Target regimen profiles for TB treatment

Candidates: rifampicin-susceptible, rifampicin-resistant and pan-TB treatment regimens

WHO Library Cataloguing-in-Publication Data

Target regimen profiles for TB treatment: candidates: rifampicin-susceptible, rifampicin-resistant and pan-TB treatment regimens.

1. Tuberculosis – therapy. 2. Tuberculosis, multidrug-resistant 3. Antitubercular agents.
4. Rifampin – therapeutic use. I. World Health Organization.

ISBN 978 92 4 151133 9 (NLM classification: WF 360)

WHO/HTM/TB/2016.16

CONTENTS

ABBREVIATIONS AND ACRONYMS

ART	antiretroviral therapy
ARV	antiretrovirals
CNS	central nervous system
DDI(s)	drug-drug interaction(s)
DALY	disability-adjusted life year
DOT	directly observed treatment
DST E	drug susceptibility testing
EMA	ethambutol European Medicines Agency
FDA	United States Food and Drug Administration
FDC	fixed-dose combination
GDF	Global Drug Facility
GRADE	grading of recommendations assessment, development and evaluation
H or INH	isoniazid
HDPE	high density polyethylene
HIV	human immunodeficiency virus
M. tuberculosis	Mycobacterium tuberculosis
MDR-TB	multidrug-resistant tuberculosis
OBR	optimized background regimen
P	pyrazinamide
PDP	product development partnership
PK/PD	pharmacokinetics/pharmacodynamics
S	streptomycin
SAE	serious adverse event
SRA	stringent regulatory authority
TAG	technical advisory group
TEAE	treatment-emergent adverse event
TB	tuberculosis
WGS	whole genome sequencing
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

ACKNOWLEDGEMENTS

This document was developed by a team led by Christian Lienhardt, with the assistance of Lice González-Angulo. The core work was produced by the *Task Force on new TB drug policy development* comprising Gavin Churchyard (Chair), Grania Brigden, Frank Cobelens, Geraint Davies, Kelly Dooley, Joel Keravec, Payam Nahid, Norbert Ndjeka, Nguyen Viet Nhung, Michael Rich, Alena Skrahina, and Andrew A. Vernon. Additional contributions were made by Emily Kendall and David Dowdy from the Johns Hopkins University School of Medicine.

The World Health Organisation (WHO) would like to thank the group leads Cathy Bansbach, Payam Nahid and Michael Rich for their important roles in the development of this document.

WHO would like to thank the many contributors to the development of these target regimen profiles, including the participants of the Consensus Meeting for finalization of proposed targets: Koen Andries, Draurio Barreira, Henry Blumberg, Martin Boeree, Esteban Burrone, Marco Cavaleri, Yao Cheng, Daniel Chin, Alicia Chou, Daniela Cirillo, Francesca Conradie, Edward Cox, Charles Daley, Claudia Denkinger, Marc Destito, Keertan Dheda, Thomas Forissier, Lawrence Geiter, Jan Gheuens, Jeffrey Hafkin, Debra Hannah, Myriam Haxaire-Theuwes, Michael Kimerling, Giovanni Battista Migliori, Carol Nacy, Bern-Thomas Nyang'wa, Regina Osih, Patrick Phillips, Rada Savic, Géraldine Sbihi-Bouvier, Marco Schito, Cherise Scott, Sourya Shrestha, Melvin Spigelman, Zaid Tanvir, Wim Vandevelde, Robert Wallis, and Brenda Waning.

WHO/HQ Secretariat: Christian Lienhardt, Lice González-Angulo, Anna Dean, Inés García-Baena, Christopher Gilpin, Malgorzata Grzemska, Dennis Falzon, Ernesto Jaramillo, Avinash Kanchar, Linh Nhat Nguyen, Piero Olliaro, Hazim Timimi, Matteo Zignol, and Lou Maureen Comia. Overall guidance was provided by the Director of the Global TB Programme, Mario Raviglione.

The Bill and Melinda Gates Foundation is also gratefully acknowledged for its support for the development of this document, through grant project number OPP1052577.

ABSTRACT

There is an urgent need for safer, simpler, more efficacious and accessible treatment regimens for all forms of TB. The development of *target product profiles for TB drug regimens* (hereafter referred as *target regimen profiles*) is meant to assist drug regimen developers in identifying important regimen features and aligning these with patient and programmatic needs at country level.

Aimed at the pharmaceutical industry, research institutions, product development partnerships, donors, non-governmental organizations and civil society organizations, these target regimen profiles are based on the idea that TB drug research and development (R&D) is moving towards developing and testing TB regimens rather than individual drugs. The proposed target regimen profiles, which describe prioritized characteristics, take into account the needs of end users, care providers and policy-makers. The novelty of the target profile approach is to have the goal of a treatment regimen in mind very early in the process of drug development, with a desired outcome of shorter, less toxic, and operationally feasible regimens.

In selecting for the appropriate target regimen profiles, it was considered that a rapid drug susceptibility test—such as Xpert MTB/RIF, which allows simultaneous diagnosis of TB and detection of rifampicin resistant strains—would be an ideal triage test for current and novel regimens under routine programmatic conditions. Subsequently, profiles were developed for the treatment of rifampicin-susceptible (RS) and rifampicin-resistant (RR) TB, respectively—the latter being considered a proxy for MDR-TB. In addition, premised on the potential for a regimen of 3-4 entirely new anti-TB drugs for which minimal or no resistance would exist as a result of prior use in the community, a target regimen profile was developed for 'pan-TB treatment'. This regimen would be implemented in a simple and streamlined manner without need for drug-susceptibility testing—or for a separate treatment pathway for patients with at least RR-TB .

The target regimen profiles presented in this document specify the clinical indication of the regimen(s), the goals to be met, the measure of efficacy, the main safety aspects, the target population that will receive the treatment, and the intended end-users. In addition, they outline the most important performance and operational characteristics—with the term "minimal" used to refer to the lowest acceptable output for a characteristic, and "optimal" used to refer to the ideal target for a characteristic. The optimal and minimal characteristics define a range: it is therefore expected that new TB treatment regimens meet at least all of the required minimal characteristics, and, preferably, as many of the optimal characteristics as possible. In addition, certain attributes should be considered as 'priority' (i.e. their minimal targets must be met in order to make a 'go/no-go' decision), but others, deemed less essential, could be considered as potential trade-offs, and are therefore defined as 'desirable'.

The specific attributes and target criteria of each of these three target regimen profiles are presented in this document, together with the rationale for their selection.

1. INTRODUCTION

1.1 BACKGROUND

Treatment of tuberculosis (TB) relies on several bactericidal and sterilising drugs administered in combination for an adequate duration that is long enough to ensure the antimicrobial diversity and synergy of action to achieve durable cure and prevent the selection of drug-resistant mutants *(1, 2)*. Current treatment regimens are, however, unsatisfactory due to low efficacy, high toxicity, long duration and high cost, as in the conventional treatment of multidrug-resistant TB (MDR-TB); or interaction with other drugs, as is the case with rifampicin and some antiretrovirals (ARVs). Some combinations include drugs that have been registered for indications other than TB and are therefore used 'off-label,' such as oxazolidinones, carbapenems, or clofazimine, for the treatment of highly-resistant TB cases *(3, 4)*.

TB, including its drug-resistant forms, continues to be a major health problem worldwide (Figures 1 & 2). New TB drugs and regimens are urgently needed to improve cure rates for people with drug resistant TB (currently around 50% globally) and to shorten the treatment of both drug-susceptible and drug-resistant TB (currently at least six and at least 20 months respectively) *(5, 6)*. For the first time in decades, two new TB drugs, bedaquiline and delamanid, have become available. These are recommended by the World Health Organization (WHO) for the treatment of drug-resistant TB under certain conditions *(7, 8)*. These drugs have, however, been tested for efficacy as add-ons to the conventional (or longer) WHO-recommended treatment regimen for MDR-TB, though their optimal use in combinations that would lead to increased treatment efficacy while improving safety, toxicity and reducing treatment duration remains to be established[1] *(9)*. Other novel compounds are in clinical trials at time of writing, as are some re-purposed drugs, either as part of set treatment regimens or in addition to standard regimens *(10)*.

The development of new, efficacious combination regimens for TB treatment is lengthy and costly. Under the current system, if new drugs were added or substituted into existing regimens one at a time, it would take 20 to 30 years to develop a new regimen of three to four new drugs (5). Developing a regimen without the need to obtain individual drug approvals separately before testing novel combinations would substantially reduce both the duration of the regimen development pathway and the expenditure required to make progress *(11)*. It is therefore highly desirable that combination regimens including promising new drugs with current and/or repurposed drugs be tested early in the clinical development phase. This will aid early identification of optimal combination regimens for the treatment of drug-susceptible and drug-resistant TB that should be tested in phase II and phase III trials. The GTB treatment pipeline has expanded over the last decade, with various innovative candidate drugs and regimens being tested (Figure 3). However, more actions are needed to develop effective, accessible treatment combinations.

Development of shorter, simpler regimens combining new and existing drugs requires detailed information on their respective safety and toxicity *(12, 13)*; their potential for drug-drug interactions (DDIs) *(14)*; their propensity for development of drug resistance while on therapy *(15, 16)*; and their use in specific patient populations such as persons infected with human immunodeficiency virus (HIV), pregnant women, and children. The development of target product profiles allows the identification of desired product attributes or priorities to be considered during the product development process; expanding on this, the determination of target profiles for TB treatment regimens (i.e. target regimen profiles) is expected to assist developers in aligning the characteristics of new TB treatment regimens with programmatic needs at country level.

The elements of any target profile are usually chosen based on expert consensus, but no formal framework exists for identifying and prioritizing the components of TB treatment regimens that could determine their patient- and population-level impact. At a minimum, the target profiles for TB treatment regimens should specify: the clinical indication of the regimen; the goal to be met and the measure of efficacy (e.g. non-relapsing cure); the target population that will receive the treatment; the level of implementation in the healthcare system; and the intended end users. In addition, these targets should outline the most important performance and operational characteristics (with the term "minimal" used to refer to the lowest acceptable output for a characteristic, and "optimal" used to refer to its ideal target), and the likely set of users. The optimal and minimal characteristics define a range: it is therefore expected that the resultant products—TB treatment regimens—will at least meet all of the required minimal characteristics, and as many of the optimal characteristics as possible.

1. The possibility for inclusion of bedaquiline as an element of an all-oral and/or shorter combination treatment of MDR-TB is currently being tested. Working Group on New TB Drugs, 2016. Drug TB Pipeline. Available from: http://www.newtbdrugs.org/pipeline.php

Fig. 1: Estimated TB incidence rates, 2015
Source: *Global TB Report 2016*

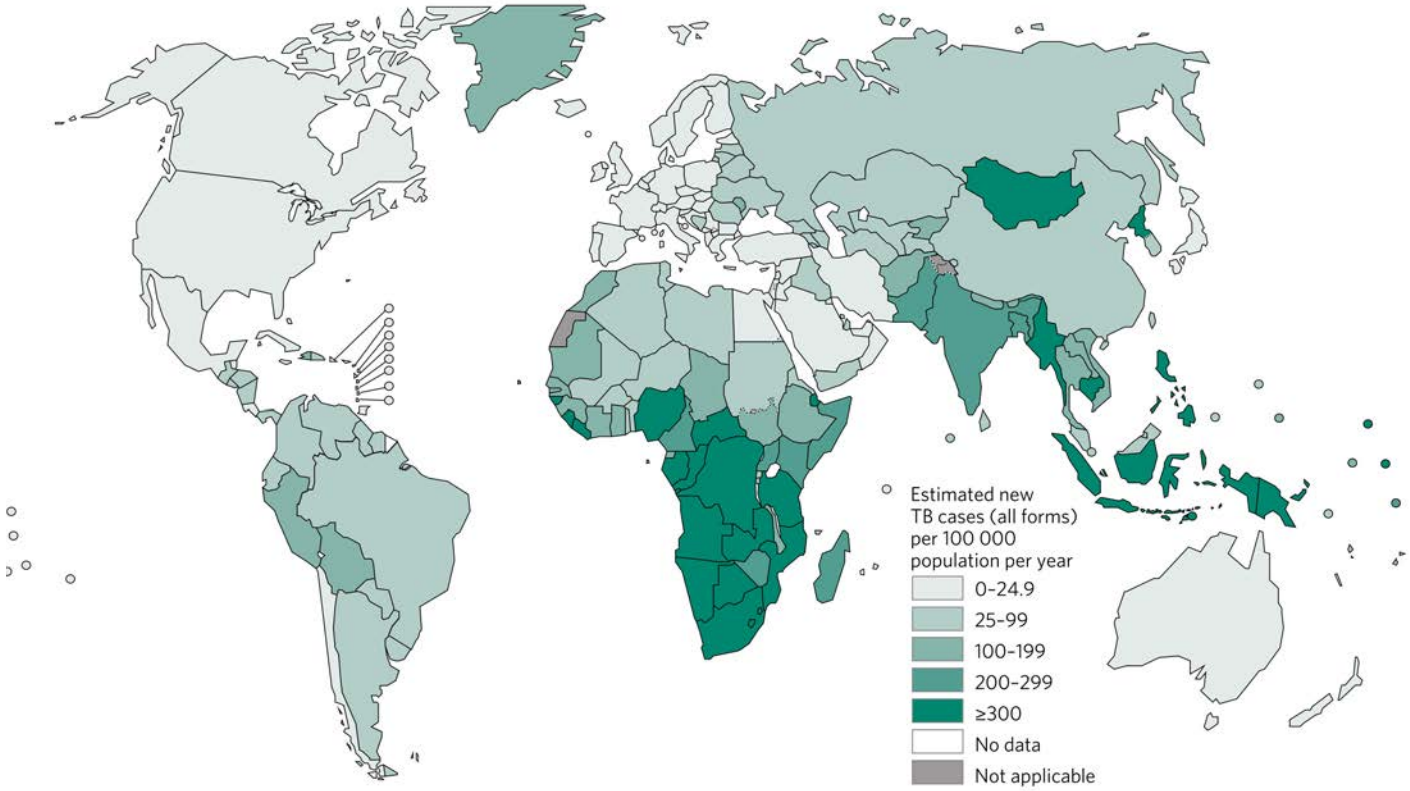

Fig. 2: Percentage of new TB cases with MDR/RR-TB, 2015
Source: *Global TB Report 2016*