HHS Public Access

Author manuscript

Eur Respir J. Author manuscript; available in PMC 2018 January 25.

Published in final edited form as:

Eur Respir J. 2017 January ; 49(1): . doi:10.1183/13993003.02352-2016.

Target regimen profiles for treatment of tuberculosis: a WHO document

Christian Lienhardt[1], **Payam Nahid**[2], **Michael L. Rich**[3], **Cathy Bansbach**[4], **Emily A. Kendall**[5], **Gavin Churchyard**[6], **Lice González-Angulo**[1], **Lia d'Ambrosio**[7], **Giovanni Battista Migliori**[7], and **Mario Raviglione**[1]

[1]Research for TB Elimination, Global TB Program (GTB), World Health Organization, Geneva, Switzerland [2]Division of Pulmonary and Critical Care Medicine, University of California, San Francisco, San Francisco General Hospital, San Francisco, CA, USA 94110 [3]Division of Global Health Equity, Brigham and Women's Hospital; Harvard Medical School; Partners In Health, Boston, MA, USA 02199 [4]Global Health Program, Bill & Melinda Gates Foundation; Seattle, WA, USA 98102 [5]Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, MD, USA 21205 [6]Aurum Institute, Johannesburg, South Africa, School of Public Health, University of Witwatersrand, Johannesburg, South Africa [7]World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Maugeri Care and Research Institute, IRCCS, Tradate, Italy

Keywords

WHO; target regimen profiles; tuberculosis; treatment; DS-TB; DR-TB

Treatment of tuberculosis (TB) relies on a combination of bactericidal and sterilising drugs administered for an adequate duration of time to ensure synergy of action to achieve definitive cure and prevent the selection of drug-resistant mutants (1). Current treatment regimens are, however, not ideal, due to long duration and some toxicity. Particularly unsatisfactory are regimens recommended for the treatment of multi-drug resistant (MDR)[1] or extensively drug-resistant (XDR) TB that have lower efficacy, significant toxicity, longer duration and high costs (2–5). New TB drugs and regimens are needed to improve cure rates, lessen toxicity, and shorten the treatment of both drug-susceptible and drug-resistant TB (currently at least 6 and 9–20 months, respectively) (6, 7). Two TB drugs (bedaquiline and delamanid) (8, 9) have become available and are recommended by the World Health Organization (WHO) for the treatment of MDR-TB under certain conditions(10, 11). However, these drugs have so far been tested for efficacy as add-on to conventional WHO-recommended treatment for MDR-TB only, and their optimal use in combinations that could lead to increased treatment efficacy while improving safety and reducing toxicity still remains to be established[2] (12, 13). Other novel compounds, as well as re-purposed drugs,

Author for correspondence: Christian Lienhardt.

[1]A form of tuberculosis with bacilli strains resistant to at least rifampicin and isoniazid

[2]DR-TB Clinical Trials Progress Report -http://www.resisttb.org/?pageid=1602.

are currently in clinical trials, either as part of novel treatment regimens or in addition to current standard of care (14).

The development of TB drugs is lengthy and costly: if new drugs are added to or substituted within existing regimens one at a time, it would take 15 to 20 years to develop a new regimen of three to four new drugs to treat TB (6, 7). Developing a novel regimen without going through intermediary steps to obtain individual drug approvals separately and only then beginning to test novel combinations would substantially reduce the duration of the whole regimen development. It will also reduce the expenditures needed to make significant progress in the field (15, 16). Combination regimens including one or more promising new or re-purposed drugs should be tested early in the clinical development process to identify *optimal combination regimens* for the treatment of drug-susceptible and drug-resistant TB to be tested in Phase II and III trials.

Development of shorter and simpler regimens combining new and existing drugs requires detailed information on their respective activity, safety and toxicity (17–19), including potential drug-drug interactions, propensity for development of drug resistance while on therapy (20–23) and clinical use in specific patient populations (such as persons with HIV/AIDS, pregnant women, children (4)). Given these complexities, Target Product Profiles (TPPs) are usually composed as a guide to identify desired product attributes and characteristics to be considered during the development process (24).

The aim of this paper is to discuss the concept and role of TPPs for new anti-TB regimens, referred hereafter as *"Target Regimen Profiles"*, and describe the outcomes of the recent process led by WHO to develop these profiles (25).

Objective and role of Target Regimen Profiles for TB treatment

Considering the need for safer, simpler, more efficacious and accessible treatment regimens for all forms of TB, target regimen profiles for TB treatment have been developed in a synergistic effort by the WHO/Global TB Programme and the WHO Task Force on New TB Drug Policy Development, with the contribution of a large range of experts and stakeholders.

The novelty of this approach is to have the goal of the treatment regimen in mind very early in the process of drug development, and relies on the fact that TB drug research and development should move rapidly towards developing and testing TB *regimens* rather than *individual drugs.* On this basis, target regimen profiles for TB treatment have been developed to describe the targets and specifications that developers should meet for appropriate performance and adequate operational characteristics of new TB treatment regimens, considering the needs of end-users. At a minimum, the target regimen profiles specify the clinical indication of the regimen(s), the goal 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 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 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.

The target audience includes pharmaceutical industry, academia, research institutions, product development partnerships, non-governmental organisations, potential investors and donors (25).

Methods to develop the Target Regimen Profiles

The initial profiles were drafted on the basis of outcomes of expert group meetings, an initial stakeholder survey, mathematical modelling, and interviews of a wide range of experts and stakeholders.

First, the candidate regimen will consist of a minimum combination of drugs targeting all possible populations of bacilli in the patient (i.e. including those proliferating in local acidic conditions or in states of brief sporadic metabolism or replication) and having a clear sterilizing effect (so as to ensure non-relapsing cure within a few months after starting the treatment). In defining the potential target regimen profiles, Xpert MTB/RIF was assumed to be widely available as a 'triage test' under routine programmatic conditions, based on the current worldwide implementation process and scale-up. In that scenario, indication on whether the bacilli harboured by the TB patient are rifampicin-susceptible or not will be known from the start. 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 (i.e. excluding rifampicin, isoniazid, pyrazinamide) 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[3].

Mathematical modelling was then used to estimate the relative impact of selected regimen characteristics on population-wide TB incidence and mortality. The selected characteristics were: (1) efficacy (achieving high non-relapsing cure rates), (2) treatment duration, (3) adherence, (4) medical contraindications, (5) barrier to resistance, and (6) baseline prevalence of resistance to drugs in the regimen. The influence of each characteristic on expected incidence and mortality outcomes was evaluated as the characteristic ranged from a minimum acceptable value to an optimistic target.

Then, an internet-based survey was conducted to identify what would be the priority attributes that a wide audience of stakeholders would value for the development of the target regimen profiles. It contained core questions distributed in four main categories (efficacy; safety; adherence; and operational considerations) (25). Finally, a Delphi web–based consultation was organised to gather input from the larger TB control and research community and a consensus meeting took place to review the draft target profiles. The final

[3]Then, whichever rapid tests of drug-resistance might be developed/available, they would suitably come as a complement to further refine the patients' needs given the resistance profile.

document was formally launched at the European Respiratory Society Congress in London (Figure 1).

The details of the three target regimen profiles are presented below.

1. Target regimen profile for rifampicin-susceptible TB

Rationale—Despite the wide availability of a highly efficacious, low-cost regimen of 6 months duration for the treatment of RS-TB, improvements are still needed if we are to achieve the WHO targets set within the context of the End TB Strategy (26). The current 6-months regimen has several limitations including drug-related adverse events, challenging drug-drug interactions (in particular with some anti-retroviral medicines), and difficulty in ensuring adherence for the full duration of treatment across all settings. By improving adherence to treatment, shorter regimens would result in better outcomes and lower risk of acquisition of resistance, faster recovery, shorter period at risk of side effects, and lower patient and programme costs (6,7). Future RS-TB regimens would ideally be active also against strains that are mono-resistant to any other first-line drug except rifampicin.

Key attributes—The characteristics of the target regimen profile for RS-TB treatment are summarised in Table 1. To achieve these, it will be necessary to use multiple-drug combinations with both bactericidal and sterilizing efficacy according to well established principles of TB chemotherapy (1) to assure durable and relapse-free cure.

2. Target regimen profile for rifampicin-resistant TB

Rationale—About 480,000 new MDR-TB cases and an additional 100,000 cases of rifampicin-resistant disease were estimated to have occurred in the world in 2015 (27). However only 125,000 MDR-TB patients were reported by countries to have initiated treatment (27). The conformity of these regimens to those recommended by WHO and the quality of medicines used is usually unknown, and only about one half of patients treated globally is reported to complete treatment successfully(27, 28).

In the absence of formal randomized controlled trials, the *conventional* (or *longer*) MDR-TB treatment recommended by WHO (based on a minimum of 5 drugs) is the result of expert opinion based on observational studies (29), and there has been no head-to-head comparison of one MDR regimen versus another MDR regimen of any kind[4] (30, 31). As a consequence, using the GRADE system definitions, the available evidence is generally of “low” or “very low” quality (32). In addition, the complexity and limited efficacy of current regimens may predispose to development of additional resistance (22, 23). Finally, it is imperative to lower the cost of MDR-TB regimens to make them accessible in the poorest settings (15, 16).

The newly WHO-recommended *shorter* MDR-TB treatment regimen of 9–12 months has shown rates of relapse-free cure topping 85% in different Asian and African countries as part of observational studies[5] (33–35). This regimen is composed of 7 drugs (5 of which also

[4]Of note, a trial is currently underway to evaluate a short MDR regimen versus the 20-month WHO Standard.

part of the *longer* regimen) known to have good bactericidal activity against MDR-TB strains. The 2 newly available agents, bedaquiline (9, 10) and delamanid (8, 11), have shown potential to improve efficacy of MDR regimens *on top of* the conventional WHO-recommended regimen. Some new drugs currently in the drug development pipeline (e.g. pretomanid, sutezolid) (36) show promise for use in MDR-TB regimens together with re-purposed drugs (eg. linezolid, clofazimine, fluoroquinolones) (3, 37). The goal of this TRP is to identify a suitable combination regimen early in the development process that would be together safe, efficacious, and of short duration (38).

Key attributes—The characteristics of this TRP are summarised in Table 2. The optimal regimen is expected to be efficacious and safe in all RR-TB patients – whether they have already received a TB treatment or not. DST may be needed at the start of treatment to diagnose the resistance pattern to determine whether a particular regimen is indicated. Furthermore, DST will be needed for monitoring amplification of resistance in an individual patient and resistance prevalence in a population.

In the optimal case, efficacy[6] should approach that of the standard WHO regimen for DS-TB. Furthermore, it is expected that, as the efficacy of drugs included in the regimens increases, the total number of drugs constituting the regimen can decrease. This should minimize the probability of drug-drug interaction/toxicity and increase the ability to co-formulate the individual drugs into fixed dose combinations. Decreased complexity of a RR-TB regimen will likely be readily accepted by national TB programmes as they will be easier to implement.

3. Target regimen profile for Pan-TB treatment

Rationale—A highly effective, safe and well tolerated 3–4 drug fully oral regimen that could be administered to any TB patient regardless of drug resistance profile would revolutionize the treatment of TB (25). To allow for universal adoption, the regimens should be simple to administer (ideally once daily), and have low propensity for drug-drug interactions. As there should be no or minimal prior resistance to the drugs included in the regimen, it may be used empirically without the need for drug susceptibility testing (DST), eliminating treatment delays.

Key attributes—The intended use case assumes this simple, novel regimen is simultaneously studied and approved for *empirical use* in both RS- and RR-TB patients with bacilli strains sensitive to the new drugs. This would be particularly important in areas with high prevalence of MDR-TB and low availability of DST, where patients may be treated inappropriately and continue to transmit disease for extended periods (see Table 3)

[5]WHO recommends the use of this regimen conditionally among selected MDR/RR-TB patients, i.e. pulmonary TB cases with no previous exposure or known resistance to fluoroquinolones or injectable drugs

[6]bacteriologic cure without relapse in at least one-year follow up, among patients who are not lost to follow up

Forecasted role of TRPs for new regimens

The target regimen profiles presented here describe the series of attributes that are considered essential for novel treatment of TB, such as efficacy, safety, toxicity, drug-drug interactions, potential of acquisition of drug resistance. Satisfying all of these characteristics in a single regimen, however, will be difficult to achieve in the short term, and regimen developers might have to face trade-offs: for example, increasing efficacy (cure rates) or safety *vs*. shortening treatment duration, or making regimens simple and well tolerated vs. making them more complex and robust to emergence of drug resistance.

It should be understood that, for an infectious disease such as TB with large global burden and ongoing person-to-person transmission, the efficacy of the new regimens will depend heavily on operational factors that also affect a regimen's ability to fulfil its role (e.g. background antimicrobial resistance, resistance in the MDR-TB patient population to important existing TB drugs, development of resistance to new drugs and slow uptake of new drugs). For these reasons, these target regimen profiles give indications on the respective attributes to be considered at the *developmental* stage – but these should not be dissociated from the factors to be considered at *implementation* stage.

All drugs used in a study regimen should meet either WHO prequalification or certification from a stringent regulatory authority or be study drugs that are tested in a facility with good manufacturing practice certification for quality assurance. It would be suitable that each individual drug component *or* the regimen as a whole be approved for use in TB by at least one stringent regulatory authority. If a regimen is recommended by the WHO using GRADE evidence review, it is expected that the regimen, or its individual components, be widely available in quality assured formulations within two years.

Strategies to lower the regimen costs should be considered from the outset, with adherence to the principles of access to medicine. Once a new regimen is established to be superior to current regimens in terms of safety or efficacy, then stakeholders should continue to work to bring down the cost of the regimen by working on costs of individual drugs, as well increasing the demand for the new regimen. Finally, it is assumed that within a few years of release, the production for supply of the drugs in the new regimen could be rapidly scaled-up to match demand with a corresponding decrease in the price. It is also expected that a new regimen will reduce non-drug costs aspects (e.g. monitoring visits, adherence, patient support, safety aspects, etc.) thereby improving simplicity of use, and these benefits may offset increased drug costs.

In conclusion, the *target regimen profiles* proposed in this document represent a milestone towards the development of new regimens for the treatment of all forms of TB and will serve consortia linking drug developers, academics, researchers, public health institutions and non-governmental organisations.

References

1. Grosset J. Bacteriologic basis of short-course chemotherapy for tuberculosis. Clin Chest Med. 1980; 1(2):231–41. [PubMed: 6794976]

2. Falzon D, Jaramillo E, Schunemann HJ, Arentz M, Bauer M, Bayona J, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Eur Respir J. 2011; 38(3):516–28. [PubMed: 21828024]
3. Hughes J, Isaakidis P, Andries A, Mansoor H, Cox V, Meintjes G, et al. Linezolid for multidrug-resistant tuberculosis in HIV-infected and -uninfected patients. Eur Respir J. 2015; 46(1):271–4. [PubMed: 25837033]
4. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016; 63(7):e147–95. [PubMed: 27516382]
5. Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori GB. Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. Eur Respir J. 2016; 47(2):394–402. [PubMed: 26828052]
6. Lienhardt C, Raviglione M, Spigelman M, Hafner R, Jaramillo E, Hoelscher M, et al. New drugs for the treatment of tuberculosis: needs, challenges, promise, and prospects for the future. J Infect Dis. 2012; 205(Suppl 2):S241–9. [PubMed: 22448022]
7. Zumla A, Chakaya J, Centis R, D'Ambrosio L, Mwaba P, Bates M, et al. Tuberculosis treatment and management–an update on treatment regimens, trials, new drugs, and adjunct therapies. Lancet Respir Med. 2015; 3(3):220–34. [PubMed: 25773212]
8. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med. 2012; 366(23):2151–60. [PubMed: 22670901]
9. Pym AS, Diacon AH, Tang SJ, Conradie F, Danilovits M, Chuchottaworn C, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J. 2016; 47(2): 564–74. [PubMed: 26647431]
10. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance (WHO/HTM/TB/2013.6). Geneva: World Health Organization; 2013.
11. World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance (WHO/HTM/TB2014.23). Geneva: World Health Organization; 2014.
12. Migliori GB, Lienhardt C, Weyer K, van der Werf MJ, Blasi F, Raviglione MC. Ensuring rational introduction and responsible use of new TB tools: outcome of an ERS multisector consultation. Eur Respir J. 2014; 44(6):1412–7. [PubMed: 25435528]
13. Nunn AJ, Rusen ID, Van Deun A, Torrea G, Phillips PP, Chiang CY, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials. 2014; 15:353. [PubMed: 25199531]
14. Working Group for New TB Drugs. Clinical pipeline. Available at: http://www.newtbdrugs.org/pipeline/clinical. Last access: 19 September 2016
15. Gospodarevskaya E, Tulloch O, Bunga C, Ferdous S, Jonas A, Islam S, et al. Patient costs during tuberculosis treatment in Bangladesh and Tanzania: the potential of shorter regimens. Int J Tuberc Lung Dis. 2014; 18(7):810–7. [PubMed: 24902557]
16. Diel R, Vandeputte J, de Vries G, Stillo J, Wanlin M, Nienhaus A. Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. Eur Respir J. 2014; 43(2):554–65. [PubMed: 23949960]
17. Winters N, Butler-Laporte G, Menzies D. Efficacy and safety of World Health Organization group 5 drugs for multidrug-resistant tuberculosis treatment. Eur Respir J. 2015; 46(5):1461–70. [PubMed: 26381514]
18. Semvua HH, Kibiki GS, Kisanga ER, Boeree MJ, Burger DM, Aamoutse R. Pharmacological interactions between rifampicin and antiretroviral drugs: challenges and research priorities for resource- limited settings. Ther Drug Monit. 2015; 37(1):22–32. [PubMed: 24943062]

19. Tiberi S, Payen MC, Sotgiu G, D'Ambrosio L, Alarcon Guizado V, Alffenaar JW, et al. Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. Eur Respir J. 2016; 47(4):1235–43. [PubMed: 26965290]
20. Cegielski JP, Dalton T, Yagui M, Wattanaamomkiet W, Volchenkov GV, Via LE, et al. Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. Clin Infect Dis. 2014; 59(8):1049–63. [PubMed: 25057101]
21. Vasakova M. Challenges of antituberculosis treatment in patients with difficult clinical conditions. Clin Respir J. 2015; 9(2):143–52. [PubMed: 24521461]
22. Koser CU, Javid B, Liddell K, Ellington MJ, Feuerriegel S, Niemann S, et al. Drug-resistance mechanisms and tuberculosis drugs. Lancet. 2015; 385(9965):305–7. [PubMed: 25706840]
23. Gao J, Ma Y, Du J, Zhu G, Tan S, Fu Y, et al. Later emergence of acquired drug resistance and its effect on treatment outcome in patients treated with Standard Short-Course Chemotherapy for tuberculosis. BMC Pulm Med. 2016; 16:26. [PubMed: 26846562]
24. Guidance for Industry and Review Staff: Target Product Profile — A Strategic Development Process Tool. United States Food and Drug Administration; Dec 31. 2012 (Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080593.pdf) [press release]2007
25. World Health Organization. Target Regimen Profiles for TB Treatment (WHO/HTM/TB/2016.16). Geneva: World Health Organization; 2016. (Available at: http://apps.who.int/iris/bitstream/10665/250044/l/9789241511339-eng.pdf)
26. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new End TB Strategy. The Lancet. 2015; 385(9979):1799–801.
27. World Health Organization. Global tuberculosis report 2016 (WHO/HTM/TB/2016.13). Geneva: World Health Organization; 2016. (Available at: http://apps.who.int/iris/bitstream/10665/250441/l/9789241565394-eng.pdf?ua=l):
28. Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox H, Holtz TH, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on MDR-TB outcomes. European Respiratory Journal. 2012 erj01347-2012.
29. World health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis-2011 update. (WHO/HTM/TB/2011.6) [Internet]. Geneva: World Health Organization; 2011. Available from: http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf
30. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012; 9(8):el001300.
31. Falzon D, Mirzayev F, Wares F, Baena IG, Zignol M, Linh N, et al. Multidrug-resistant tuberculosis around the world: what progress has been made? European Respiratory Journal. 2015; 45(1):150–60. [PubMed: 25261327]
32. WHO treatment guidelines for drug-resistant tuberculosis 2016 update (WHO/HTM/TB/2016.04). Geneva: World Health Organization; 2016. (Available at: http://www.who.int/tb/MDRTBguidelines2016.pdf)
33. Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. American journal of respiratory and critical care medicine. 2010; 182(5):684–92. [PubMed: 20442432]
34. Kuaban C, Noeske J, Rieder H, Ait-Khaled N, Abena Foe J, Trébucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. The International Journal of Tuberculosis and Lung Disease. 2015; 19(5):517–24. [PubMed: 25868018]
35. Piubello A, Harouna SH, Souleymane M, Boukary I, Morou S, Daouda M, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. The International Journal of Tuberculosis and Lung Disease. 2014; 18(10):1188–94. [PubMed: 25216832]
36. Dawson R, Diacon AH, Everitt D, van Niekerk C, Donald PR, Burger DA, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients

with drug-susceptible or drug-resistant pulmonary tuberculosis. The Lancet. 2015; 385(9979): 1738–47.

37. Sotgiu G, Centis R, D'Ambrosio L, Alffenaar J-WC, Anger HA, Caminero JA, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. European Respiratory Journal. 2012; 40(6):1430–42. [PubMed: 22496332]
38. Brigden G, Nyang'wa B-T, du Cros P, Varaine F, Hughes J, Rich M, et al. Principles for designing future regimens for multidrug-resistant tuberculosis. Bulletin of the World Health Organization. 2014; 92(1):68–74. [PubMed: 24391302]
39. Migliori GB, Sotgiu G. Treatment of tuberculosis: have we turned the comer? Lancet. 2012; 380(9846):955–7. [PubMed: 22828484]

Figure 1.
Picture of the official launch of the WHO document at the ERS Congress 2016

Table 1

Characteristics of the Target Regimen profile for rifampicin-susceptible tuberculosis (TB)

	Attribute	**Minimum** ***The minimal target should be considered as a potential go/no go decision point***	**Optimum** ***The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact***
1	*Indication*	Active against rifampicin-susceptible *M. tuberculosis* strains	Active against rifampicin-susceptible *M. tuberculosis* strains including monoresistance to any drug except rifampicin.
2	*Efficacy and duration of treatment*	A regimen of four months or less with efficacy not inferior to the current standard of care six-month regimen for drug-susceptible TB.	A regimen of two months or less with efficacy not inferior to the current standard of care six-month regimen for drug- susceptible TB.
3	*Target population*	All age groups, irrespective of HIV status.	All age groups, irrespective of HIV status.
4	*Safety and Tolerability*	Incidence and severity of adverse events no worse than for standard of care. No more than monthly clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes etc.).	Incidence and severity of adverse events better than for standard of care. No active clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes, etc.).
5	*Drug-drug interaction and metabolism*	Ability to use safely without active laboratory testing or monitoring with: • First-line antiretroviral therapy (ART) regimen(s) • Rifamycins (if a rifamycin is included in the regimen) • Drugs that induce or inhibit P450 liver enzymes • Proarrhythmic drugs that prolong QT/QTc interval.	*No dose adjustment* with other medications and ability to use safely without active laboratory testing or monitoring with: • First-line ART regimens and co-trimoxazole • Rifamycins (if a rifamycin is included in the regimen) • Drugs that induce or inhibit P450 liver enzymes • Proarrhythmic drugs that prolong QT/QTc interval.
6	*Formulation dosage and route of administration*	Formulation to be oral for all drugs in regimen, including paediatrics. Well tolerated and simple to administer to enhance adherence.	Exclusively *oral delivery* (preferably once daily); ideally without the need for weight band adjustments, and suitable for fixed dose combination formulations. Parenteral formulations would allow to treat severe cases. 3 or less pills per day
7	*Stability/Shelf Life*	Without cold storage requirements; with shelf lives of at least 3 years for all the drugs composing the regimen.	Without cold storage requirements; with shelf lives of at least 5 years for all the drugs composing the regimen.
8	*Special Populations*	Safe on a wide range of patients (children, pregnant women, and patients with co-morbidities -HIV, viral hepatitis, diabetes, others)- and low to no drug-drug interactions.	For women of child bearing potential and pregnant women, availability of human data that do not indicate that the component drugs increase the overall risk of structural abnormalities, and the drugs are safe with breastfeeding.
9	*Barrier to emergence of drug resistance (propensity to develop resistance, generation of cross-resistance)*	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than $1/10^7$ mutations/bacterium/ generation. New resistance to one or more drugs in the regimen emerges in less than 1% of treatment courses when taken as prescribed and when no pre-existing resistance to the drugs in the regimen exists.	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than $1/10^9$ mutations/bacterium/ generation. Essentially no acquired resistance (<0.01%) when regimen is taken as prescribed and no pre-existing resistance to the drugs in the regimen exists.

*The term “not inferior” is intentionally used in place of non-inferiority, which is a trials design and methodology term.

Table 2

Characteristics of the Target Regimen profile for rifampicin-resistant TB

	Attribute	Minimum *The minimal target should be considered as a potential go/no go decision point*	Optimum *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact*
1	*Indication*	The rifampicin-resistant TB regimen is indicated for patients infected with rifampicin-resistant strains (including MDR-TB). Indication may be contingent upon additional resistance to existing first or second line drugs, and supported by appropriate DST.	The rifampicin-resistant TB regimen is indicated for all patients infected with rifampicin-resistant TB strains, with usage consistent with principles of good antibiotic stewardship.
2	*Efficacy and duration of treatment*	A 6–12 months treatment regimen. Efficacy (bacteriologic cure without relapse in at least one-year follow up, among patients who are not lost to follow up) should be not inferior to the WHO recommended standard of care for MDR-TB.	Less than or equal to 6 months treatment regimen. Efficacy should be greater than 90%.
3	*Target population in respect to age.*	At least adolescent (age 12–19) and adults	All age groups irrespective of severity of disease, pulmonary or extrapulmonary, or HIV status.
4	*Safety and Tolerability*	Serious adverse events (SAEs) no more than 5%, and treatment discontinuation due to treatment emergent adverse events (TEAEs) no more than 2.5%. The QT prolongation and proarrhythmic effects of the regimen would not put the patient at a moderate or high risk of arrhythmias or sudden death.	SAEs are no more than 2%, and treatment discontinuation due to TEAEs no more than 2%. The regimen would have no or insignificant QT prolongation or proarrhythmic effects.
5	*Drug-drug interactions and metabolism*	Ability to adjust dosing or perform safe monitoring for DDIs with: • At least one first-line ART regimen • Drugs that induce or inhibit P450 liver enzymes • Pro-arrhythmic QT prolonging drugs	No dose adjustment with other medications and ability to safely use without active laboratory tests monitoring with: • ART regimens and cotrimoxizole • Drugs that induce or inhibit P450 liver enzymes • Pro-arrhythmic QT prolonging drugs
6	*Formulation dosage, route of administration, and dosing (including schedule)*	Formulation to be oral for all drugs in regimen. Ability to deliver paediatric dosing of the regimen. Twice daily dosing and manageable food restrictions.	Formulation to be oral. FDC formulations available (desirable to have no weight adjustment for adults) Paediatric (oral), and IV formulations must also be available. One daily or intermittent dosing. (Preference for once weekly or only monthly as the intermittency)
7	*Stability/Shelf-Life*	3 years for all drugs in the regimen. No cold chain requirements.	5 years for all drugs in the regimen. No cold chain requirements.
8	*Special populations*	Adults and women of childbearing potential. Increased acceptable risk (benefits outweigh the risk in most cases) for pregnancy women, paediatrics, and those with significant renal or hepatic disease. Inclusions of patients with co-morbidities including: • HIV • Diabetes • Alcoholism • Viral hepatitis	Adults, paediatrics, women of childbearing potential, pregnant women. Ability to use the regimen with patients with significant renal disease. Inclusions of patients with comorbidities including: • HIV • Diabetes • Alcoholism • Viral hepatitis • Opiate addiction
9	*Barrier to emergence of drug resistance (propensity to develop*	New resistance to one or more drugs in the regimen emerges in fewer than 2% of treatment courses when taken as prescribed and when no pre-existing resistance to the drugs in the regimen exists.	Essentially no acquired resistance (<0.1%) when regimen is taken as prescribed and no pre-existing resistance to the drugs in the regimen exists.

	Attribute	**Minimum** ***The minimal target should be considered as a potential go/no go decision point***	**Optimum** ***The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact***
	resistance, generation of cross-resistance)		

Table 3

Characteristics of the Target Regimen profile for pan-TB treatment

	Attribute	Minimum *The minimal target should be considered as a potential go/no go decision point*	Optimum *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact*
1	*Indication*	Indicated as first-line treatment for pulmonary TB without need to determine rifampicin resistance	Indicated as first-line treatment for pulmonary TB without need to determine rifampicin resistance
2	*Efficacy and duration of treatment*	Not inferior to rifampicin-susceptible TB standard of care in a six-month regimen.	Not inferior to rifampicin-susceptible TB standard of care in regimen of four months or less.
3	*Target Population*	Indicated for all cases (adults and children, including HIV co-infected).	Same
4	*Safety and Tolerability*	Incidence and severity of adverse events no worse than RS-TB standard of care	Incidence and severity of adverse events better than for RS-TB standard of care.
5	*Drug-Drug Interactions and Metabolism*	Ability to adjust dosing or perform safe monitoring for DDIs with at least one ART regimen, drugs metabolized by P450 liver enzymes and pro-arrhythmic QT interval prolonging drugs	No need for dose adjustment and ability to safely use without active laboratory test monitoring. Specifically, not interfering with antiretrovirals, drugs metabolized by P450 liver enzymes and pro-arrhythmic QT interval prolonging drugs.
6	*Formulation Dosage and Route of Administration*	Oral, once (or, if balanced by exceptional performance on other attributes, twice) daily, containing ≤ 4 novel antibacterial compounds. Suitable for fixed-dose combination.	Oral, once daily dosing with no special weight banding.
7	*Stability / Shelf Life*	Stable for ≥ 3 years in climate zones 3 and 4 at 30C / 75% RH	Stable for ≥ 5 years in climate zones 3 and 4 at 30C/75% RH
8	*Barrier to emergence of drug resistance, generation of cross-resistance)*	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than $1/10^7$ mutations/bacterium/ generation. New resistance to one or more drugs in the regimen emerges in fewer than 2% of treatment courses when taken as prescribed and no pre-existing resistance to the drugs in the regimen exists.	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than $1/10^9$ mutations/bacterium/ generation. Essentially no acquired resistance (<0.1%) when regimen is taken as prescribed and no pre-existing resistance to the drugs in the regimen exists.