive treatment should be extremely safe and as little disruptive to the lives of these persons. Since shorter regimens are associated with higher treatment completion rates (17), any potential gain in completion from a shorter duration must not be offset by worse safety and tolerability.

Also, any regimen that appears promising for TB prevention should be evaluated carefully for safety and tolerability in the same populations as the ones likely to receive it. Therefore, clinical trials should be performed to define the benefits and harms of TPT in vulnerable groups, including HIV-positive people, children, pregnant and breast-feeding women, recent contacts of infectious TB cases, as well as patients with immunosuppressed conditions (30).

2. *Diagnosis of TB infection*: an efficacious preventive treatment, *if coupled with a test to identify those at highest risk for disease progression*, especially in HIV co-infected persons, would be an important step to accelerate progress towards TB elimination. Going forward, TPT drug/regimen development should be carried out with consideration of diagnostic technologies that identify those at greatest risk of progression to active TB disease (31).
3. *Rule-out TB test*: in each and every situation where TPT is indicated and considered, it is imperative that active TB disease be formally ruled out. Inadvertent use of TPT in people with active TB may generate drug resistance. Details of appropriate strategies need to be clearly explicated at time of scale-up.
4. *Availability of DST for the index TB case*: a single, rapid, molecular, rifampicin-susceptibility test shall be provided to the index TB case to formally rule-out rifampicin-resistant TB. In optimal conditions, however, the new TPT regimen should be usable in all conditions and settings, particularly in settings in which there is moderate to high likelihood of rifampicin-resistant TB transmission, and delivered without requiring a susceptibility profile in the presumed source case.
5. *Adherence to preventive therapy*: once high-risk individuals with TBI have been identified, TB control programmes must ensure optimal treatment adherence. Available adherence support strategies include remote support through digital techniques (mobile phone-based methods) (32). Long acting formulations may be alternatives to these techniques. In any case, self-administered treatment would be the preferred mode of delivery. Of note, in a survey carried out in preparation of the 2018 WHO guidelines for TBI treatment,

shorter duration and fewer side-effects were considered important attributes of preventive treatment, but ‘*no specific requirement for DOT*’ was considered an essential attribute (33).

6. *Monitoring*: Clinical monitoring is imperative to identify and manage adverse events, AND drug-drug interactions rapidly, as well as to detect any development of active TB disease. As stipulated in the 2018 WHO Guidelines: “*active TB disease must be excluded before TB preventive treatment is initiated and regular follow-up is required to ensure early identification of people who develop active TB while receiving TB preventive treatment*”.

7. *Scalability, health equity and access*: these are key elements to be considered for the success of the End TB Strategy. The reported lack of generalization of TB infection treatment in household contacts of TB cases at the time of isoniazid monotherapy is an example to keep in mind. Recent experiences with 3HP scale-up should be considered fully and serve for further information. This is one of the objectives of the Unitaid-funded IMPAACT4TB project that provides access to 3HP for PLHIV and children under five years old with the view to establish an affordable, quality-assured, less-toxic and shorter therapy suitable for wide introduction in countries most affected by TB (34).

The TPPs presented here describe the series of attributes that are considered essential for novel TPT, i.e. efficacy, safety, toxicity, drug-drug interactions and barrier to emergence of drug resistance. Satisfying all of these characteristics in a single regimen at once might be, however, difficult to achieve, and regimen developers might have to face *trade-offs* – e.g. increasing efficacy and safety vs. shortening treatment duration, or increasing dosing frequency (e.g. once a day vs. once a week) if it allows significant reduction in duration of treatment, as well as improvements in safety and tolerability that would offset the challenges associated with longer duration (e.g. treatment adherence and completion).

It should be understood that, for an infectious disease such as TB with large global burden and ongoing person-to-person transmission, the efficacy of the new TPT regimen(s) will depend heavily on operational factors that also impact regimen’s ability to fulfil its role (e.g. access to diagnostics, capacity of ruling out active TB, access to new treatments, education of health care workers, patients and contacts, etc.). For these reasons, these target product profiles give indications on the respective attributes to be considered at the *developmental* stage - but these should not be dissociated from the factors to be considered at *implementation* stage within the larger frame of overall TB oriented activities, including enhanced detection and treatment of active TB (all forms), provision of ARVs to PLHIV, BCG coverage, and sustained infection control activities.

VI. Use Case Scenarios:

1. Essential use case scenario:

Under an essential (baseline) use case scenario, the preferred (optimal) TPT regimen should:

- be indicated for treatment of all individuals and age groups with TB infection at risk of developing active TB disease, irrespective of HIV status;
- be safe, tolerable, and efficacious in individuals of all ages (including neonates, infants, and young children, as well as women of reproductive age, pregnant and lactating women, and for a wide range of patients with co-morbidities, including HIV infection, other infectious or tropical diseases, as well as chronic diseases;
- have no drug-drug interactions, specifically with ARVs, drugs metabolized by P450 liver enzymes, pro-arrhythmic QT prolonging drugs, contraceptive medicines, etc.;
- have an exclusively oral delivery and simple dosing schedule (preferably once daily dosing with no food restrictions, no need for weight adjustment and in a fixed-dose combination), and be child-friendly (e.g. dispersible, scored and palatable formulations with low pill burden). Parenteral formulations of medicines could be considered if long acting formulations.
- be affordable and available in low- and middle-income countries;
- contain medicines that may be prescribed in decentralized settings;
- be simple to implement and include easy monitoring for efficacy of TB prevention through simple checks.

2. Intended use case scenarios:

2.1 High vs. low transmission settings

Although there should not be any difference in the development of regimens for treatment of TB infection, consideration should be given to the fact that situation may differ between *low incidence* and *high incidence* settings:

- In *high incidence* settings, with ongoing TB transmission enhanced by concurrent HIV epidemics, the protective effect of preventive therapy may be transient – given the potential for re-infection – but has particular value to cover periods of high vulnerability, such as infection in young household contact children or HIV-infected individuals.¹ Thus, treatment of TB infection will be highly dependent on the capacity to initiate and sustain targeted campaigns for prevention of TB in those high-risk groups. These efforts should complement the sustained provision of ART, which is a highly effective preventive measure against TB and other opportunistic infection in PLHIV.
- In *low incidence* settings with minimal TB transmission, the protection provided by preventive therapy is more durable (given the limited risk of re-infection), but with a reduced population benefit given the low transmission of TB infection. In deciding whether to recommend preventive therapy, clinicians must weigh the likely benefits and harms of treatment (once active TB has been ruled out), considering the risk that an individual will subsequently progress to disease, as well as the potential toxicity of therapy, which requires consideration of the patient's age and comorbidities. Recent contacts of infectious individuals and migrants arriving from endemic areas within the preceding 2 years are often considered as high-risk populations. In these situations, all means should be available for (i) ruling out active TB; (ii) testing for TB infection in a reliable way; and (iii) initiating therapy, assessing the risk that an individual will

1 subsequently progress to active disease, and capacity to monitor treatment adherence
2 and completion.
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5 **2.2 Testing for TB infection:**

6 With regards to formal demonstration of TB infection, recent WHO guidelines stipulate that
7 “[Latent] (L)TBI testing by TST or IGRA is not a requirement for initiating preventive treatment
8 in people living with HIV or child household contacts aged <5 years”. This is different, though,
9 (i) in adults, adolescents and children aged ≥5 years who are household contacts of
10 bacteriologically confirmed pulmonary TB cases, and who should be tested for TB infection
11 before treatment is provided; and (ii) in migrants arriving from endemic areas who should all
12 be tested for TB infection in a reliable way. The strategy is therefore different according to
13 these specific population groups, hence the possibility to develop different use case scenarios
14 - which may be at stake with global use and scale up of treatments. It is hoped that cheap,
15 rapid, accurate point of care diagnostic tests for TB infection and incipient disease would be
16 available for further refinement of the TB prevention strategy.
17

18 **2.3. Rif susceptible or Rif resistant strains:**

19 As mentioned in the introduction, a practical approach is taken that expanded scale-up and
20 access to treatment of TB infection under programmatic conditions in high-risk group
21 populations might have a drastic impact on TB incidence and mortality, in addition to
22 optimized case-finding and treatment. Thus, TB infection treatment regimen is intended for
23 all patients infected with *Mtb* whether susceptible or resistant to rifampicin or to other oral
24 first-line drugs potentially used in the regimen (e.g. isoniazid), or to key second-line drugs
25 included in DR-TB treatment (fluoroquinolones, bedaquiline, delamanid). The potential use
26 case scenario may thus consider that either TB infection treatment regimen is intended for *all*
27 individuals infected with *Mtb* strains - whether susceptible or resistant to rifampicin or to
28 other oral first-line drugs potentially used in the regimen (e.g. isoniazid), or to key second-line
29 drugs included in DR-TB treatment (fluoroquinolones, bedaquiline, delamanid) - or that
30 contacts of known DR-TB cases with no active TB require specific drugs/regimens for TB
31 infection therapy. This scenario will therefore highly depend on the class of the drug(s) used
32 in the proposed TPT.
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DRAFT

Annex 1

Treatment of Tuberculosis Infection for Prevention of TB Disease: Background and current situation.

The aim of treatment of TB infection (TBI)^w is to prevent progression to active clinical disease through killing of potentially resident bacilli in the host. Isoniazid administered daily for 6 to 12 months has been the mainstay of treatment for more than half a century, with efficacy ranging from 54% to 88% (13,14). A re-analysis of the U.S. Public Health Service isoniazid trials of the 1950s-1960s showed that the benefit of isoniazid increased progressively when administered for up to 9 or 10 months and stabilized thereafter, leading to the recommendation of the 9-month isoniazid regimen as adequate treatment (15). However, further studies showed similarities between the 6 and 12 months regimens in non-HIV infected persons: a meta-analysis of 11 isoniazid trials involving 73,375 HIV-uninfected persons showed that, as compared with placebo, the risk of progression to active TB at 6 months (relative risk (RR), 0.44; 95% confidence interval (CI), 0.27 to 0.73) is similar to that at 12 months (RR, 0.38; 95% CI, 0.28 to 0.50) (35). A meta-analysis of placebo controlled studies found the odds of subsequent TB in individuals with LTBI was 0.65 (95% credible interval 0.50–0.83) when treated with INH for 6 months and 0.50 (0.41, 0.62) when treated with INH for 12 months compared with placebo (16). **(Table 1).**

Table 1. Odds ratios for the prevention of active tuberculosis and treatment rankings, derived from a network meta-analysis*

Regimen	OR vs. placebo (95% CrI)	OR vs. no treatment (95% CrI)
No treatment	1.62 (1.06, 2.47)	1 (ref)
Placebo	1 (ref)	0.62 (0.41, 0.94)
INH 3-4m	0.93 (0.55, 1.50)	0.57 (0.31, 1.02)
INH 6m	0.65 (0.50, 0.83)	0.40 (0.26, 0.60)
INH 9m	0.75 (0.35, 1.62)	0.46 (0.22, 0.95)
INH 12m	0.50 (0.41, 0.62)	0.31 (0.21, 0.47)
RPT-INH	0.58 (0.30, 1.12)	0.36 (0.18, 0.73)
RMP	0.41 (0.19, 0.85)	0.25 (0.11, 0.57)
RMP-INH 1m	1.05 (0.37, 2.77)	0.65 (0.23, 1.71)
RMP-INH 3-4m	0.53 (0.36, 0.78)	0.33 (0.20, 0.54)

Abbreviations: INH, isoniazid; RMP, rifampicin; RPT, rifapentine.

***Adapted from:** Zenner et al. *Treatment of latent tuberculosis infection: an updated network meta-analysis* (16).

^w Given that the main difference from active TB is the absence of disease and infection cannot always be considered latent, in this document, unless otherwise stated, we use the term *Tuberculosis Infection* (TBI) to represent all states of infection with *M. tuberculosis* without clinical manifestations of active TB disease.

1 Other treatment regimens have been investigated and proven to be safe and efficacious
2 including rifampicin, INH and rifampicin, or INH and rifapentine regimens. In the network
3 meta-analysis of different preventive therapies cited above, daily rifampicin for 3–4 months
4 was found to reduce the risk of incident TB by 59% compared to placebo (odds ratio 0.41, 95%
5 credible interval 0.19–0.85). A multicentre clinical trial comparing 4 months of self-
6 administered rifampicin to 9 months of daily INH therapy among 6859 subjects showed that
7 4-months of daily rifampicin was non-inferior to 9-months of isoniazid for the prevention of
8 active TB, and was associated with a higher rate of treatment completion and better safety
9 (19). Among an additional 829 children aged less than 18 years recruited in a companion trial,
10 treatment with 4 months of rifampicin had similar rates of safety and efficacy but a better rate
11 of adherence than 9 months of isoniazid (85.3% vs. 76.4%, adjusted difference in the rates of
12 treatment completion, 13.4 % [95% confidence interval, 7.5 to 19.3]) (20).

13
14 Several randomized studies have compared 3–4 months of daily INH and rifampicin to daily
15 INH alone. A meta-analysis of five randomized controlled trials in adults found that daily
16 therapy with INH plus rifampicin for 3 or 4 months (3-4HR) and standard therapy with INH for
17 6–12 months were equivalent in terms of efficacy, severe side effects, and mortality.¹⁷
18 Significant heterogeneity was observed among the trials regarding the outcome of severe
19 adverse drug reactions, but a sub-analysis that included only high-quality studies indicated
20 that the two regimens were equally safe. A randomized controlled trial in children <15 years
21 found that 3-4 months of INH plus rifampicin (3-4HR) was at least equivalent to INH for 9
22 month (9H) (18). No child from either group experienced a clinical episode of active TB.

23
24 In an open-label, registration-quality clinical trial conducted in the USA, Canada, Brazil, and
25 Spain, once-weekly directly observed isoniazid and rifapentine for 3 months (3HP) regimen
26 was shown to be non-inferior to 9-months of self-administered isoniazid alone (9H) (21).
27 Further, the 3HP regimen was associated with higher treatment-completion rates (82.1% vs.
28 69.0%) and less hepatotoxicity (0.4% vs. 2.7%), although permanent discontinuation of the
29 regimen due to side effects was more frequent with the 3HP regimen (4.9% vs. 3.7%). Similar
30 results were observed in the extension of the study involving 1058 children aged 2 to 17 years,
31 and no hepatotoxic effects attributed to treatment were observed in either study group (22).
32 A follow-up study involving 399 HIV infected adults showed that the 3HP regimen was as
33 effective as the 9H regimen and was associated with a higher treatment-completion rate (89%
34 vs. 64%) (23). The weekly isoniazid–rifapentine regimen was also evaluated in South African
35 adults who had HIV infection and a positive tuberculin skin test (TST) and were not receiving
36 antiretroviral therapy (ART); the efficacy of that regimen was shown to be similar to a 6-month
37 isoniazid regimen (24).

38
39 In a 3,288 participant post-marketing evaluation of 3HP use across 16 US TB programs and in
40 routine health care settings, completion of 3HP was greater overall than rates reported from
41 clinical trials, and greater than historically observed using other regimens among reportedly
42 non-adherent populations (25). Further, a systematic review published in 2018 showed that
43 3HP was *similar* to other TB infection regimens (including 6H, 9H, 3-4HR, 2-3RZ) in
44 effectiveness, risk of adverse events risk of discontinuation due to adverse events, and risk of
45 death, but had higher completion rate (26).

1 More recently, a 1-month regimen of daily rifapentine plus isoniazid (1HP) delivered to HIV-
2 infected patients aged 13 years and above, living in areas of high TB prevalence or who had
3 evidence of LTBI, was shown to be non-inferior to 9 months of isoniazid alone (9H) in a Phase
4 III randomized, open-label, controlled trial (27). The primary end point was the first diagnosis
5 of TB or death from TB or an unknown cause. A total of 3000 patients were enrolled and
6 followed for a median of 3.3 years. The primary endpoint was reported in 32 of 1488 patients
7 (2%) in the 1HP and in 33 of 1498 (2%) in the 9H group, for an incidence rate of 0.65 per 100
8 person-years and 0.67 per 100 person-years, respectively (rate difference, -0.02 per 100
9 person-years (95% CI: -0.30; 0.34). The 1HP regimen was also found to be non-inferior to 9H
10 in the subset of participants with a positive test for LTBI (tuberculin skin test or IGRA). Serious
11 adverse events occurred in 6% of the patients in the 1HP group and in 7% of those in the 9H
12 group (P = 0.07). Treatment completion was higher in the 1HP arm than in the 9H arm (97%
13 vs. 90%, P<0.001). Of note, most of the participants were on ART.
14
15

Annex 2

Preventive Treatment of TB in special populations

1. Contacts of MDR-TB cases:

Contacts of patients with known multidrug-resistant (MDR)-TB have a high risk of infection with a drug-resistant organism (36). Limited evidence is available to inform decision-making about the optimal approach to individuals likely to have TBI with drug-resistant bacteria. An observational study in Micronesia showed that contacts of MDR-TB patients who received preventive therapy with a regimen including moxifloxacin or levofloxacin, together with either ethambutol or ethionamide did not develop MDR-TB, while 20% of infected contacts who refused treatment developed the disease (37). In a prospective study in South Africa, six of 186 (3.2%) children who were contacts of MDR-TB and received 6 months of ofloxacin with INH and ethambutol developed TB – substantially less than historical controls (38).

Three randomized controlled trials of preventive therapy following household MDR exposure are being carried out currently, using various regimens. The V-QUIN Trial is comparing levofloxacin to placebo among infected contacts of MDR-TB in Vietnam. TB CHAMP compares the same regimens but with dispersible formulation in children under the age of 5 years in South Africa. The PHOENIX study in Africa, South America, and Asia compares delamanid to INH. However, the results of these three studies will not be available until after 2020. Details of these trials are provided in **Table 2**.

Table 2. Ongoing clinical trials for treatment of TB infection in contacts of MDR-TB cases

	TB-CHAMP	V-QUIN	Phoenix
Intervention	LFX (novel paediatric dispersible formulation) vs. placebo daily for 6 months	LFX vs. placebo daily for 6 months	DLM vs standard dose INH daily for 26 weeks
Design	Cluster randomized; superiority Community-based	Cluster randomized; superiority Community-based	Cluster randomized; superiority Community-based
Target Population	0-5 y regardless of IGRA or HIV status	<ul style="list-style-type: none"> TST + No age limit 	<ul style="list-style-type: none"> HIV + Children 0-5 yrs TST/IGRA + > 5 y
Assumptions	LFX decreases TB incidence from 7% to 3.5% 80% power	LFX decreases TB incidence by 70% from 3% untreated 80% power	DLM decreases TB incidence by 50% from 5% to 2.5% 90% power
Sample size	778 Households 1556 contacts	1326 Households 2785 contacts	1726 Households 3452 contacts
Sites	South Africa	Viet Nam NTP	ACTG & IMPAACT sites
Timelines	Open (Q4 2018) (completed and intending to publish by end 2020)	Open (Q1 2016) date for end of data collection March 2022	Q3 2019 estimated completion in mid-2025
Funder	BMRC/Wellcome Trust/DFID, SA MRC SHIP;	Australian MRC	DAIDS, ACTH/IMPAACT
Trial websites	http://www.isrctn.com/ISRCTN92634082	https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=369817	https://clinicaltrials.gov/ct2/show/NCT03568383

2. Preventive Treatment of TB in HIV-infected persons:

In a Cochrane Database review of 12 randomized clinical trials of TBI treatment in 8578 randomized HIV-infected persons, preventive therapy with any anti-TB drugs administered for 6–12 months versus placebo resulted in an overall 32% reduction in the incidence of active TB (relative risk [RR] 0.68; 95% confidence interval [CI] 0.54, 0.85) (39). The effect was greater for those with a positive tuberculin skin test (62% reduction; RR 0.38; [95% CI 0.25, 0.57]) than for those with a negative TST (11% reduction; RR 0.89; [95% CI 0.64, 1.24]). Of note, due to the uncertain performance and limitations of existing TBI diagnostic tests in HIV-infected persons, treatment recommendations in this special population do not require systematic testing for infection.

The benefit provided by isoniazid preventive therapy (IPT) in HIV-infected persons was shown to remain in the presence of concurrent ART (40). Further, while in South Africa the protective effect of isoniazid against TB among people living with HIV was found to wane over time (41), in Ivory coast, 6 months of IPT had a durable protective effect (up to 6 years of follow-up) in reducing mortality in HIV-infected people (by 37%), even in people with high CD4 cell counts and who have started ART (42). This likely additive effect of IPT and ART suggests that receiving both treatments is a better option than receiving either therapy alone. In Brazil, a country with low rates of transmission of TB, isoniazid therapy for 6 months has been shown to have long-term protective benefits in HIV-infected adults (43).

Short-course preventive therapy with 3-months once-weekly rifapentine/isoniazid (3HP) has the potential to transform TB control efforts, but drug interactions with antiretrovirals pose potential implementation challenges. Studies have shown that co-administration of efavirenz and daily rifapentine (600 mg), with or without isoniazid, did not result in reduced efavirenz exposure that could jeopardize antiviral activity (44). Administration of once-weekly 3HP with raltegravir was found to be safe and well tolerated in healthy volunteers (45). One of the most urgent remaining acceptability questions is whether rifapentine can be safely given together with dolutegravir, which is purported to be the most widely prescribed integrase inhibitor in the world and a key component of WHO-recommended first-line regimens for HIV (46, 47). Recent data from DOLPHIN, a single-arm study evaluating the safety and PK of 3HP with dolutegravir (DTG)-based ART in adults with HIV (48), showed that co-administration of DTG and HP was well-tolerated, with no HP-related adverse events of Grade>3, and all participants maintained viral suppression (34).

Annex 3

WHO consolidated guidelines on tuberculosis Tuberculosis preventive treatment – 2020 update

Summary of Recommendations*

These recommendations are being listed here as a reference point with regard to current status of TBI treatment. These do not preclude on any forthcoming recommendation arising from newly available data and evidence.

A. Identifying populations for LTBI testing and treatment
<i>People living with HIV</i>
1. 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.
2. 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.
3. 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.
4. All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment.
<i>Household contacts (regardless of HIV status)</i>
5. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if LTBI testing is unavailable.
6. 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 or according to national guidelines may be given TB preventive treatment.
7. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification.
<i>Other people at risk</i>
8. People who are initiating anti-TNF treatment, or receiving dialysis, or preparing for an organ or haematological transplant, or who have silicosis should be systematically tested and treated for LTBI.
9. 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.

10. Systematic LTBI testing and treatment is not recommended for people with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people unless they also belong to other risk groups included in the above recommendations.

B. Algorithms to rule out active TB disease

11. Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of 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.

12. Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report 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.

13. Chest radiography may be offered to people living with HIV on ART and preventive treatment given to those with no abnormal radiographic findings.

14. 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 or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age.

15. The absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out active TB disease among HIV-negative household contacts aged ≥ 5 years and other risk groups before preventive treatment.

C. Testing for LTBI

16. Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI.

D. Treatment options for LTBI

17. The following options are recommended for the treatment of LTBI regardless of HIV status: 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3 month regimen of daily isoniazid plus rifampicin. A 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin alone may also be offered as alternatives.

18. In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive LTBI test and are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive therapy (IPT). Daily IPT for 36 months should be given whether or not the person is on ART, and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have a high TB transmission as defined by national authorities.

1

2 *Source: WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment. Geneva:
3 World Health Organization; 2020 (49).

4

5

Table 3. Recommended dosages of drugs for the treatment of LTBI*

Regimen	Dose by weight band					
6 or 9 months of daily isoniazid monotherapy (6H, 9H)	Adults, 5 mg/kg/day Children, 10 mg/kg/day (range, 7–15 mg)					
Four months of daily rifampicin (4R)	Adults, 10 mg/kg/day Children, 15 mg/kg/day (range, 10–20 mg)					
Three months of daily rifampicin plus isoniazid (3HR)	Isoniazid: Adults, 5 mg/kg/day Children, 10 mg/kg/day (range, 7–15 mg) Rifampicin: Adults, 10 mg/kg/day Children, 15 mg/kg/day (range, 10–20 mg)					
Three months of rifapentine plus isoniazid weekly (12 doses) (3HP)	Individuals aged 2–14 years					
	<i>Medicine, formulation</i>	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg
	Isoniazid, 100 mg*	3	5	6	7	7
	Rifapentine, 150 mg	2	3	4	5	5
	Individuals aged >14 years					
	<i>Medicine, formulation</i>	30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg
	Isoniazid, 300 mg	3	3	3	3	3
	Rifapentine, 150 mg	6	6	6	6	6
	* 300mg formulation can be used to reduce pill burden					
One month of rifapentine plus isoniazid daily (30 doses) (1HP)	Individuals aged ≥13 years (regardless of weight band) Isoniazid, 300 mg/day Rifapentine, 600 mg/day					
Six months of levofloxacin daily (preventive treatment of MDR-TB)	Adults (>14y), by body weight: < 46 kg, 750 mg/day; >45 kg, 1g/day Children (<15y) (range, approx. 15–20 mg/kg/day), by body weight: 5–9 kg, 150 mg/day; 10–15 kg, 200–300mg/day; 16–23 kg, 300–400mg/day; 24–34 kg, 500–750mg/day					

***Source:** WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment. Geneva: World Health Organization; 2020 (49).

Notes:

Regimens based on isoniazid and rifampicin can be used in individuals of all ages. There are no or very limited data on the efficacy and safety of rifapentine in children < 2 years and the 3HP regimen is only recommended for use in children aged 2 years and more. The data from the 1HP trial relates only to individuals aged 13 years and more. The Guideline Development Group (GDG) considered that extrapolation of effects to children aged 2-12 years is reasonable, although the dosage of *daily* rifapentine in this age group has yet to be established. The suitability of this regimen in people <13 years needs to be reviewed once results from studies of pharmacokinetics and safety in children of all ages become available in a near future.

In addition to PLHIV on ART, other populations who may be more commonly at risk of drug-drug interactions from rifampicin include women of childbearing age on contraceptive medicines (who need to be counselled about potential interactions and consider nonhormonal birth control while receiving rifampicin) and opiate users on substitution therapy with methadone.

Contacts of patients with laboratory confirmed isoniazid-resistant, rifampicin-susceptible TB (Hr-TB) may be offered a four-month regimen of daily rifampicin.

Individuals at risk for peripheral neuropathy, such as those with malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes, or who are pregnant or breastfeeding, should receive pyridoxine (vitamin B6) when taking isoniazid-containing regimens. A lowering of isoniazid dosage from the one proposed may be required to avoid toxicity if there is a high population prevalence of "slow acetylators". Combination tablets of co-trimoxazole, isoniazid and pyridoxine could be helpful in PLHIV. However, unavailability of pyridoxine should not be a reason to withhold TB preventive treatment.

Annex 4

Long acting drug formulations for the treatment of TBI

Adherence and completion rates for preventive treatment of TB are low in many programme settings, and represent major obstacles to the effectiveness of this strategy. An important and novel solution could be the development of long-acting/extended-release (LA/ER) injectable anti-TB drugs that can be administered periodically in a clinic setting, eliminating the problems of suboptimal adherence and treatment completion (50). This strategy may be especially important for vulnerable populations, including children, adolescents, and pregnant women. The potential for a single administration providing a “one shot cure” would render directly observed therapy requirements obsolete. In addition, avoiding oral delivery and associated first metabolic passage through the liver may bring additional benefits in terms of drug-drug interactions, and improved bioavailability.

Rifapentine, delamanid, bedaquiline and rifabutin have pharmacological and physicochemical characteristics that make them potential candidates for long acting administration using the drug nanoparticle suspension approach (half-life > 12 hours, therapeutic concentrations < 1000 ng/mL and water solubility < 50 mg/mL). Recently, activity of a long-acting injectable bedaquiline formulation was demonstrated in a paucibacillary mouse model of TBI (51). ‘Coupled with a field-friendly diagnostic test to identify those at highest risk for progression to disease, an LA/ER TB formulation could enable a test-and-treat strategy that would greatly increase the possibility of TB elimination’.