

Target product profiles for tuberculosis preventive treatment



**World Health
Organization**

Target product profiles for tuberculosis preventive treatment

Target product profiles for tuberculosis preventive treatment

ISBN 978-92-4-001013-0 (electronic version)

ISBN 978-92-4-001014-7 (print version)

© World Health Organization 2020

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: “This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition”.

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (<http://www.wipo.int/amc/en/mediation/rules/>).

Suggested citation. Target product profiles for tuberculosis preventive treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

Sales, rights and licensing. To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Designed by Fiona Byrne

Cover image: LuckyStep/Shutterstock.com

Contents

Acknowledgements	iv
Abbreviations and acronyms	v
Definitions	vi
1 Introduction	1
2 Tuberculosis preventive treatment: background and current situation	1
3 Target product profiles for tuberculosis preventive treatment	3
3.1 New medicines and regimens for the treatment of tuberculosis infection	3
3.2 Objective and target audience	3
3.3 Methods	4
3.3.1 Baseline elements	4
3.3.2 Mathematical modelling	4
3.3.3 Cost-effectiveness analysis	5
3.3.4 Development of target product profiles	8
3.4 Description of the target product profiles for tuberculosis preventive treatment	9
3.4.1 Principles	9
3.4.2 Priority attributes	9
3.4.3 Desirable attributes	11
4 Cross-cutting aspects	18
5 Use case scenarios	19
5.1 Essential use case scenario	19
5.2 Intended use case scenarios	20
5.2.1 High- and low-transmission settings	20
5.2.2 Testing for tuberculosis infection	20
5.2.3 Rifampicin-susceptible and rifampicin-resistant strains	20
References	21
Annex 1. Treatment of tuberculosis infection for prevention of disease	24
Annex 2. Tuberculosis preventive treatment in special populations	27
Annex 3. Technical consultation on latent TB infection management: target regimen profiles, 17 September 2019, Montréal, Canada	30
Annex 4. WHO recommendations on TB preventive treatment (2020 update)	34
Annex 5. Long-acting drug formulations for the treatment of tuberculosis infection	36

Acknowledgements

This document was prepared by Christian Lienhardt (Institute for Research on Sustainable Development, Montpellier, France) on the basis of consensus achieved at a technical consultation on target product profiles for tuberculosis preventive treatment convened by the Global TB Programme of WHO on 17 September 2019 in Montréal, Canada.

WHO thanks Payam Nahid, Christian Lienhardt, Olivia Oxlade, Kevin Schwartzman, Dick Menzies and Richard Chaisson for presenting or moderating discussions during the technical consultation and Kevin Schwartzman, Nimalan Arinaminpathy, Juan Vesga Gaviria, Ntwali Placide Nsengiyumva, Jonathon Campbell and Olivia Oxlade for conducting modelling for this document.

This document was finalized after consideration of all comments and suggestions made by members of the scoping group: Jay Achar, Menonli Adjobimey, Faiz Ahmad Khan, Sevim Ahmedov, Teeb Al-Samarrai, Nimalan Arinaminpathy, Cathy Bansbach, Draurio Barreira Cravo Neto, Grania Brigden, Jonathon Campbell, Martina Casenghi, Richard Chaisson, Gavin Churchyard, Isabelle Cieren-Puiseux, Daniela Cirillo, William Coggin, Timothy Evans, Unyeong Go, Celeste Gracia Edwards, David Hermann, Jeremy Hill, Christian Lienhardt, Alberto Matteelli, Ariel Pablos Mendez, Richard Menzies, Payam Nahid, Sumathi Nambiar, Thu Anh Nguyen, Olivia Oxlade, Madhukar Pai, Morten Ruhwald, Nicole Salazar-Austin, Kevin Schwartzman, Susan Swindells, Ezio Távora dos Santos Filho, Anete Trajman, Andrew Vernon, Juan Vesga Gaviria and Brenda Waning.

The contributions of various anonymous individuals during the public consultation are gratefully acknowledged.

WHO secretariat: Saskia Den Boon, Dennis Falzon, Avinash Kanchar, Corinne Merle, Martina Penazzato, Matteo Zignol and Lou Maureen Comia. Overall guidance and direction were provided by Tereza Kasaeva, Director of the Global TB Programme.

The meeting, reviews and document were funded through grants provided by the Russian Federation and the United States Agency for International Development (USAID).

Abbreviations and acronyms

ART	antiretroviral treatment
CI	confidence interval
DOT	directly observed treatment
IPT	isoniazid preventive treatment (or monotherapy)
MDR-TB	multidrug-resistant tuberculosis
PLHIV	people living with HIV
TB	tuberculosis
TPP	target product profile
TPT	tuberculosis preventive treatment
USAID	United States Agency for International Development

Definitions

Note: The definitions listed below apply to this document. They may have different meanings in other contexts.

Adolescent: A person aged 10–19 years

Adult: A person > 19 years of age

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

Child: A person < 10 years of age

Contact: Any person who has been exposed to a person with TB

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

High TB transmission setting: Setting with a high frequency of individuals with undetected or undiagnosed active TB or in which infectious TB patients are present and there is a high risk of TB transmission. TB patients are most infectious when they are untreated or inadequately treated. Transmission is increased by aerosol-generating procedures and by the presence of highly susceptible individuals.

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

Incipient disease: Infection with viable *Mycobacterium tuberculosis* that is likely to progress to active disease in the absence of further intervention but has not yet induced clinical symptoms, radiographic abnormalities or microbiological evidence consistent with TB disease (1).

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

Infant: A child < 1 year of age

Target product profile (TPP): The desired characteristics of a product for a particular disease or diseases. The profile includes the intended use, target populations and other desired attributes of products, including safety and efficacy. Such profiles usually guide product research and development.

TB preventive treatment (TPT): Treatment offered to individuals who are considered at risk of TB disease in order to reduce that risk. Also referred to as “treatment of TB infection”, “treatment of latent TB infection” or “TB preventive therapy”.

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

TB infection: Refers to a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest TB disease. This is commonly referred to as “latent” TB infection, but, given that infection cannot always be considered latent, the term “TB infection” better reflects the whole spectrum of infection to which the TPPs apply. TB infection should not be confused with TB disease.

Underweight: Usually refers to a body mass index < 18.5 in adults and to a weight-for-age < -2 z-scores in children < 10 years.

1 Introduction

Tuberculosis (TB) is a major yet preventable global health problem, with an estimated 10 million new cases worldwide in 2018 that resulted in more than 1.5 million deaths, making it the leading infectious disease cause of death worldwide (2). One quarter of the global population is estimated to be infected with *Mycobacterium tuberculosis* (3). TB infection is classically defined as a “state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifested TB disease”. The vast majority of infected people have no signs or symptoms and are not infectious, although they are at risk of progression from infection to disease and becoming infectious. On average, 5–10% of people who are infected will develop disease over the course of their lives, with the highest risk in the first year after infection (4). Children aged < 2 years, adolescents (≥ 10 years) and people living with HIV (PLHIV) are at high risk of TB disease after infection, including severe life-threatening forms such as TB meningitis (5). As TB infection is more likely to progress rapidly to TB disease in children and adolescents, household contacts of infectious TB patients in these age groups are at particular risk (6, 7). Untreated HIV infection is the strongest risk factor for progression from TB infection to TB disease, with an overall annual estimated risk of 10% (8), particularly in children (9, 10). For these reasons, prevention of TB disease is a crucial component of the WHO End TB Strategy, which calls for 90% coverage of treatment for TB infection among PLHIV and household contacts of infectious TB patients by 2035 (11). The United Nations high-level meeting on TB, in September 2018, further emphasized the importance of strengthening implementation of TB preventive treatment (TPT), with the goal of 30 million people, including 4 million children < 5 years of age, receiving TPT by 2022 (12).

Although TPT has been available for more than 60 years and in spite of strong evidence of its effectiveness, its uptake and scale-up have been slow, mainly because of the limitations of both available diagnostic assays and regimens (long duration, cost, toxicity, adherence issues and operational aspects). Critical gaps remain in achieving global targets: in the 16 countries with a high burden of TB or TB–HIV that reported having provided treatment to PLHIV in 2018, TPT coverage reached only 49% (13). Globally, TPT was initiated in only 27% of the 1.3 million household contact children aged < 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 time and with fewer adverse events than the current 6–12-month TB preventive strategies is essential to ensure wider-scale implementation.

Even with improved TPT options in the future, treatment of infection will remain essential for effective TB control. Scaling-up of TPT would have to be accompanied by active case finding, better treatment for TB disease and other measures to reduce transmission and unfavourable outcomes of disease episodes. Parallel improvements in these areas and the development of new TB vaccines will be critical.

2 Tuberculosis preventive treatment: background and current situation

The aim of treatment of TB infection is to prevent progression to TB disease by killing resident bacilli in the host. Administration of isoniazid daily for 6–12 months has been the mainstay of treatment for more than 50 years, with an efficacy of 54–88% (14, 15). Re-analysis of trials with isoniazid conducted by the Public Health Service in the USA in the 1950s and 1960s showed that the benefit of isoniazid increased progressively when administered for up to 9 or 10 months and stabilized thereafter, leading to recommendation of a 9-month isoniazid regimen as adequate treatment (16). Further studies, however, showed similar results with the 6- and 12-month regimens in non-HIV-infected people (17) (Annex 1).

Other treatments have been investigated, including rifampicin, isoniazid and rifampicin and isoniazid and rifapentine, and proven to be safe and efficacious (17) (Table 1). A meta-analysis of several

randomized studies to compare 3–4 months of daily isoniazid and rifampicin with daily isoniazid alone for 6–12 months in adults found that the two were equivalent in terms of efficacy, safety and mortality (18). A randomized controlled trial in children < 15 years showed that 3–4 months of daily isoniazid and rifampicin was at least equivalent to 9 months of daily isoniazid; no child in either group experienced an episode of TB disease (19). Recently, a multicentre trial with 6859 people showed that 4 months of daily rifampicin was not inferior to 9 months of daily isoniazid monotherapy for the prevention of TB disease and was associated with a higher rate of treatment completion and better safety in both adults and children (20, 21).

Table 1. Regimens for TB preventive treatment according to pooled efficacy, risk of hepatotoxicity and main adverse events

Drug regimen	Dosage	Odds ratio (95% confidence interval)			Adverse events
		Efficacy vs placebo ^a	Efficacy vs 6H ^a	Hepatotoxicity vs 6H ^a	
6H or 9H	Adults, 5 mg/kg; children, 10 mg/kg (maximum, 300 mg)	6H: 0.61 (0.48–0.77); 9H: 0.39 (0.19–0.83)	Not applicable for 6H and not available for 9H	Not applicable for 6H and not available for 9H	Drug-induced liver injury, nausea, vomiting, abdominal pain, rash, peripheral neuropathy, dizziness, drowsiness and seizure
3–4R	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)
3–4HR	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)
3HP	Adults and children: rifapentine, 15–30 mg/kg (maximum, 900 mg) ^b ; isoniazid, 15 mg/kg (maximum, 900 mg)	Not available	vs 9H: 0.44 (0.18–1.07) ^c	vs 9H: 0.16 (0.10–0.27)	Hypersensitivity reactions, petechial rash, drug-induced liver injury, anorexia, nausea, abdominal pain and hypotensive reactions
1HP	Adults and adolescents (≥ 13 years): 300 mg daily for a weight of < 35 kg, 450 mg daily for a weight of 35–45 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 9H: Risk difference: 0.02 per 100 person-years (–0.30–0.34)	vs 9H: 0.47 (0.30–0.75)	Nausea, vomiting, drug-associated fever, anaemia, neutropenia, elevated liver enzyme levels, peripheral neuropathy

Adapted from reference 8

6H, isoniazid alone for 6 months; 9H, isoniazid alone for 9 months; 3–4R, rifampicin alone for 3–4 months; 3–4HR, isoniazid plus rifampicin for 4 months; 3HP, weekly rifapentine plus isoniazid for 3 months; 1HP, daily rifapentine plus isoniazid for 1 month

^a Data on efficacy and hepatotoxicity from references 17 and 22.

^b The following incremental adjustments are required for people weighing < 50 kg: 10.0–14.0 kg, 300 mg; 14.1–25.0 kg, 450 mg; 25.1–32.0 kg, 600 mg; and 32.1–49.9 kg, 750 mg.

^c The comparison is with 9H.

A once-weekly, directly observed regimen of combined isoniazid and rifapentine for 3 months was shown to be non-inferior to 9 months of daily self-administered isoniazid monotherapy and associated with

higher treatment-completion rates (82.1% vs. 69.0%) and less hepatotoxicity (0.4% vs. 2.7%) (23). Similar results were observed in an extension of the study to children aged 2–17 years, and no hepatotoxic effects attributed to treatment were observed in either study group (24).

A follow-up study in HIV-infected adults showed that 3 months of weekly rifapentine plus isoniazid was as effective as 9 months of daily isoniazid monotherapy and was associated with a higher treatment completion rate (89% vs. 64%) (25). The 3 months of weekly rifapentine plus isoniazid regimen was also evaluated in South African adults with HIV infection and a positive tuberculin skin test who were not receiving antiretroviral therapy (ART); the efficacy was shown to be similar to that of a 6-month isoniazid regimen (26).

In a large post-marketing evaluation of 3 months of weekly rifapentine plus isoniazid in 16 TB programmes and routine health care settings in the USA, completion was greater overall than the rates reported from clinical trials and greater than that for other regimens among reportedly non-adherent populations (27). A systematic review published in 2018 showed that the effectiveness, risk of adverse events, risk of discontinuation due to adverse events and risk of death were similar with 3 months of weekly rifapentine plus isoniazid and with other TB infection treatment regimens, including 6 months of daily isoniazid monotherapy, 9 months of daily isoniazid monotherapy, 3–4 months of daily rifampicin plus isoniazid and 2–3 months of daily rifampicin plus pyrazinamide (28).

A 1-month regimen of daily isoniazid plus rifapentine delivered to PLHIV aged ≥ 13 years 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 (22). The regimen was also found to be non-inferior to 9 months of daily isoniazid monotherapy in a subset of participants with a positive test for TB infection (tuberculin skin test or interferon- γ release assay). Serious adverse events occurred in 6% of the patients in the group receiving 1 month of daily rifapentine plus isoniazid and in 7% of those receiving 9 months of daily isoniazid monotherapy ($P = 0.07$). The treatment completion rate was higher with 1 month of daily rifapentine plus isoniazid than with 9 months of daily isoniazid monotherapy (97% vs 90%, $P < 0.001$). Most of the participants were on ART. Annex 2 describes studies of TPT in special populations.

3 Target product profiles for tuberculosis preventive treatment

3.1 New medicines and regimens for the treatment of tuberculosis infection

The development of short, safe, efficacious, easy-to-take regimens for the treatment of TB infection and prevention of TB disease requires detailed information on the safety and toxicity of the regimen's components, their potential for drug–drug interactions, their propensity for development of resistance and their use in specific patient populations such as PLHIV, pregnant women and children (29). The aim of the TPPs is to identify the product attributes to be considered in developing the best, most suitable TB prevention treatments (30). Thus, TPPs for the treatment of TB infection are expected to assist developers in aligning the characteristics of new treatment regimens with national programme requirements. It should be noted that target products are either an individual medicine or a combination of medicines.

3.2 Objective and target audience

The overall objective of the TPPs is to align developers' performance and operational targets for new TPT regimens with the needs of users. The target audience comprises the pharmaceutical industry, academia, research institutions, product development partnerships, nongovernmental and civil society organizations and donors.

3.3 Methods

The WHO Global TB Programme followed the WHO *Standard procedures for the development of target product profiles, preferred product characteristics and target regimen* (31) and used a stepwise approach to identify regimen features that could have an impact for both patients and populations. The activities included a series of expert meetings, mathematical modelling, cost-effectiveness analysis and a wide web-based consultation with stakeholders.

3.3.1 Baseline elements

After establishment of a scoping group, a systematic literature review and a rigorous analysis of the different TPT treatments and regimens that are currently being developed were undertaken to assess the context for developing TPPs for the treatment of TB infection and to prepare an initial draft of TPP attributes. The scoping group then met in Montréal, Canada, in September 2019 to review the evidence and baseline elements of the TPPs and to discuss potential targets. Teleconferences with the scoping group and consultations with various stakeholders were held to adjust the proposed targets, with the results of complementary analyses, described below (Annex 3).

3.3.2 Mathematical modelling

The TPPs for TPT are designed to improve TB control with the use of shorter, simpler, more tolerable, more efficacious regimens that are affordable and accessible and can rapidly reduce morbidity and mortality from TB disease. Individual treatment success rates, disease transmission, antimicrobial resistance and operational factors may all determine whether a regimen can fulfil its role. To prioritize certain characteristics when constructing and evaluating new preventive regimens, a mathematical model was developed to identify the regimen properties that would best predict its epidemiological impact in different settings. The following attributes were adopted as a minimal set of properties that could influence the epidemiological impact:

- duration: length of administration of the regimen (months);
- efficacy against drug-susceptible TB: reduction in cumulative incidence that would be observed under trial conditions during a 5-year follow-up, with and without preventive treatment;
- drug-resistant barrier: proportion of treated individuals with drug-susceptible infection who do not acquire rifampicin-resistant infection as a result of receiving the regimen;¹
- “forgiveness” for non-completion of the regimen: among those who interrupt treatment after completing at least half the regimen, the proportion who nonetheless receive the full benefit of the regimen; and
- ease of adherence: proportion of patients who complete the regimen.

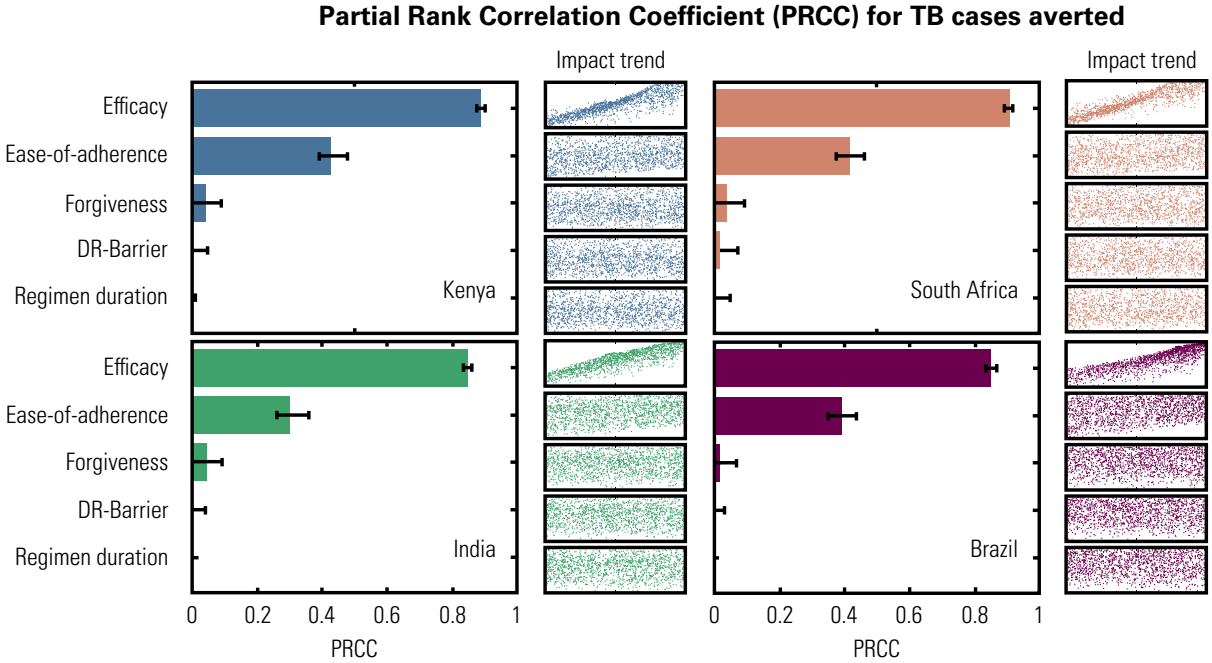
The analysis was conducted for four countries representing different epidemiological conditions: Brazil, India, Kenya and South Africa. In each country, the potential impact of achieving the United Nations high-level meeting targets for preventive therapy was modelled for PLHIV and for household contacts of notified TB cases. On the assumption that the coverage targets are fully met by 2022 and maintained thereafter, impact was quantified as the percentage reduction in cumulative incidence of TB disease between 2020 and 2035 from a base case of 6 months of isoniazid administered daily, with coverage remaining at current levels during the same period.

The influence of each attribute on incidence of TB disease is shown in Fig. 1, which illustrates the modelled impact of 1000 regimens representing different combinations of attributes on the continuum between minimal and optimal scenarios. The regimen’s *efficacy* was found to be the attribute that best predicted a

1 It was assumed that a rifamycin-containing regimen would have half the efficacy against drug-resistant as against drug-susceptible TB. For simplicity, a non-rifamycin-containing regimen (such as 6 months of daily isoniazid monotherapy) would be considered as having no capacity to generate drug-resistant TB, thus effectively having a 100% drug-resistant barrier.

reduction in TB disease incidence in all countries. Ease of adherence was found to play a strong secondary role, while remaining attributes, including forgiveness, were found to have only minimal influence on incidence in these settings. Sensitivity analysis (not shown) showed that the relative roles of forgiveness and adherence depend on the point in the regimen at which forgiveness is assumed to act (50%, as stated above); however, these variations do not change the overall qualitative results shown in Fig. 1.

Fig. 1. Influence of each attribute on TB incidence



Bars represent PRCC between individual attributes and impact. Scatter plots show each attribute plotted against impact.

3.3.3 Cost-effectiveness analysis

On the basis of the results of the epidemiological modelling, a cost-effectiveness analysis was conducted. The analysis was for Brazil and South Africa, which represent a relatively low-transmission, low-HIV prevalence setting and a high-transmission, high-HIV prevalence setting. A bottom-up, or micro-costing, approach was used to capture detailed costs for treatment of TB disease and TB infection in the two countries by estimating use of health system personnel and resources for care of a typical or “average” patient. For TB disease, it includes cost components such as personnel time to administer clinical care, equipment for diagnosis, TB medication and other supplies, expressed in 2019 US\$. For TB infection, costs are assumed only for preventive treatment, which includes an initial medical visit, treatment medication (assumed in this analysis to be 6 months of isoniazid administered daily in the base case) and follow-up medical visits. Costs of treatment-related adverse events are considered on a pro-rated basis for the entire cohort. Costs of diagnosing TB infection or excluding TB disease are not included, i.e. it is assumed that people eligible for treatment have already been identified, regardless of regimen.

Costs related to TB disease were calculated separately for patients with drug-susceptible- and drug-resistant-TB. Costs for inpatient stays and outpatient visits and for monitoring treatment were included. For treatment supervision, two treatment modes were considered, i.e. directly observed treatment (DOT) and mixed DOT plus self-administered treatment. Costs for monitoring treatment, inpatient and outpatient visits and corresponding proportions were obtained from national TB programmes and the published literature.

To “anchor” the analysis, two novel preventive treatment regimens were modelled: a “minimal” and an “optimal” regimen, with the attributes listed in Table 2.

Table 2. Regimen attributes and input costs

Attribute	Baseline (isoniazid)	Minimal	Optimal
Regimen duration (months)	6	3	1
Efficacy	70%	70%	100%
Drug-resistance barrier	100%	95%	100%
Forgiveness	25%	50%	80%
Treatment completion	70%	80%	90%
Cost of regimen: medication ^a	US\$ 3.45	US\$ 3.45	US\$ 3.45
Brazil: cost of regimen: visits, monitoring, adverse events ^b	US\$ 37.79	US\$ 23.54	US\$ 14.04
South Africa: cost of regimen: visits, monitoring, adverse events ^b	US\$ 41.53	US\$ 26.56	US\$ 16.57
Brazil: cost of DS-TB treatment	US\$ 866	US\$ 866	US\$ 866
Brazil: cost of MDR-TB treatment	US\$ 10 800	US\$ 10 800	US\$ 10 800
South Africa: cost of DS-TB treatment	US\$ 524	US\$ 524	US\$ 524
South Africa: cost of MDR-TB treatment	US\$ 9 527	US\$ 9 527	US\$ 9 527

DS, drug-susceptible; MDR, multi-drug-resistant

^a Medication costs for the two novel regimens assumed to be equal to those of 6 months of daily isoniazid monotherapy

^b For the minimal regimen, the rate of adverse events was assumed to be equivalent to that of 6 months of daily isoniazid monotherapy. With the optimal regimen, it is assumed that there will be no adverse events that require additional monitoring, hospitalization or intervention.

Epidemiological modelling was used to project the costs of TPT and TB disease care through 2035 in Brazil and South Africa, in the following scenarios:

- reported baseline TPT coverage with 6 months of daily isoniazid monotherapy;
- expansion of treatment with 6 months of daily isoniazid monotherapy to meet the United Nations high-level meeting targets;
- TPT with a regimen with the “minimal” set of attributes, reaching the targets; and
- TPT with a regimen with the “optimal” set of attributes, reaching the targets.

The primary analysis included a rifamycin-containing regimen, but a rifamycin-free regimen was also considered. No discounting was applied.

Epidemiological projections for Brazil and South Africa are shown in Table 3.

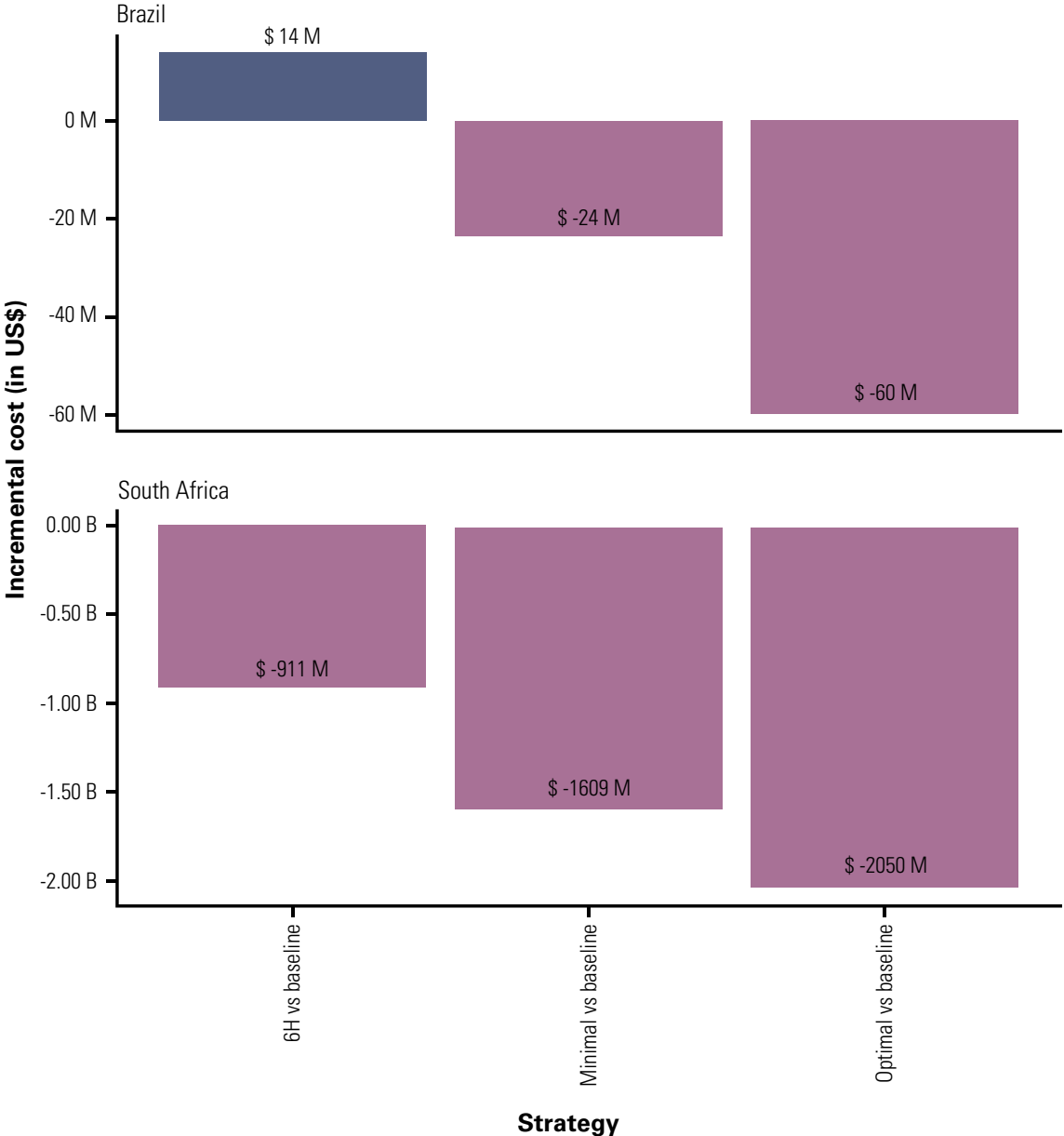
Table 3. Epidemiological projections, Brazil and South Africa, 2018–2035

	Baseline	Scale up 6H	Minimal TPT	Optimal TPT
Brazil				
No. of people on TPT	110 775	1 286 644	1 283 271	1 280 422
TB cases (drug-susceptible and MDR)	1 358 958	1 328 541	1 309 655	1 295 106
MDR-TB cases	46 714	45 753	45 733	44 824
TB deaths	187 208	183 212	180 681	178 750
DALYs	5 164 722	5 052 558	4 982 683	4 926 308
South Africa				
No. of people on TPT	4 594 449	8 301 001	8 122 022	8 069 326
TB cases (drug-susceptible and MDR)	4 463,872	3 247 354	2 429 083	2 179 961
MDR-TB cases	185 817	152 312	146 274	124 892
TB deaths	852 281	641 033	493 689	448 153
DALYs	29 888 441	22 270 743	16 784 278	15 222 462

DALY, disability-adjusted life year; MDR, multidrug-resistant; TPT, TB preventive treatment; 6H, isoniazid alone for 6 months

The analysis suggests that the cost of scaling up TPT and of new regimens is largely outweighed by savings due to fewer TB patients. In comparison with the baseline scenario, implementation of TPT corresponding to the *minimal* regimen in Brazil was estimated to cost an additional US\$ 32 million but resulted in projected savings of US\$ 56 million due to 49 000 fewer TB patients, hence net savings of US\$ 24 million (1.3%). In South Africa, the epidemiological impact and cost savings were much greater, given the higher HIV prevalence, the high rate of transmission and the burden of drug-resistant TB. Use of the minimal regimen to meet the United Nations high-level meeting targets was projected to cost US\$ 37 million as compared with baseline but to generate net savings of US\$ 1.6 billion (34%), reflecting 2 million TB patients averted. Greater savings were projected with the *optimal* TPT regimen. The results are summarized in Fig 2.

Fig. 2. Incremental cost projections, Brazil and South Africa, 2018–2035



M, million; 6H, 6 months daily isoniazid monotherapy

In a sensitivity analysis, we considered an alternative scenario involving a rifamycin-sparing regimen. This regimen, with a drug resistance barrier of 100% but with other characteristics of the “minimal” regimen unchanged, resulted in modest additional gains. In comparison with the “minimal” rifamycin-containing regimen, it was projected to avert 119 additional TB cases in Brazil and 4556 in South Africa, leading to additional cost savings of US\$ 4 million (0.3%) in Brazil and US\$ 91 million (2%) in South Africa. Additional savings in South Africa are largely driven by averting 9331 additional cases of drug-resistant TB.

3.3.4 Development of target product profiles

The above results were used to prepare a first draft of the TPPs and related tables, which were revised by the scoping group, with group discussions by webinar.

3.4 Description of the target product profiles for tuberculosis preventive treatment

3.4.1 Principles

The WHO standard procedures for the development of TPPs, preferred product characteristics and target regimens (31) list the elements that should (obligatory) and could (optional) be part of any TPP. At a minimum, they usually specify the following characteristics: the clinical indication of the therapeutics or regimen; the goal to be met and the measure of efficacy; the target population for the treatment; the level of implementation in the health care system; and the intended users. The targets selected represent the most important performance and operational characteristics, the term “minimal” being used for the lowest acceptable output for a characteristic, and “optimal” for its ideal target. The “minimum requirements” include instructions for targets to improve current standard of care and which therefore represent an acceptable minimum for a global health impact of a candidate regimen. These criteria provide the context for defining clear minimal “go” or “no-go” decisions to be used throughout development. The “optimal requirements” specify the performance and use characteristics of an “ideal” product, the global health impact of which would be broader, deeper and potentially quicker.

The attributes that can be identified as specific, quantifiable targets for treatment of TB infection are listed in the TPP tables, which include the respective regimen attributes and relevant minimum and optimum targets to be met (see pp. 12–17). Annotations to both the minimum and the optimal categories provide elements of the rationale for each attribute of the selected targets.

A number of regimen attributes or characteristics were identified and included as proposed targets. Certain attributes are defined as “priority”, as their minimum targets should be met in order to make a “go” or “no-go” decision, while others, which are less essential, could be considered potential trade-offs and are defined as “desirable”. For example, if a new regimen were to be better tolerated or have greater efficacy, a trade-off in a desirable area such as the number of drugs in the regimen or its duration could be justified. Note that the “go” or “no-go” decision does not apply to desirable attributes.

This document outlines the minimal levels of acceptable performance and use characteristics for novel TPT regimens and also the optimal performance for a number of priority and desirable attributes. The minimal and optimal characteristics thus define a range: it is therefore expected that the resulting products – regimens to treat TB infection – will have all the minimal characteristics of the *priority* attributes and as many of the *desirable* attributes as possible. It is hoped that these criteria will provide a baseline for developing candidates that are best suited for prevention of TB disease.

3.4.2 Priority attributes

Indication

Ideally, a new treatment for TB infection should be efficacious against all *M. tuberculosis* strains harboured by an individual and be independent of their resistance profile. As contacts of infectious TB patients and PLHIV are priorities for TB prevention and the vast majority of infected people harbour bacilli that are susceptible to rifampicin, the “minimum” target scenario addresses mainly these populations. The “optimal” scenario is the capacity to treat TB infection in all individuals, regardless of the resistance profile of the *M. tuberculosis* strains they harbour: the proposed new TPT regimen would have to be efficacious in recent contacts of both drug-susceptible and drug-resistant TB patients. In any case, TB disease must be formally excluded, and treatment for TB infection should be given only to people without TB disease.

Efficacy

In clinical trials, the efficacy of treatment for TB infection is usually defined as the proportion of participants who remain free of TB disease for a reasonable period of follow-up after treatment completion, which is usually 2–5 years. The expected duration of protection provided by a regimen, however, depends on the subject (as the risk of TB disease depends on age, sex and host immune response capacity) and on the

setting (i.e. high and low TB transmission areas, defining various degrees of reinfection and reactivation). Observational studies showed a long average duration of protection; however, a meta-analysis indicated that treatment was generally more efficacious in populations with low rather than high TB incidence (odds ratio, 1.58; 95% confidence interval [CI], 1.01; 2.48) (17).

In terms of treatment duration, meta-analyses show that shorter regimens are generally associated with higher treatment completion rates. This is important, as shorter regimens remove some of the specific barriers to completion of isoniazid preventive treatment (17), because they are associated with better adherence.

Safety and tolerability

As the target population is likely to be healthy, safety and tolerability are particularly important attributes. The main reported risk identified so far is hepatotoxicity, but other adverse events should be considered, including cutaneous reactions, hypersensitivity reactions, gastrointestinal intolerance, peripheral neuropathy and cardiotoxicity, as these can lead to temporary or permanent cessation of treatment. Clearly, the safer the regimen, the easier it will be to implement, as it will not require careful, complex or possibly expensive monitoring. Furthermore, more providers (front-line workers) will be able to use it.

Drug–drug interactions

Targets are provided for the most common drug–drug interactions observed to date, with current TB infection treatments given to PLHIV receiving ART. Other concurrent diseases should be considered as well, especially with regard to reported increases in noncommunicable diseases that require long-term treatment (diabetes, hypertension, post-transplant, rheumatological diseases) as well as infectious and parasitic diseases in the tropics (e.g. malaria). It might not be possible to avoid all drug–drug interactions, but they should be manageable with simple clinical algorithms.

Barrier to emergence of drug resistance or risk of drug resistance after treatment

The likelihood of emergence of resistance to isoniazid has long been an argument against provision of TB infection treatment in programmes, especially when isoniazid was provided as monotherapy for long periods (6–12 months) (5, 8, 16). There is, however, no evidence that monotherapy for TB infection creates resistance. Although a newly proposed regimen should not result in emergence of resistance, the barrier to resistance should be considered for repeated dosing, for instance in PLHIV.

Target population

The target populations include PLHIV, household (and other close) recent contacts of confirmed infectious TB cases, including neonates and young children, and other at-risk populations. These include patients with immunosuppressive conditions such as poorly controlled diabetes mellitus, initiation of anti-TNF treatment, chronic renal failure being treated with dialysis, preparation for organ or haematological transplant and silicosis.

Formulation, dosage, frequency and route of administration

The aspects to be considered are the availability of a treatment regimen in a fixed-dose combination, the availability of scored or dispersible, palatable tablets for easy treatment of children and the dosing frequency (e.g. daily vs weekly). If a regimen is to be intermittent (e.g. once weekly), it is essential that it retains its priority attributes. More frequent dosing (e.g. more than once a day) could be considered if it significantly reduces the total duration of treatment and improves safety and tolerability or provides any other substantial improvement that would offset the challenges associated with longer duration, such as treatment adherence and completion. Development of fixed-dose combinations for PLHIVs should take into consideration combinations with ART or co-trimoxazole.

Stability and shelf life

Currently available treatments are stable for at least 24 months. As TPT would have to be provided in high-TB burden countries that are likely to be hot and humid, the medicines must be stable in all climate zones and, preferably, not require a cold chain.

3.4.3 Desirable attributes

Cost

Projected treatment costs should be compatible with wide access and scale-up. An improved regimen may decrease the costs for both programmes and patients if it is shorter, safer, better tolerated, requires minimal to no monitoring and fewer clinical visits and reduces the management of adverse events or toxicity. The price and the associated resources required to use the regimen should be set against considerations of equity, non-discrimination and transparency, with the goal of affordable access for all, ensuring that vulnerable and marginalized groups do not bear disproportionate costs.

Pregnancy and breast-feeding

Formulations should be safe for pregnant women and women of reproductive age. Appropriate care during the antenatal and postnatal periods and during delivery is necessary to reduce the risk of adverse pregnancy outcomes.

Treatment adherence and completion

To maximize adherence to therapy, current guidelines recommend use of a broad range of patient-centred care and case management strategies, including DOT or virtually observed therapy provided with electronic or mobile health devices, education and incentives to encourage compliance with long regimens. Studies have shown that shorter treatments (4 months of daily rifampicin monotherapy, 3 months of weekly rifapentine plus isoniazid, 1 month of daily rifapentine plus isoniazid) are associated with higher completion rates than longer control regimens (19, 22, 24). For the minimum target, most patients on a new regimen should be able to complete self-administered therapy, only selected populations requiring DOT or virtually observed therapy. For the optimal target, self-administered therapy should be the standard in all populations. Clinical follow-up and monitoring should be conducted to assess any adverse events.

Drug susceptibility testing in index TB patients

When molecular diagnostic tests are available, a single, rapid, molecular test for rifampicin susceptibility will suffice to assess the drug susceptibility profile of the bacilli population in an index patient and confirm the suitability of 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 patient and, in particular, irrespective of the likelihood of rifampicin-resistant TB transmission.

Summary tables of proposed attributes for TB preventive treatment

1. Priority attributes

Attribute	Minimum <i>The minimal target should be considered a potential "go" or "no go" decision point for the given "priority attribute"</i>	Optimal <i>The optimal target should have a broader, deeper, quicker global health impact</i>	Annotations <i>For each variable, the rationale for why it is important and for the target value</i>
Indication	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.	The regimen is indicated for the treatment of TB infection to prevent development of TB disease in <i>all</i> individuals recognized as being at risk of TB disease, regardless of the drug susceptibility profile of the harboured bacilli population.	<p>According to the latest WHO recommendations on TPT (2020) (13), populations prioritized for TPT are as follows:</p> <ul style="list-style-type: none"> • <i>Adults and adolescents living with HIV</i> who are unlikely to have active TB should receive TPT as part of a comprehensive package of HIV care. Treatment should also be given to those on ART, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if testing for TB infection is unavailable. • <i>Infants living with HIV</i> 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 TPT. • <i>Children aged ≥ 12 months living with HIV</i> who are considered unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should be offered TPT 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. • <i>Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB</i> and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TPT even if testing for TB infection is unavailable. <p>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 <i>may be given TPT</i>.</p> <p>In selected high-risk household contacts of patients with MDR-TB, preventive treatment may be considered after an individual risk assessment and sound clinical justification.</p>

Attribute	Minimum <i>The minimal target should be considered a potential “go” or “no go” decision point for the given “priority attribute”</i>	Optimal <i>The optimal target should have a broader, deeper, quicker global health impact</i>	Annotations <i>For each variable, the rationale for why it is important and for the target value</i>
Efficacy	A regimen with efficacy <i>not inferior</i> to the current standard of care for treatment of TB infection (e.g. 6H or 3HP).	A regimen with efficacy <i>superior</i> to the current standard of care regimen for treatment of TB infection, leading to lifetime protection in areas of low risk of re-infection.	<p>To be effective, TPT regimens must be able to kill bacteria with low growth rates and those that undergo occasional growth spurts (sterilizing), in addition to killing those with high growth rates (bactericidal). If not, the risk of reactivation will persist after prophylactic treatment has been completed.</p> <p>Efficacy in TB prevention is currently defined in clinical trials as occurrence-free (defined as a combination of breakthrough TB disease and TB deaths) 2–5 years after treatment completion. The targets provided take into consideration the odds of efficacy of the current 6H and 3HP regimens for TB infection treatment vs placebo: 0.65 (0.50, 0.83) and 0.58 (0.30, 1.12), respectively (17).</p> <p>Notes:</p> <ul style="list-style-type: none"> • The term “not inferior” refers to the results of investigational trials with the non-inferiority design. Non-inferiority trials of new TPT regimens should be designed and conducted under the most rigorous conditions in order to provide reliable results (including careful selection of the control regimen and appropriate choice of the margins of non-inferiority (delta)) (32, 33). • The expected efficacy and duration of imparted protection depends on the population (e.g. PLHIV; children) and setting (i.e. high vs low TB transmission areas). Observational studies showed a long average duration of protection (34); however, in a meta-analysis, treatment was generally less efficacious in high- than in low-incidence populations (relative odds ratio, 1.58; 95% CI, 1.01; 2.48) (35).
Duration of treatment administration	< 3 months	≤ 2 weeks	<p>This attribute refers to the <i>total duration of administration of treatment</i>, whatever the frequency (e.g. 1 month daily or 3 months weekly).</p> <p>Systematic reviews showed that shorter regimens were associated with higher treatment completion rates (35, 36).</p> <p>Treatment duration should be independent of the resistance profile of the strains harboured by the individual (i.e. fully susceptible or resistant TB bacilli strains).</p>

Attribute	Minimum	Optimal	Annotations
Safety and tolerability	<p><i>The minimal target should be considered a potential “go” or “no go” decision point for the given “priority attribute”</i></p> <p>Safety: Incidence and severity of adverse events <i>better</i> than the current standard of care treatment.</p> <p>Requirement of no more than monthly clinical monitoring and no laboratory monitoring for drug toxicity necessary, except for special populations (e.g. pre-existing kidney or liver disease, diabetes).</p> <p>The target product should not require any additional medication to allay toxicity (e.g. pyridoxine in IPT).</p> <p>Tolerability: The frequency of adverse events leading to treatment cessation should be <i>no worse</i> than with current paired isoniazid and rifamycin regimens (e.g., 3HP, 3HR, 1HP).</p>	<p><i>The optimal target should have a broader, deeper, quicker global health impact</i></p> <p>Safety: Incidence and severity of adverse events <i>better</i> than the current <i>safest</i> treatment.</p> <p><i>No</i> requirement for active clinical monitoring or for laboratory monitoring for drug toxicity and preferably no requirement for additional monitoring or encounters for special populations (e.g. pre-existing liver disease, diabetes).</p> <p>The target product should not require any additional medication to allay toxicity (e.g. pyridoxine in IPT).</p> <p>Tolerability: No adverse events 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 TB disease, either alone or in combination. Neuropathy is a frequent adverse event with isoniazid.</p> <p>A standard meta-analysis gave odds ratios for hepatotoxicity with 6H and 9H vs 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 resulted in lower rates of hepatotoxicity than 6H or 9H. Regimens containing pyrazinamide were more hepatotoxic than 6H or 12 weeks of HP.</p>
Drug–drug interaction and metabolism	<p>Can be used safely with any other medication with minimal dose adjustment, particularly with current first- and second-line ART, opioid substitution therapies, hormone-based contraceptives and directly acting antivirals to treat viral hepatitis.</p>	<p>No dose adjustment when given with any other medication <i>and</i> can be used 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 associated with use of rifamycins plus ART, which may complicate their use in PLHIV.</p> <p>For the <i>minimum</i> target, dose adjustment of component drug(s) <i>may</i> be required to manage drug–drug interactions. Such adjustments would require that different dose sizes and formulations are readily available.</p> <p>For the <i>optimistic</i> target, <i>no</i> dose adjustments should be required, including for HIV therapies, so that regimen can be used easily and in a standardized way in different populations.</p>

Attribute	Minimum	Optimal	Annotations
<p>Barrier to emergence of drug resistance (propensity to develop resistance, generation of cross-resistance)</p>	<p><i>The minimal target should be considered a potential “go” or “no go” decision point for the given “priority attribute”</i></p> <p>Potential for acquisition of resistance is <i>no worse</i> than with current regimens and current methods of excluding TB disease.</p>	<p>Rate of in-vitro mutations conferring resistance is <i>lower</i> than with rifampicin.</p> <p>Fewer than two gene targets linked to development of resistance.</p> <p>No cross-resistance with existing drugs.</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 rifamycins for treatment of TB infection in the absence of TB disease (37, 38).</p> <p>Ideally, drugs included in preventive treatment should protect each other against emergence of resistance. The drugs in the regimen should have no initial resistance, and mutants with resistance against the drugs should not be cross-resistant to drugs used in first- or second-line TB regimens. The last attribute is extremely important to avoid compromising the use of potential new drugs. 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, the frequency of strains with mutations conferring resistance to rifampicin has been estimated to be 2.25×10^{-10} (39).</p>
<p>Target population</p>	<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, chronic renal failure treated with dialysis, preparation for organ or haematological transplant and silicosis. <p><i>In all these situations, TB disease is formally ruled out.</i></p>	<p>All individuals in all age groups at risk of TB disease, 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 TB disease has been formally ruled out.</p>	<p>Minimum criteria address currently recommended target groups only (32).</p> <p>Optimistic criteria address all TB-infected populations who might be screened and in whom TB disease has been formally ruled out.</p> <p><i>Note:</i></p> <ul style="list-style-type: none"> • In children, pharmacokinetics and safety studies will be required in <i>both</i> the minimum and the optimistic scenarios, but efficacy trials in this population are not necessarily required. TB regimen developers should consider initiating pharmacokinetics and safety studies for all paediatric age groups for drugs that show promising efficacy and safety in phase-2A trials in adults (40). • Patients with end-stage renal and liver disease may require significant adjustments to doses and frequency of administration and may require more clinical and laboratory monitoring. It would be desirable, however, for the optimal TPT regimen to be usable in patients with severe renal or hepatic disease.

Attribute	Minimum <i>The minimal target should be considered a potential “go” or “no go” decision point for the given “priority attribute”</i>	Optimal <i>The optimal target should have a broader, deeper, quicker global health impact</i>	Annotations <i>For each variable, the rationale for why it is important and for the target value</i>
Formulation, dosage, frequency and route of administration	<p>Formulation to be oral, with a daily intake as a maximum for all drugs in the regimen, including paediatric forms (dispersible, scored tablets, palatability).</p> <p>If long-acting formulation: injection with or without oral lead-in no more than once a month.</p> <p>Single dissolvable implant for complete course of therapy.</p>	<p>Formulation to be oral, without a requirement for weight adjustment, including paediatric forms (dispersible, scored tablets). Ideally, a single pill per day or week for the duration of treatment (depending on daily or weekly formulation).</p> <p>No specific food requirements.</p> <p>Single injection of long-acting formulation without oral lead-in to be given once or twice or a single dissolvable implant with long-lasting protection.</p>	<p>If the regimen consists of two or more drugs orally, fixed-dose combinations of proven bioavailability and bioequivalence for all components are optimal to facilitate use by all targeted recipients of TPT. For PLHIVs, fixed-dose combinations could combine TPT medicines with ART or co-trimoxazole.</p> <p>Dosing frequency:</p> <ul style="list-style-type: none"> • Daily intake is advantageous for PLHIVs, as they can be ingested with daily ART. In addition, daily treatment may be more forgiving of poor adherence than weekly treatment. • Conversely, weekly intake might be more advantageous in terms of lower toxicity and clinical requirements but may require stricter conditions of treatment adherence. <p>No special requirement for food or companion drugs; ideally, no restriction with alcohol.</p> <p>Long-acting injection or implant formulations have strong practical and operational advantages, as they cancel the requirement for DOT (41). A long-lasting or extended-release formulation could be particularly suitable for long-term treatment of PLHIV who are at high risk of TB re-infection in high-transmission settings. In addition, avoiding oral delivery and its associated first-pass metabolism through the liver may have additional benefits in terms of drug–drug interactions.</p>
Stability and shelf life	<p>Oral regimen: Stable to heat, humidity and light, with a shelf life for all drugs ≥ 2 years.</p> <p>No cold chain required.</p> <p>Injectable: stable in all climate zones. If cold chain required, to be compatible with current vaccine cold chain requirements (2–8 °C).</p>	<p>Oral regimen: Stable to heat, humidity and light, with a shelf life for all drugs ≥ 5 years.</p> <p>No cold chain required.</p> <p>Injectable: stable in all climate zones, and no cold chain required.</p>	<p>Current therapies are stable for ≥ 2 years.</p> <p>Climatic zones:</p> <p>I, temperate</p> <p>II, subtropical, with possible humidity</p> <p>III, hot and dry</p> <p>IV, hot and humid</p>

2. Desirable attributes

Attribute	Minimum	Optimal	Annotations
Cost of regimen	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 that affect the price, demand and availability of regimens depend on factors including how well the new regimens meet or surpass the attributes described herein (e.g. efficacy, safety, adherence).</p> <p>An improved regimen may provide advantages in other costs to programmes and patients by being e.g. shorter, better tolerated and/or requiring minimal to no monitoring, thus reducing non-drug costs. The cost and associated resource demands to implement the regimen at the scale necessary to reduce the global TB incidence should not upset the balance of health equity to the disadvantage of any subpopulation in either low- or high-resource settings.</p>
Special populations	<p>For women of reproductive age, pharmacokinetics and safety studies support use of the regimen with <i>minimal</i> dose adjustment.</p> <p>There must be no foetal toxicity in preclinical data.</p> <p>The drugs can be taken safely during breastfeeding and are compatible with common forms of hormone-based birth control for women of reproductive age who wish not to become pregnant.</p> <p>Safe and tolerable for patients with co-morbid conditions.</p>	<p>For women of reproductive age and pregnant women, pharmacokinetics and safety studies support use of the regimen <i>without</i> dose adjustment.</p> <p>There must be no foetal toxicity in preclinical data.</p> <p>The drugs can be taken safely during breastfeeding and are compatible with common forms of hormone-based birth control for women of reproductive age who wish not to become pregnant.</p> <p>Safe and tolerable for patients with co-morbid conditions.</p>	<p>Formulations are required that are safe for pregnant women and women of reproductive age. A study of 6H in HIV-infected pregnant and post-partum women showed that the risk of an adverse pregnancy outcome (stillbirth or spontaneous abortion, low birth weight, preterm delivery or congenital anomalies) was greater when 6H was initiated during pregnancy than during the postpartum period (42), whereas three observational studies suggested no higher risk of adverse pregnancy outcomes in women who initiated IPT during pregnancy (43–45). According to the latest WHO guidelines (13), there are insufficient grounds to change previous guidance, and systematic deferral of IPT to the post-partum period would deprive women of its protective effect at a time when they are more vulnerable to TB. Appropriate care during the antenatal and postnatal periods and during delivery is recommended to reduce the risk of adverse pregnancy outcomes.</p> <p><i>Note: As malformations and foetal loss were observed in experimental animals, use of alternatives to rifapentine for TB treatment and prophylaxis in pregnancy is recommended.</i></p>
Treatment adherence and completion	<p>At least as good adherence and chance of treatment completion as with existing recommended short-course regimens (4R, 3HP).</p> <p>Suitable for self-administration in all populations (not for long-acting formulation).</p>	<p>Better adherence and chance of completion than with existing recommended short-course regimens.</p> <p>Suitable for self-administration in all populations (not for long-acting formulation).</p>	<p>To maximize adherence to therapy, current guidelines recommend use of a broad range of patient-centred care and case management strategies, including DOT, video-supported treatment, education and incentives.</p> <p>For the <i>minimum</i> target, most patients on the new regimen should be able to complete therapy with minimum support, only selected populations requiring DOT or virtually observed therapy or other labour- or cost-intensive activities.</p> <p>For the <i>optimal</i> target, all populations should be able to complete therapy by self-administration, without requiring DOT or other interventions.</p>
Need for drug-susceptibility testing	Drug-susceptibility test available for the index TB patient when required.	No need to test index TB patient.	Where molecular diagnostic tests are available, a single, rapid molecular rifampicin-susceptibility test will suffice. Optimally, the new TPT regimen should be usable in all conditions and settings, particularly in those in which there is a moderate-to-high likelihood of rifampicin-resistant TB transmission.

1HP, 1 month daily rifapentine plus isoniazid; 3HP, 3 months weekly rifapentine plus isoniazid; 3HR, 3 months daily rifampicin plus isoniazid; 4R, 4 months daily rifampicin monotherapy; 6H, 6 months daily isoniazid monotherapy; 9H, 9 months daily isoniazid monotherapy.

Annex 4 summarises the latest WHO recommendations on TB preventive treatment.

4 Cross-cutting aspects

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

Safety

It is essential to keep in mind that, apart from HIV-infected or other immune-suppressed people, treatment of TB infection is 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 disrupt the lives of these people as little as possible. As shorter regimens are associated with higher treatment completion rates (18), any potential gain in completion from a shorter duration must not be offset by poorer safety or tolerability.

Furthermore, any regimen that appears to be promising for TB prevention should be evaluated carefully for safety and tolerability in the same populations as those likely to receive it. Therefore, clinical trials should be performed to define the benefits and harms of TPT in vulnerable groups, including PLHIV, children, pregnant and breast-feeding women, recent contacts of infectious TB patients and patients with immunosuppressed conditions (46).

Diagnosis of TB infection

An efficacious preventive treatment, *if coupled with a test to identify those at highest risk for disease progression*, especially in people co-infected with HIV, would be an important step to accelerate progress towards TB elimination. TPT drug and regimen development should include consideration of diagnostic technologies for identifying those at greatest risk of progression to TB disease (47,48).

Rule-out TB test

In every situation in which TPT is indicated and considered, it is imperative that TB disease be formally ruled out. Inadvertent use of TPT in people with TB disease may generate drug resistance. Details of appropriate strategies must be clearly explained at the time of scale-up.

Availability of drug-susceptibility testing for the index TB patient

A single, rapid, molecular test for susceptibility to rifampicin should be carried out on the index TB patient to rule out rifampicin-resistant TB. In optimal conditions, however, the new TPT regimen should be usable in all conditions and settings, particularly where there is a moderate-to-high likelihood of rifampicin-resistant TB transmission, and delivered without requiring the susceptibility profile of the presumed source case.

Adherence to preventive therapy

Once high-risk individuals with TB infection have been identified, TB control programmes must ensure optimal adherence to treatment. Strategies to support adherence include remote use of digital techniques (through mobile phones) (49). Long-acting formulations may be alternatives to these techniques. In all cases, self-administered treatment is the preferred mode of delivery.

Monitoring

Clinical monitoring is essential to identify and manage adverse events and drug–drug interactions rapidly and to detect any TB disease. 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 (13).

Scalability, health equity and access

These are key elements for the success of the End TB Strategy. The reported limited use of TB infection treatment to household contacts of TB cases globally at the time of isoniazid monotherapy is an example to keep in mind. Recent experience with scaling up 3HP should be considered fully for further information. This is one of the objectives of the Unitaid-funded IMPAACT4TB project, which provides access to 3HP for PLHIV and children < 5 years, in order to establish an affordable, quality-assured, less toxic, shorter therapy suitable for wide introduction in the countries most affected by TB (50).

The TPPs presented here include the attributes that are considered essential for novel TPT, i.e. efficacy, safety, toxicity, lack of drug–drug interactions and a barrier to emergence of drug resistance. It might be difficult to satisfy all these characteristics in a single regimen, however, and regimen developers might have to consider trade-offs, such as increasing efficacy and safety rather than shortening treatment duration, or increasing dosing frequency (e.g. once a day rather than once a week) if it significantly reduces the duration of treatment, or improvements in safety and tolerability that would offset the challenges associated with longer duration (e.g. treatment adherence and completion).

For an infectious disease such as TB, with a large global burden and continuing person-to-person transmission, the efficacy of new TPT regimen(s) will depend heavily on operational factors that also affect a regimen's ability to fulfil its role (e.g. access to diagnostics, capacity to rule out TB disease, access to new treatments, education of health care workers, patients and contacts). While the TPPs indicate the attributes to be considered at the *developmental* stage, these should not be dissociated from the factors to be considered at the *implementation* stage in the framework of overall TB-oriented activities, including enhanced detection and treatment of TB disease (all forms), provision of antiretrovirals to PLHIV, BCG vaccine coverage and sustained infection control activities.

5 Use case scenarios

5.1 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 TB disease, irrespective of HIV status;
- be safe, tolerable and efficacious in individuals of all ages (including neonates, infants and young children, women of reproductive age and pregnant and lactating women) and for patients with a wide range of co-morbid conditions, including HIV infection, other infectious or tropical diseases and chronic diseases;
- not result in drug–drug interactions, specifically with antiretrovirals, drugs metabolized by P450 liver enzymes, pro-arrhythmic QT-prolonging drugs, contraceptive medicines and others;
- be delivered exclusively orally by a simple dosing schedule (preferably once daily, with no food restrictions, no requirement for weight adjustment and in a fixed-dose combination) and be child-friendly (e.g. dispersible, scored and palatable formulations with few pills); parenteral formulations to be considered for long-acting formulations (see Annex 5);
- be affordable and available, particularly in low- and middle-income countries;
- contain medicines that may be prescribed in decentralized settings; and
- be simple to use and easy to monitor for efficacy in TB prevention by simple checks.

5.2 Intended use case scenarios

5.2.1 High- and low-transmission settings

Although there should be no difference in regimens for treatment of TB infection in different settings, consideration should be given to the different situations in *low-incidence* and *high-incidence* settings.

In *high-incidence* settings with continuous TB transmission and concurrent HIV epidemics, the protective effect of TPT may be transient, given the potential for re-infection, but it is particularly valuable during periods of high vulnerability, such as infection of young household contacts or PLHIV (2). Thus, treatment of TB infection will depend strongly on the capacity to initiate and sustain targeted campaigns for the prevention of TB in these high-risk groups. This should complement sustained provision of ART, which is a highly effective measure against TB and other opportunistic infections in PLHIV.

In *low-incidence* settings with minimal TB transmission, the protection provided by TPT is more durable, given the limited risk of re-infection, but has a reduced population benefit because of low TB transmission. In deciding whether to recommend preventive therapy, clinicians should weigh the probable benefits and harms of treatment (once TB disease has been ruled out), considering the risk of subsequent progression to disease and the potential toxicity of therapy, which require consideration of the patient's age and comorbid conditions. *Recent* contacts of infectious individuals and migrants arriving from endemic areas within the preceding 2 years are often considered high-risk populations. In these situations, all means should be available to (i) rule out TB disease; (ii) test for TB infection in a reliable way; and (iii) initiate therapy, assess the risk of subsequent progression to TB disease and monitor treatment adherence and completion.

5.2.2 Testing for TB infection

For formal demonstration of TB infection, recent WHO guidelines (13) stipulate that “testing for TB infection by tuberculin skin test or interferon- γ release assay is not a requirement for initiating preventive treatment in PLHIV or child household contacts aged < 5 years”. This is not the case, however, for adults, adolescents and children aged ≥ 5 years who are household contacts of bacteriologically confirmed pulmonary TB cases, who should be tested for TB infection before treatment is provided, or for migrants arriving from endemic areas, who should all be tested for TB infection in a reliable way. The strategy therefore differs according to population group, and different use case scenarios may be developed for global use and scale-up of treatments. It is hoped that cheap, rapid, accurate point-of-care-diagnostic tests for TB infection and incipient disease will become available for further refinement of the TB prevention strategy.

5.2.3 Rifampicin-susceptible and-resistant strains

As mentioned in the introduction, a practical approach of extended scale-up and access to treatment of TB infection under programmatic conditions in high-risk populations might have a drastic impact on TB incidence and mortality, in addition to optimized case-finding and treatment. Thus, TB preventive treatment regimens are intended for all patients infected with *M. tuberculosis*, whether the infection is susceptible or resistant to rifampicin or to other oral first-line drugs that may be used in the regimen (e.g. isoniazid) or to second-line drugs included in drug-resistant TB treatment (fluoroquinolones, bedaquiline, delamanid). The potential use case scenario may thus be either (i) that treatment of TB infection is intended for *all* individuals infected with *M. tuberculosis* strains whether susceptible or resistant to rifampicin or to other oral first-line drugs potentially used in disease-susceptible regimen (e.g. isoniazid) or to second-line drugs included in drug-resistant TB treatment (fluoroquinolones, bedaquiline, delamanid), or (ii) that contacts of known drug-resistant TB cases with no TB disease require specific drugs or regimens for TB preventive treatment. The scenario will therefore strongly depend on the class of the drugs proposed in the TPT.

References

1. Drain PK, Bajema KL, Dowdy D, Dheda K, Naidoo K, Schumacher SG, et al. Incipient and subclinical tuberculosis: a clinical review of early stages and progression of infection. *Clin Microbiol Rev.* 2018;31(4):e00021-18.
2. Global tuberculosis report 2019. Geneva: World Health Organization; 2019 (http://www.who.int/tb/publications/global_report/en/).
3. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med.* 2016;13(10):e1002152.
4. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol.* 1974;99(2):131–8.
5. Marais BJ, Gie RP, Schaaf HS, Hesselting AC, Obihara CC, Starke JJ, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis.* 2004;8:392–402.
6. Behr MA, Edelstein PH, Ramakrishnan L. Revisiting the timetable of tuberculosis. *BMJ.* 2018;362:k2738.
7. Marais B. Preventing tuberculosis in household contacts crucial to protect children and contain epidemic spread. *Lancet Glob Health* 2018;6(12):E1260–1.
8. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent *Mycobacterium tuberculosis* infection. *N Engl J Med.* 2015;372(22):2127–35.
9. Hesselting AC, Cotton MF, Jennings T, Whitelaw A, Johnson LF, Eley B, et al. High incidence of tuberculosis among HIV-infected infants: evidence from a South African population-based study highlights the need for improved tuberculosis control strategies. *Clin Infect Dis.* 2009;48:108–14.
10. Dodd PJ, Seddon JA. Understanding the contribution of HIV to the risk of developing tuberculosis in children: a systematic review and meta-analysis. *Int J Tuberc Lung Dis.* 2015;19(12 (S2)):S64.
11. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new end TB strategy. *Lancet.* 2015;385(9979):1799–801.
12. United Nations General Assembly. Political declaration of the high-level meeting of the General Assembly on the fight against TB. October 2018. New York City (NY): United Nations; 2018 (http://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/73/3, accessed September 2019).
13. WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment. Geneva: World Health Organization; 2020 (<https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment>).
14. Horsburgh CR Jr, Rubin EJ. Latent tuberculosis infection in the United States. *N Engl J Med.* 2011;364:1441–8.
15. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev.* 2010;(1):CD000171.
16. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis.* 1999;3:847–50.
17. Zenner D, Beer N, Harris RJ, Lipman MCI, Stagg HR, van der Werf MJ. Treatment of latent tuberculosis infection: an updated network meta-analysis. *Ann Intern Med.* 2017;167(4):248–55.
18. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis.* 2005;40:670–6.
19. Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. *Clin Infect Dis.* 2007;45:715–22.

20. Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med*. 2018;379:440–53.
21. Diallo T, Adjobimey M, Ruslami R, Trajman A, Sow O, et al. Safety and side effects of rifampin versus isoniazid in children. *N Engl J Med*. 2018;379:454–63.
22. Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med*. 2019;380:1001–11.
23. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365:2155–66.
24. Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. *JAMA Pediatr*. 2015;169:247–55.
25. Sterling TR, Scott NA, Miro JM, Calvet G, La Rose A, Infante R, et al. Three months of weekly rifapentine and isoniazid for treatment of *M. tuberculosis* infection in HIV coinfecting persons. *AIDS*. 2016;30(10):1607–15.
26. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. 2011;365:11–20.
27. Sandul AL, Nwana N, Holcombe JM, Lobato MN, Marks S, Webb R, et al. High rate of treatment completion in program settings with 12-dose weekly isoniazid and rifapentine for latent *Mycobacterium tuberculosis* infection. *Clin Infect Dis*. 2017;65(7):1085–93.
28. Njie GJ, Morris SB, Woodruff RZW, Moro RN, Vernon A, Borisov AS. Isoniazid–rifapentine for latent tuberculosis infection: a systematic review and meta-analysis. *Am J Prev Med*. 2018;55(2):244–52.
29. Semvua HH, Kibiki GS, Kisanga ER, Boeree MJ, Burger DM, Aarnoutse R. Pharmacological interactions between rifampicin and antiretroviral drugs: challenges and research priorities for resource limited settings. *Ther Drug Monit*. 2015;37(1):22–32.
30. Guidance for industry and review staff: target product profile—a strategic development process tool. Rockville (MD): Food and Drug Administration; 2007.
31. WHO target product profiles, preferred product characteristics, and target regimen: standard procedures. Geneva: World Health Organization; 2019.
32. 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.
33. Olliaro PL, Vaillant M. Designing noninferiority tuberculosis treatment trials: identifying practical advantages for drug regimens with acceptable effectiveness. *PLoS Med*. 2019;16(7):e1002850.
34. 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.
35. Stuurman AL, Vonk Noordegraaf-Schouten M, van Kessel F, Oordt-Speets AM, Sandgren A, van der Werf MJ. Interventions for improving adherence to treatment for latent tuberculosis infection: a systematic review. *BMC Infect Dis*. 2016;16:257.
36. Pease C, Hutton B, Yazdi F, Wolfe D, Hamel C, Quach P, et al. Efficacy and completion rates of rifapentine and isoniazid (3HP) compared to other treatment regimens for latent tuberculosis infection: a systematic review with network meta-analyses. *BMC Infect Dis*. 2017;17(1):265.
37. 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.
38. den Boon S, Matteelli A, Getahun H. Rifampicin resistance after treatment for latent tuberculosis infection: a systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2016;20(8):1065–71.
39. David HL. Probability distribution of drug-resistant mutants in unselected populations of *Mycobacterium tuberculosis*. *Appl Microbiol*. 1970;20(5):810–4.
40. 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. *Lancet Infect Dis*. 2015;15(6):711–20.

41. 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;22(2):125–32.
42. 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.
43. 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. *Infect Dis Obstet Gynecol.* 2013;2013:1–5.
44. 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. *Clin Infect Dis.* 2019;ciz1024.
45. 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. *Reprod Toxicol.* 2018;80:155.
46. Gupta A, Hughes MD, Garcia-Prats AJ, McIntire K, Hesselning AC. Inclusion of key populations in clinical trials of new antituberculosis treatments: current barriers and recommendations for pregnant and lactating women, children, and HIV-infected persons. *PLoS Med.* 2019;16(8):e1002882.
47. Development of a target product profile (TPP) and a framework for evaluation for a test for predicting progression from tuberculosis infection to active disease. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/bitstream/handle/10665/259176/WHO-HTM-TB-2017.18-eng.pdf?sequence=1>).
48. Framework for the evaluation of new tests for tuberculosis infection. Geneva, World Health Organization. 2020. (<https://www.who.int/publications/i/item/9789240007185>)
49. Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. *Cochrane Database Syst Rev.* 2012;(3):CD009756.
50. Dooley K, Churchyard G, Savic R, Gupta A, Mazinke MA, Zhang N, et al. Safety and PK of weekly rifapentine/isoniazid (3HP) in adults with HIV on dolutegravir. Abstract 80. Conference on Retroviruses and Opportunistic Infections, Seattle (WA), 4–7 March 2019 (<http://www.croiconference.org/sessions/safety-pk-weekly-rifapentineisoniazid-3hp-adults-hiv-dolutegravir>, accessed June 2020).

Annex 1.

Treatment of tuberculosis infection for prevention of tuberculosis disease

Background and current situation.

The aim of treatment of TB infection is to prevent progression to active clinical disease by killing potential resident bacilli in the host. Isoniazid administered daily for 6–12 months has been the mainstay of treatment for more than half a century, with an efficacy of 54–88% (1, 2). A re-analysis of the United States Public Health Service trials conducted in 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 recommendation of the 9-month isoniazid regimen as adequate treatment (3). Further studies, however, showed similarities between the 6- and 12-month regimens in non-HIV-infected people. A meta-analysis of 11 isoniazid trials involving 73 375 HIV-uninfected people showed that, as compared with placebo, the risk of progression to TB disease at 6 months (relative risk, 0.44; 95% CI, 0.27; 0.73) was similar to that at 12 months (relative risk, 0.38; 95% CI, 0.28; 0.50) (4). A meta-analysis of placebo-controlled studies found that the odds of subsequent TB disease in individuals with TB infection was 0.65 (95% credible interval, 0.50; 0.83) after treatment with isoniazid for 6 months and 0.50 (0.41; 0.62) after treatment with isoniazid for 12 months as compared with placebo (5) (Table A1.1).

Table A1.1. Odds ratios for the prevention of TB disease and treatment rankings, derived from a network meta-analysis

Regimen	Odds ratio vs placebo (95% CrI)	Odds ratio vs no treatment (95% CrI)
No treatment	1.62 (1.06–2.47)	1 (reference)
Placebo	1 (reference)	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 3m	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)

Adapted from reference 5.

CrI, credible interval; INH, isoniazid; RMP, rifampicin; RPT, rifapentine.

Other treatment regimens have been investigated and proven to be safe and efficacious, including rifampicin, isoniazid and rifampicin, and isoniazid and rifapentine regimens. In the network meta-analysis of preventive therapies cited above, daily rifampicin for 3–4 months was found to reduce the risk of incident TB by 59% as compared with placebo (odds ratio, 0.41; 95% credible interval, 0.19; 0.85). A multicentre clinical trial in which 4 months of self-administered rifampicin was compared with

9 months of daily isoniazid therapy in 6859 people, 4 months of daily rifampicin was non-inferior to 9 months of isoniazid for the prevention of TB disease and was associated with a higher rate of treatment completion and better safety (6). In an additional 829 children aged < 18 years recruited in a companion trial, treatment with 4 months of rifampicin resulted in similar rates of safety and efficacy but a better rate of adherence than 9 months of isoniazid (85.3% vs 76.4%, adjusted difference in the rates of treatment completion, 13.4 % [95% CI, 7.5; 19.3]) (7).

Several randomized studies have been conducted to compare 3–4 months of daily isoniazid and rifampicin with daily isoniazid alone. A meta-analysis of five randomized controlled trials in adults showed that daily therapy with isoniazid plus rifampicin for 3 or 4 months and standard therapy with isoniazid for 6–12 months were equivalent in terms of efficacy, severe side-effects and mortality (8). The trials were significantly heterogeneous with regard to the outcome of severe adverse drug reactions, but a sub-analysis of only high-quality studies indicated that the two regimens were equally safe. A randomized controlled trial in children < 15 years showed that 3–4 months of isoniazid plus rifampicin was at least equivalent to 9 months of daily isoniazid monotherapy (9). No child in either group experienced a clinical episode of TB disease.

In an open-label, registration-quality clinical trial conducted in Brazil, Canada, Spain and the USA, 3 months of weekly rifapentine plus isoniazid was shown to be non-inferior to 9 months of daily isoniazid monotherapy (10). Further, the 3 months of weekly rifapentine plus isoniazid regimen was associated with higher treatment completion rates (82.1% vs 69.0%) and less hepatotoxicity (0.4% vs 2.7%), although permanent discontinuation of the regimen due to side-effects was more frequent with the 3 months of weekly rifapentine plus isoniazid regimen (4.9% vs 3.7%). Similar results were observed in an extension of the study involving 1058 children aged 2–17 years, and no hepatotoxic effects attributed to treatment were observed in either study group (11). A follow-up study involving 399 HIV-infected adults showed that 3 months of weekly rifapentine plus isoniazid was as effective as 9 months of daily isoniazid monotherapy and was associated with a higher treatment completion rate (89% vs 64%) (12). The weekly isoniazid–rifapentine regimen was also evaluated in South African adults with HIV infection and a positive tuberculin skin test, who were *not* receiving ART; the efficacy of that regimen was shown to be similar to a 6-month isoniazid regimen (13).

In a post-marketing evaluation of 3 months of weekly rifapentine plus isoniazid in 16 TB programmes and routine health care settings in the USA involving 3288 participants, completion of 3 months of weekly rifapentine plus isoniazid was better overall than the rates reported from clinical trials, and better than with other regimens in reportedly non-adherent populations (14). Further, a systematic review published in 2018 showed that 3 months of weekly rifapentine plus isoniazid was *similar* to other TB infection regimens (6 months of daily isoniazid monotherapy, 9 months of daily isoniazid monotherapy, 3–4 months of isoniazid plus rifampicin and 2–33 months of daily rifampicin plus pyrazinamide) in effectiveness, risk of adverse events, risk of discontinuation due to adverse events and risk of death but resulted in higher completion rates (15).

In a study conducted in 2019, 1 month of daily rifapentine plus isoniazid delivered to HIV-infected patients aged ≥ 13 years living in areas of high TB prevalence or who had evidence of TB infection was shown to be non-inferior to 9 months of daily isoniazid monotherapy in a phase-III randomized, open-label, controlled trial (16). The primary end-point was a first diagnosis of TB or death from TB or an unknown cause. A total of 3000 patients were enrolled and followed for a median of 3.3 years. The primary end-point was reported in 32 of 1488 patients (2%) receiving 1 month of daily rifapentine plus isoniazid and in 33 of 1498 patients (2%) receiving 9 months of daily isoniazid monotherapy, for incidence rates of 0.65 per 100 person-years and 0.67 per 100 person-years, respectively (rate difference, –0.02 per 100 person-years; 95% CI, –0.30; 0.34). The 1 month of daily rifapentine plus isoniazid regimen was also found to be non-inferior to 9 months of daily isoniazid monotherapy in the subset of participants with a positive test for TB infection (tuberculin skin test or Interferon- γ release assay). Serious adverse events occurred in 6% of the patients receiving 1 month of daily rifapentine plus isoniazid and in 7% of those

given 9 months of daily isoniazid monotherapy ($P = 0.07$). The treatment completion rate was higher with 1 month of daily rifapentine plus isoniazid than with 9 months of daily isoniazid monotherapy (97% vs 90%, $P < 0.001$). Most of the participants were on ART.

References

1. Horsburgh CR Jr, Rubin EJ. Latent tuberculosis infection in the United States. *N Engl J Med*. 2011;364:1441–8.
2. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev*. 2010;(1):CD000171.
3. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis*. 1999;3:847–50.
4. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database Syst Rev* 2000; 2: CD001363.
5. Zenner D, Beer N, Harris RJ, Lipman MCI, Stagg,HR, van der Werf MJ. Treatment of latent tuberculosis infection: an updated network meta-analysis. *Ann Intern Med*.2017;167(4):248–55.
6. Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med*. 2018;379:440–53.
7. Diallo T, Adjobimey M, Ruslami R, Trajman A, Sow O, et al. Safety and side effects of rifampin versus isoniazid in children. *N Engl J Med*. 2018;379:454–63.
8. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a metaanalysis. *Clin Infect Dis*. 2005;40:670–6.
9. Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. *Clin Infect Dis*. 2007;45:715–22.
10. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365:2155–66.
11. Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. *JAMA Pediatr*. 2015;169:247–55.
12. Sterling TR, Scott NA, Miro JM, Calvet G, La Rose A, Infante R, et al. Three months of weekly rifapentine and isoniazid for treatment of *M. tuberculosis* infection in HIV coinfecting persons. *AIDS*. 2016;30(10):1607–15.
13. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. 2011;365:11–20.
14. Sandul AL, Nwana N, Holcombe JM, Lobato MN, Marks S, Webb R, et al. High rate of treatment completion in program settings with 12-dose weekly isoniazid and rifapentine for latent *Mycobacterium tuberculosis* infection. *Clin Infect Dis*. 2017;65(7):1085–93.
15. Njie GJ, Morris SB, Woodruff RZW, Moro RN, Vernon A, Borisov AS. Isoniazid–rifapentine for latent tuberculosis infection: a systematic review and meta-analysis. *Am J Prev Med*. 2018;55(2):244–52.
16. Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med*. 2019;380:1001–11.

Annex 2.

Tuberculosis preventive treatment in special populations

1. Contacts of MDR-TB cases

Contacts of patients with known MDR-TB are at high risk of infection with a drug-resistant organism (1). Limited evidence is available for deciding on the optimal approach for individuals who are likely to have TB infection with drug-resistant bacteria. An observational study in Micronesia showed that contacts of MDR-TB patients who received preventive therapy in a regimen including moxifloxacin or levofloxacin with either ethambutol or ethionamide did not develop MDR-TB, while 20% of infected contacts who refused treatment developed the disease (2). 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 isoniazid and ethambutol developed TB, which was a substantially lower rate than in “historical” controls (3).

Three randomized controlled trials of preventive therapy after household exposure to MDR-TB are being conducted currently, with various regimens. The V-QUIN trial is a comparison of levofloxacin with placebo in infected contacts of MDR-TB patients in Viet Nam. The TB CHAMP trial is a comparison of the same regimens but with a dispersible formulation for children < 5 years in South Africa. The PHOENIX study in Africa, Asia and South America is a comparison of delamanid with isoniazid. The results of the three studies will not be available until after 2020. Details are provided in Table A2.1.

Table A2.1. Ongoing clinical trials for the treatment of TB infection in contacts of MDR-TB patients

	TB-CHAMP	V-QUIN	Phoenix
Intervention	Levofloxacin (novel paediatric dispersible formulation) vs placebo daily for 6 months	Levofloxacin vs placebo daily for 6 months	Delamanid vs standard dose isoniazid daily for 26 weeks
Design	Cluster randomized; superiority Community-based	Cluster randomized; superiority Community-based	Cluster randomized; superiority Community-based
Target population	0–5 years, regardless of interferon- γ release assay result or HIV status	Tuberculin skin test + No age limit	HIV + Children 0–5 years Tuberculin skin test or interferon- γ release assay + > 5 years
Assumptions	Levofloxacin decreases TB incidence from 7% to 3.5%. 80% power	Levofloxacin decreases TB incidence by 70% from 3% in untreated. 80% power	Delamanid 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 and IMPAACT sites
Timelines	Completed and intended to be published by end 2020	Planned end of data collection in March 2020	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. TB preventive treatment in PLHIV

In a Cochrane database review of 12 randomized clinical trials of TB infection treatment in 8578 randomized PLHIV, preventive therapy with any anti-TB drug administered for 6–12 months versus placebo resulted in an overall 32% reduction in the incidence of TB disease (relative risk, 0.68; 95% CI, 0.54; 0.85) (4). The effect was greater for people with a positive tuberculin skin test (62% reduction; relative risk, 0.38; 95% CI, 0.25; 0.57) than for those with a negative tuberculin skin test (11% reduction; relative risk, 0.89; 95% CI, 0.64; 1.24). Because of the uncertain performance and limitations of existing diagnostic tests for TB infection in PLHIV, the treatment recommendations in this special population do not require systematic testing for infection.

The benefit provided by IPT in PLHIV was shown to remain in the presence of concurrent ART (4). Further, while in South Africa the protective effect of isoniazid against TB disease among PLHIV was found to wane over time (5), in Côte d'Ivoire, 6 months of IPT had a durable protective effect (up to 6 years of follow-up) in reducing mortality of PLHIV (by 37%), even in those with a high CD4 cell counts and who had started ART (6). The probable 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 long-term protective benefits in HIV-infected adults (7). In settings with high TB prevalence and transmission, daily isoniazid preventive therapy for 36 months for PLHIV was shown to reduce the risk for TB disease by 38% more than 6 months of daily isoniazid (8).

Short-course preventive therapy with 3 months of weekly rifapentine plus isoniazid could transform TB control, but drug interactions with antiretrovirals pose potential challenges. Co-administration of efavirenz and daily rifapentine (600 mg), with or without isoniazid, did not reduce exposure to efavirenz that could jeopardize antiviral activity (9). Administration of 3 months of weekly rifapentine plus isoniazid with raltegravir was found to be safe and well tolerated in healthy volunteers (10). One of the most urgent remaining questions about acceptability is whether rifapentine can be safely given 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 infection (11, 12). Recent data from DOLPHIN, a single-arm study of the safety and pharmacokinetics of 3 months of weekly rifapentine plus isoniazid with dolutegravir (ART in adults with HIV infection (13)), showed that co-administration was well tolerated, with no adverse events of grade > 3 after 3 months of weekly rifapentine plus isoniazid, and all participants maintained viral suppression (14).

References

1. Becerra M, Appleton S, Franke M, Chalco K, Arteaga F, Bayona J, et al. Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: a retrospective cohort study. *Lancet*. 2011;377:147–52.
2. Bamrah S, Brostrom R, Dorina F, Setik L, Song R, Kawamura LM, et al. Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009–2012. *Int J Tuberc Lung Dis*. 2014;18:912–8.
3. Seddon JA, Hesselring AC, Finlayson H, Fielding K, Cox H, Hughes J, et al. Preventive therapy for child contacts of multidrug-resistant tuberculosis: a prospective cohort study. *Clin Infect Dis*. 2013;57:1676–84.
4. Rangaka MX, Wilkinson RJ, Glynn JR, Boulle A, van Cutsem G, Goliath R, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomized double-blind, placebo-controlled trial. *Lancet*. 2014;384:682–90.
5. Churchyard GJ, Fielding KL, Grant AD. A trial of mass isoniazid preventive therapy for tuberculosis control. *N Engl J Med*. 2014;370:1662–3.

6. Badje A, Moh R, Gabillard D, Guéhi C, Kabran M, Ntakpé JB, et al. Effect of isoniazid preventive therapy on risk of death in West African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. *Lancet Glob Health*. 2017;5(11):e1080–9.
7. Golub JE, Cohn S, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, et al. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. *Clin Infect Dis*. 2015;60:639–45.
8. Den Boon S, Matteelli A, Ford N, Getahun H. Continuous isoniazid for the treatment of latent tuberculosis infection in people living with HIV. *AIDS*. 2016;30(5):797–801.
9. Podany A, Bao Y, Swindells S, Chaisson RE, Andersen JW, Mwelase T, et al. Efavirenz pharmacokinetics and pharmacodynamics in HIV-infected persons receiving rifapentine and isoniazid for tuberculosis prevention. *Clin Infect Dis*. 2015;61:1322–7.
10. Weiner M, Egelund EF, Engle M, Kiser M, Prihoda TJ, Gelfond JA, et al. Pharmacokinetic interaction of rifapentine and raltegravir in healthy volunteers. *J Antimicrob Chemother*. 2014;69(4):1079–85.
11. ViiV Healthcare receives EU marketing authorization for Juluca (dolutegravir/rilpivirine), the first 2-drug regimen, once-daily, single-pill for the treatment of HIV. Press release, 21 May 2018. Research Triangle (NC): ViiV Healthcare Ltd; 2018 (<https://viivhealthcare.com/en-gb/media/press-releases/2018/may/viiv-healthcare-receives-eu-marketing-authorisation-for-juluca-dolutegravirrilpivirine-the-first-2-drug-regimen-once-daily-single-pill-for-the-treatment-of-hiv/>).
12. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2016 (<http://www.who.int/hiv/pub/arv/arv-2016/en/>).
13. Identifier: NCT03435146, Safety, tolerability, DDI short course treatment of LTBI infection with high-dose rifapentine isoniazid in HIV+ patients (IMPAACT4TB); 2018 February 15. Bethesda (MD): National Library of Medicine; 2000 (<https://clinicaltrials.gov>).
14. Dooley K, Churchyard G, Savic R, Gupta A, Mazinke MA, Zhang N, et al. Safety and PK of weekly rifapentine/isoniazid (3HP) in adults with HIV on dolutegravir. Abstract 80. Conference on Retroviruses and Opportunistic Infections, Seattle (WA), 4–7 March 2019 (<http://www.croiconference.org/sessions/safety-pk-weekly-rifapentineisoniazid-3hp-adults-hiv-dolutegravir>, accessed June 2020).

Annex 3.

Technical consultation on latent TB infection management: target regimen profiles, 17 September 2019, Montréal, Canada

Agenda

Target regimen profiles for treatment of TB infection		
Chair: Payam Nahid		
8:30–8:45	Introductions and meeting objectives	Matteo Zignol
8:45–9:00	Declaration of Interests, management of conflict and roles	Dennis Falzon
<i>Current situation and gaps in treatment of TB infection</i>		
9:00–9:15	Background on WHO LTBI guidance uptake and updates	Dennis Falzon
9:15–9:45	Available treatments and the development pipeline – solutions and gaps	Payam Nahid
9:45–10:00	The conceptual framework for TRP of TB infection	Christian Lienhardt
10:00-10:30	Modelling input parameters to inform TRP for TB infection	Olivia Oxlade, Kevin Schwartzman
10:30-11:00	Break	
<i>I. Attributes for the TRPs</i>		
11:00-11:30	Description of the first set of attributes of the TRPs	Christian Lienhardt
11:30-13:00	Discussion	Dick Menzies (moderator)
13:00-14:00	Lunch	
<i>II. Attributes for the TRPs</i>		
14:00-14:30	Description of the second set of attributes of the TRPs	Christian Lienhardt
14:30-16:00	Discussion	Richard Chaisson (moderator)
16:00-16:20	Break	
<i>Conclusion and next steps</i>		
16:20-17:15	Recap, summary of actions and next steps	Christian Lienhardt
17:15-17:30	Closure and thanks	Dennis Falzon

List of participants

Jay Achar, Médecins Sans Frontières, UK and Ireland
Mênonli Adjobimey, Programme National contre la Tuberculose, Benin
Sevim Ahmedov, USAID, USA
Teeb Al-Samarrai, President's Emergency Plan for AIDS Relief, USA
Cathy Bansbach, Bill & Melinda Gates Foundation, USA
Draurio Barreira Cravo Neto, Unitaid, Switzerland
Grania Brigden, Union, France
Jonathon Campbell, McGill University, Canada
Martina Casenghi, Elizabeth Glaser Pediatric AIDS Foundation, Switzerland
Dick Chaisson, Johns Hopkins University, USA
Gavin Churchyard, Aurum Institute, South Africa
Isabelle Cieren-Puiseux, Sanofi, France
Daniela Cirillo, San Raffaele Scientific Institute Milan, Italy
William Coggin, United States Centers for Disease Control and Prevention, USA
Dennis Falzon, WHO Global TB Programme, Switzerland
Celeste Garcia Edwards, Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland
Unyeong Go, Korea Centers for Disease Control and Prevention, Republic of Korea
Jeremy Hill, KNCV Tuberculosis Foundation, The Netherlands
Avinash Kanchar, WHO Global TB Programme, Switzerland
Christian Lienhardt, Institut de Recherche pour le Développement, France
Alberto Matteelli, University of Brescia, Italy
Dick Menzies, McGill University, Canada
Corinne Merle, Special Programme for Research and Training in Tropical Diseases, Switzerland
Payam Nahid, University of California at San Francisco, USA
Thu Anh Nguyen, The University of Sydney, Australia
Olivia Oxlade, McGill University, Canada
Madhu Pai, McGill University, Canada
Martina Penazzato, WHO HIV Department, Switzerland
Morten Ruhwald, FIND, Switzerland
Nicole Salazar-Austin, Johns Hopkins University, USA
Kevin Schwartzman, McGill University, Canada
Sue Swindells, University of Nebraska Medical Center, USA
Ezio Távorá dos Santos Filho, Union/ Vital Strategies, Brazil
Anete Trajman, McGill University, Canada
Andy Vernon, United States Centers for Disease Control and Prevention, USA
Brenda Waning, Global Drug Facility, Switzerland
Matteo Zignol, WHO Global TB Programme, Switzerland

Statements of conflicts of interest

The following participants declared no interests that could conflict with the objectives of the meeting:

Menonli Adjobimey, Grania Brigden, Jonathon Campbell, William Coggin, Celeste Garcia Edwards, Timothy Evans, Unyeong Go, Jeremy Hill, Christian Lienhardt, Alberto Matteelli, Richard (Dick) Menzies, Sumathi Nambiar, Olivia Oxlade, Nicole Salazar-Austin, Kevin Schwartzman, Susan Swindells, Anete Trajman, Brenda Waning.

The following participants declared interests that might be relevant to the objectives of the meeting:

Jay Achar declared that his employer, Médecins Sans Frontières, has an interest in various aspects of global policy that influence TB control and receives external funding from Unitaid, the Dutch National Lottery and other sources for implementation of the endTB project and the TBPRACTECAL clinical trial.

Faiz Ahmad Khan declared that he is co-investigator in a 2-month trial of high-dose vs normal dose rifampicin in TB infection, which is supported by the Canadian Institute of Health Research. He is also principal investigator in a study to assess the accuracy of artificial intelligence for computer-aided diagnosis of TB in digital chest radiography (CA\$ 487 000 operating costs). No funding is provided by the developers or companies of the software being evaluated. Delft (CAD4TB) & QURE.AI provide technical assistance in use of their software, and QURE.AI provided access to their software free of charge for evaluation. The companies have no influence or input on study design or reporting. He was also a member of a WHO steering committee for a consultation on the use of CXR in TB diagnosis.

Martina Casenghi is in the project management leadership for the CaP TB project, funded by Unitaid. The project includes operational research on models of care for delivery of TB preventive treatment to child contacts. The 3RH regimen will be used. The study is led by the Institut pour la Recherche et le Développement, and she is a co-investigator. As a representative of one of the stakeholders supporting the roll-out of TPT in endemic countries, she has been invited to stakeholders' meetings and consultations. Her contributions have included ensuring that the specific needs of the paediatric population are taken into consideration by donors and public health organizations.

Dick Chaisson has benefited from direct and institutional (Johns Hopkins University) funding in recent years, which includes a total of about US\$ 2.6 million in research grants from the National Institutes of Health, the US Centers for Disease Control and Prevention (US CDC), Chao Foundation, Unitaid and Aurum Institute; US\$ 5000 from Sanofi for technical consulting (Johns Hopkins University); and about US\$ 5000 for speaking honoraria from the National Institutes of Health, the US CDC, Stop-TB Japan, the Portuguese Infectious Disease Society and several universities in the USA.

Gavin Churchyard declared ongoing research support from Unitaid, USAID, the National Institutes of Health and Sanofi. Unitaid provided a grant of US\$ 59 million for scaling up use of 3HP and implementation research. USAID provided a grant of US\$ 14.2 million to evaluate 3HP given once or annually. The National Institutes of Health provided minimal salary support for the PHOENIX trial. Sanofi donated 3HP for the WHIP3TB trial.

Daniela Cirillo declared that the Supranational TB Laboratory in Milan where she works is developing new diagnostics for drug-resistant TB. She declares current research support from FIND (US\$ 26 000); participation in a national expert group to establish use of bedaquiline in Italy (€ 1000; 2014); support for standardization of the drug-susceptibility methods for bedaquiline by Janssen (US\$ 10 000; 2014); and support for the drug-susceptibility methods for delamanid from Otsuka (US\$ 25 000; 2014). The Ospedale San Raffaele in which the laboratory is based, has a service agreement with the TB Alliance (US\$ 19 800).

Payam Nahid declared an active Federal US CDC contract to support clinical trial units in San Francisco, USA, and Hanoi, Viet Nam.

Thu Anh Nguyen works fulltime in Viet Nam for the Woolcock Institute of Medical Research, an Australian non-profit organization. Operational research is being conducted on TB infection with funding from Australia National Health and Medical Research Council.

Madhukar Pai serves as the Chair of the Stop TB Partnership's Public Private Mix Working Group; the Access Advisory Committee of TB Alliance (New York City (NY), USA); the Scientific Advisory Committee of FIND, Geneva, Switzerland; and the SAGE IVD and STAG TB committees of WHO, Geneva, Switzerland.

Morten Ruhwald declared that he works for FIND, which collaborates with industry (e.g. Cepheid, Hain, Alere, Roche) in the development, evaluation and distribution of novel diagnostics. No income is received or will be received from these companies. Industry partnerships are approved and monitored by an independent scientific advisory committee on the basis of due diligence and their ability to meet TPPs and public sector requirements. FIND has not allocated any financial value to the know-how or access to equipment gained by these projects.

Ezio Távora dos Santos Filho declared that he delivered a talk at the Regional IAS Conference in April 2018 in Mexico City, Mexico, on advanced tools for treatment of TB infection, without endorsing any particular study. He also declared that, as a TB advocate, he has participated in many discussions with the Global TB Community Advisory Board and the Brazilian National TB CAB on implementation of new methods for treatment of TB infection. The Brazilian TB CAB is raising awareness about 3HP and TB infection.

Andrew Vernon declared that he heads a clinical research group (TBTC) at the US CDC, which conducts trials. The group has conducted studies on TB infection, and studies are under way with rifapentine (e.g. TBTC Study 31). During the past two decades, TBTC has accepted support from commercial and pharmaceutical companies in the form of drug supplies and funding for pharmacokinetics testing. Most recently, TBTC collaborated with the US National Institutes of Health and Sanofi in undertaking a phase 3 multi-centre trial of daily rifapentine. Sanofi provided medicines and funded pharmacokinetics testing but was not involved in the design or conduct of the study. In 2007–2017, Sanofi Aventis made contributions to the CDC Foundation (about US\$ 3 million total) to facilitate or support TBTC work on rifapentine (e.g. pharmacokinetics studies, two to three staff contracts, travel for invited speakers, preparation of data to support regulatory filings). These funds have not otherwise benefited Dr Vernon or the research group and represent a small proportion of overall costs for the studies. In his capacity as a TB researcher and clinician at US CDC he has participated in both internal and external meetings on developing guidelines for the treatment of active and latent TB in the USA. His attendance was only in the context of CDC employment and never on behalf of any commercial or nongovernmental organization.

Exempted:

Funding agencies: Sevim Ahmedov, Teeb Al-Samarrai, Cathy Bansbach, Draurio Barreira Cravo Neto, Celeste Garcia Edward

Drug manufacturer: Isabelle Cieren-Puisseux

Annex 4.

WHO recommendations on TB preventive treatment (2020 update)

These recommendations (1) are listed below as a reference to the current status of TB preventive treatment. They do not preclude further recommendations based on new data and evidence.

A. Identifying populations for LTBI testing and treatment
People living with HIV
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.
Household contacts (regardless of HIV status)
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.
Other people at risk
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.

Recommended dosages of drugs for the treatment of TB infection

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

Notes:

Regimens based on isoniazid and rifampicin may be used for people of all ages. There are no or very limited data on the efficacy and safety of rifapentine in children <2 years, and the 3 months of weekly rifapentine plus isoniazid regimen is recommended only for use in children aged ≥ 2 years. Data from the trial of 1 month of daily rifapentine plus isoniazid relates only to people aged ≥ 13 years. The Guideline Development Group considered that extrapolation of effects to children aged 2–12 years is reasonable, although the *daily* dose of rifapentine for this age group has yet to be established. The suitability of this regimen for people aged < 13 years should be reviewed once the results of studies of pharmacokinetics and safety in children of all ages become available in the near future.

In addition to PLHIV on ART, other populations that may be commonly at risk of drug–drug interactions with rifampicin include women of reproductive age on contraceptive medicines (who should be counselled about potential interactions and consider non-hormonal birth control while receiving rifampicin) and opiate users on substitution therapy with methadone.

Contacts of patients with laboratory confirmed isoniazid-resistant, rifampicin-susceptible TB may be offered a 4-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. The dose of isoniazid might have to be reduced from that proposed to avoid toxicity if there is a high population prevalence of “slow acetylators”. Combination tablets of co-trimoxazole, isoniazid and pyridoxine could be useful for PLHIV; however, lack of availability of pyridoxine should not be considered a reason to withhold TPT.

Reference

1. WHO consolidated guidelines on tuberculosis: Module 1: Prevention - tuberculosis preventive treatment. Geneva, World Health Organization. 2020.

Annex 5.

Long-acting drug formulations for the treatment of tuberculosis infection

Adherence and completion rates for TB preventive treatment are low in many programmes, which represent major obstacles to the effectiveness of this strategy. An important, novel solution could be long-acting, extended-release, injectable anti-TB drugs that can be administered periodically in a clinic, thus eliminating the problems of suboptimal adherence and treatment completion (1). This strategy might be particularly important for vulnerable populations, including children, adolescents and pregnant women. The potential of a single administration, providing a “one shot cure”, would render DOT requirements obsolete. In addition, the avoidance of oral delivery and the associated first metabolic passage through the liver might have additional benefits in terms of drug–drug interactions and would improve bioavailability.

Rifapentine, delamanid, bedaquiline and rifabutin have pharmacological and physicochemical characteristics that make them appealing candidates for long-acting administration with the drug nanoparticle suspension approach (half-life > 12 h, therapeutic concentrations < 1000 ng/mL and water solubility < 50 mg/mL). The activity of a long-acting injectable bedaquiline formulation has been demonstrated in a paucibacillary mouse model of TBI (1).

Coupled with a field-friendly diagnostic test to identify those at highest risk for progression to disease, a long-acting, extended-release TB formulation could enable a test-and-treat strategy that would greatly increase the possibility of TB elimination.

Reference

1. Kaushik A, Ammerman NC, Tyagi S, Saini V, Vervoort I, Lachau-Durand S, et al. Activity of a long-acting injectable bedaquiline formulation in a paucibacillary mouse model of latent tuberculosis infection. *Antimicrob Agents Chemother.* 2019;63:e00007–19.

