Technical Basis of the endTB Observational Study

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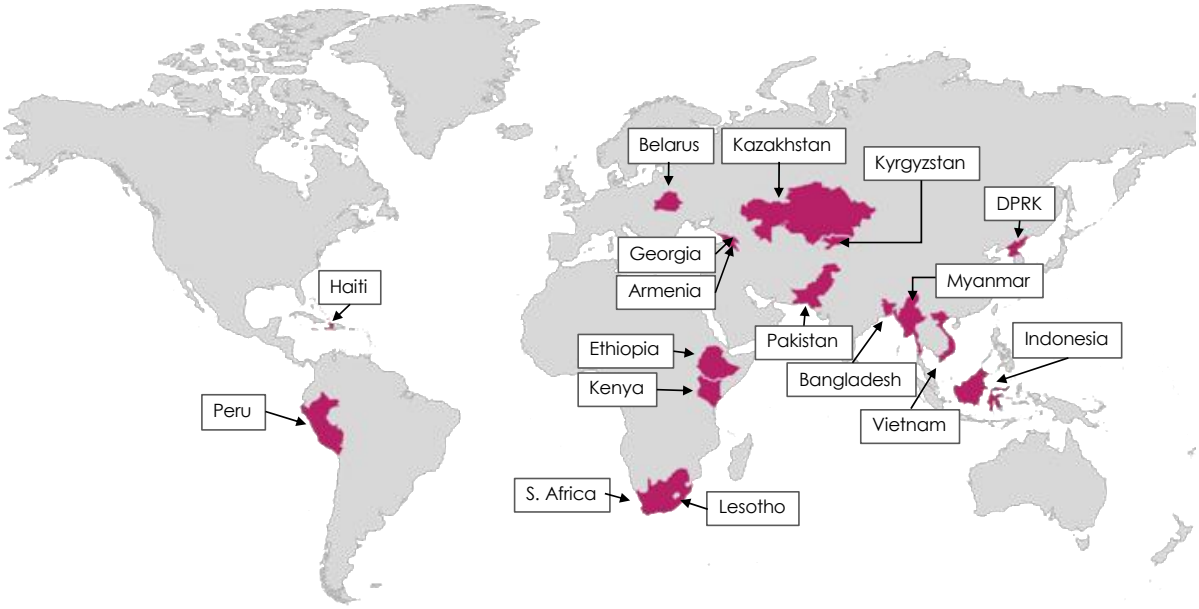
Introduction

The endTB (Expand New Drug Markets for TB) consortium consists of three NGOs: Partners In Health (PIH), Médecins Sans Frontières (MSF) and Interactive Research and Development (IRD). Funded by Unitaid, the objective of endTB is to promote better and safer MDR-TB treatment regimens. endTB works to increase access to bedaquiline, delamanid and repurposed TB drugs, while carefully studying the results of new regimens that include these drugs. There are three major studies included in endTB: the endTB Observational Study, the endTB Clinical Trial, and the endTB-Q Trial.

The endTB Observational Study currently has sites in 17 countries. In each country, sites enroll patients on treatment with bedaquiline and delamanid according to National TB Program guidelines, while collecting clinical and bacteriological data related to efficacy and safety.

endTB Observational Study countries



Many of the endTB Observational Study tools have been found to be useful for clinicians and programs that are starting to use the new TB drugs and regimens:

- *endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs* (English, Russian, Spanish, French): practical advice for clinicians, including regimen design and side effect management.
- MSF Pharmacovigilance Unit forms (English, Russian, Spanish, French): Serious Adverse Event (SAE) report form, Pregnancy report form, and the TB Severity Grading Scale used by all endTB sites to grade Adverse Events (AE).

This Technical Basis document provides the rationale for clinical decision-making, screening tools and data definitions that are used at the endTB Observational Study sites. This is a living document. If you would like to suggest an additional topic, please email us at endTB1@pih.org.

Abbreviations

ACTG	AIDS Clinical Trial Group
AE	Adverse Event
ART	Anti-retroviral therapy
BPNS	Brief Peripheral Neuropathy Screen
DR-TB	Drug-resistant Tuberculosis
DAA	Direct-Acting Antivirals
DST	Drug Susceptibility Testing
ECG	Electrocardiogram
endTB	Expand New Drugs for TB
HbA1c	Hemoglobin A1c
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IRD	Interactive Research and Development
MDR	Multidrug-resistance
MDR-TB	Multidrug-resistant Tuberculosis
MSF	Médecins Sans Frontières
MTB/RIF	Mycobacterium Tuberculosis/Rifampicin
NTP	National Tuberculosis Program
PIH	Partners In Health
PV	Pharmacovigilance
QTcF	QT interval Fridericia's correction
SAE	Serious Adverse Event
SSRI	Selective Serotonin Re-uptake Inhibitor
TB	Tuberculosis
WHO	World Health Organization
XDR	Extensive Drug Resistance
XDR-TB	Extensively Drug-resistant Tuberculosis

1. *endTB Clinical Guide*

1.1 Why use the Hain GenoType MTBDR*sl*?

Conventional phenotypic drug-susceptibility testing (DST) tends to be lengthy and can take up to four months to complete. Conventional DST can thus result in delays in prescribing appropriate treatment, which further increases the risk of treatment failure and disease transmission in high-burden settings. Molecular line-probe assays (LPA) have shorter turnaround times than conventional DSTs. These tests include the Hain GenoType MTBDR*plus* and the MTBDR*sl* assays. The MTBDR*plus* assay detects mutations in the *rpoB* gene, associated with rifampicin resistance, as well as in the *katG* gene and *inhA* promoter regions, both associated with isoniazid resistance.[1] MTBDR*plus* can therefore detect resistance to both rifampicin and isoniazid; other rapid molecular diagnostic tests such as INNO-LiPA and GeneXpert only detect rifampicin resistance. MTBDR*plus* has been shown to have excellent sensitivity and specificity for detecting rifampicin and isoniazid resistance: pooled sensitivity and specificity of MTBDR*plus* for rifampicin resistance was found to be 96% and 98%, respectively; 91% and 99%, respectively, for isoniazid resistance; and 91% and 99%, respectively, for MDR-TB status.[2] Additionally, the MTBDR*plus* assay is much faster than conventional DST. The turnaround time is eight hours with a potential for same-day results.

The MTBDR*sl* assay is used to diagnose strains that are resistant to second-line TB drugs, such as XDR- or pre-XDR-TB. It detects mutations in the *gyr*A and *rrs* genes that confer resistance to fluoroquinolones (e.g. ofloxacin, levofloxacin and moxifloxacin) and second-line injectables (e.g. amikacin, kanamycin, and capreomycin).[2] A recent cross-sectional study evaluated the performance of MTBDR*sl* compared to conventional DST in 181 sputum samples (direct testing) and 270 clinical isolates (indirect testing) among patients with culture-confirmed drug-sensitive TB, MDR-TB, or XDR-TB. When performed directly (sputum), MTBDR*sl* was found to have a sensitivity and specificity of 85.1% and 98.2%, respectively, to detect fluoroquinolone (FQ) resistance, and a sensitivity and specificity of 94.4% and 98.2%, respectively, for detection of second-line injectable drug (SLID) resistance. When performed indirectly (on culture), MTBDR*sl* was found to have a sensitivity and specificity of 83.1% and 97.7%, respectively, for detecting FQ resistance, and a sensitivity and specificity of 76.9% and 99.5%, respectively, for detecting resistance to SLIDs.[3] MTBDR*sl* uses the same platform as MTBDR*plus*, and can also provide results within 8 hours.[4]

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[1] Jacobson KR, Theron D, Kendall EA, Franke MF, Barnard M, van Helden PD, et al. Implementation of genotype MTBDRplus reduces time to multidrug-resistant tuberculosis therapy initiation in South Africa. Clin Infect Dis. 2013; 56(4): 503-8.

[2] Bai Y, Wang Y, Shao C, Hao Y, Jin Y. GenoType MTBDRplus assay for rapid detection of multidrug resistance in Mycobacterium tuberculosis: A meta-analysis. PloS One. 2016; 11(3): e0150321.

[3] Theron G, Peter J, Richardson M, Barnard M, Donegan S, Warren R, et al. The diagnostic accuracy of the MTBDRplus and MTBDRsl assays for drug-resistant TB detection when performed on sputum and culture isolates. Cochrane Database Syst Rev. 2014 Oct 29;(10):CD010705.

[4] Tomasicchio M, Theron G, Pietersen E, Streicher E, Stanley-Josephs D, van Helden P, et al. The diagnostic accuracy of the MTBDRplus and MTBDRsl assays for drug-resistant TB detection when performed on sputum and culture isolates. Sci Rep. 2016; 6: 17850.

In many countries, second-line DST is not part of the national guidelines for management of MDR-TB. Second-line drug resistance, however, is almost always more common than expected, and can easily lead to prescription of an inadequate treatment regimen. The MTBDR*sl* assay is simple, rapid and therefore a good option for programs that are not currently conducting second-line DST for all MDR-TB patients. Even for programs that are already using conventional second-line DST, MTBDR*sl* can still be helpful to clinicians by reducing the time to effective treatment in patients with XDR- or pre-XDR strains.

1.2 Should linezolid be used in patients who are taking antidepressants?

There is a small but documented risk of serotonin syndrome when starting linezolid. Serotonin syndrome is a condition caused by an increase in serotonin levels. Symptoms include restlessness, agitation, confusion, increased blood pressure or heart rate, dilated pupils, muscle rigidity, muscle twitches or loss of muscle coordination, sweating, diarrhea, headache, shivering and goosebumps. Patients who experience linezolid-related serotonin syndrome will generally start having symptoms within six hours of first starting linezolid, meaning this is an early side effect of linezolid and there is a much lower risk of developing this syndrome in a patient who has been taking linezolid for a long period of time.

Given the increased risk of serotonin syndrome, the linezolid package insert specifically mentions that linezolid should not be administered with other serotonergic drugs, including many commonly prescribed for depression, such as serotonin re-uptake inhibitors (SSRIs):

> *"Unless clinically appropriate and patients are carefully observed for signs and/or symptoms of serotonin syndrome or neuroleptic malignant syndrome-like reactions, linezolid should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, bupropion, or buspirone. In some cases, a patient already receiving a serotonergic antidepressant or buspirone may require urgent treatment with linezolid. If alternatives to linezolid are not available and the potential benefits of linezolid outweigh the risks of serotonin syndrome or NMS-like reactions, the serotonergic antidepressant should be stopped promptly and linezolid administered. The patient should be monitored for two weeks (five weeks if fluoxetine was taken) or until 24 hours after the last dose of linezolid, whichever comes first. Symptoms of serotonin syndrome or NMS-like reactions include hyperthermia, rigidity, myoclonus, autonomic instability, and mental status changes that include extreme agitation progressing to delirium and coma."*

The question of whether to stop serotonergic drugs such as SSRIs during long-term linezolid treatment first arose in relation to osteomyelitis treatment, and many of the arguments are highly relevant to MDR-TB patients—many of whom struggle with depression. Ultimately, clinicians should consider costs and benefits to determine whether the SSRI should be stopped during treatment with linezolid, and particularly consider

whether the risk of serotonin syndrome is greater than the risk of recurrent mood or anxiety disorder. As Quinn and Stern wrote:

> *"The question of whether to stop the SSRI when linezolid is administered, or leave it in the patient's medication regimen, must be decided according to cost-benefit analysis of the clinical situation. Is the risk of serotonin syndrome greater than the risk of recurrent mood or anxiety disorder? At one extreme, if a patient is intubated, sedated, paralyzed, and critically ill, continuing the antidepressant would be a lesser clinical priority than avoiding a rare but consequential episode of drug toxicity that could exacerbate the critical illness or hasten the failure of multiple organ systems.*
>
> *"At the other extreme, in a chronically mentally ill outpatient with osteomyelitis who needs oral linezolid for an indefinite period of time, the risk and consequence of an exacerbation of a brittle mental illness may be far greater than the rare risk of serotonin syndrome. This patient may be maintained on linezolid and a serotonergic agent concurrently, with frequent clinical follow-up to monitor for serotonin toxicity, especially during the first month of treatment. Because the incidence of serotonin toxicity is so low, there are no data regarding specific dosages of SSRIs that may increase the risk of serotonin toxicity; clinicians should use medication dosages as part of their cost-benefit analysis."*[5]

1.3 What is the best dose of linezolid for MDR-TB treatment?

When treating MDR-TB, it is important to identify the dosage amount that will achieve culture conversion and treatment success while also minimizing toxicity; dosages need to be high enough to limit the risk of developing further drug resistance, but also low enough to avoid potentially permanent adverse effects.

Previous studies have demonstrated efficacy of linezolid at dosages of 1200 mg/day, 600 mg/day and 300 mg/day.[6] However, treatment with linezolid can cause significant adverse effects and, in some cases, subsequent treatment termination. Adverse effects related to linezolid have mainly included bone marrow suppression, and peripheral and optic neuropathy.[7] Additional side effects may include gastro-intestinal problems, thrombocytopenia, leukopenia and anemia.[8] One systematic review of existing data collected from 367 patients showed that the type of adverse event experienced while taking

[5] Quinn DK, Stern TA. Linezolid and serotonin syndrome. Prim Care Companion J Clin Psychiatry. 2009; 11(6): 353-6.

[6] Dooley KE, Obuku EA, Durakovic N, Belitsky V, Mitnick C, Nuermberger EL. World Health Organization group 5 Drugs for the treatment of drug-resistant tuberculosis: Unclear efficacy or untapped potential? J Infect Dis. 2013; 207(9): 1352-8.

[7] Koh WJ, Kang YR, Jeon K, Kwon OJ, Lyu J, Kim WS, et al. Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. J Antimicrob Chemother. 2012; 67(6): 1503-7.

[8] Zhang X, Falagas ME, Vardakas KZ, Wang R, Qin R, Wang J, et al. Systematic review and meta-analysis of the efficacy and safety of therapy with linezolid containing regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis. J Thorac Dis. 2015; 7(4): 603-15.

linezolid varied depending on dosage level: patients receiving higher doses (600 mg versus 300 mg) had higher rates of hematopoietic toxicity and lower rates of nervous toxicity. This review also demonstrated a considerably lower mortality rate in patients receiving lower doses of linezolid.[8] However, another systematic review of data collected from 507 patients showed that only rates of myelosuppression differed between dosage groups.[9]

While higher doses of linezolid are more toxic, they may also be more potent than lower doses. A number of the previous studies found that higher doses of linezolid had higher rates of culture conversion or treatment success, though the association was not statistically significant.

Given the dosage options, body weight and tolerability should be deciding factors for determining the appropriate treatment dose of linezolid.[10,11] Additionally, de-escalation dosage models have been shown to be effective in achieving culture conversion. A small randomized controlled trial in China demonstrated this. Patients began treatment with 1200 mg of linezolid for 4-6 weeks. Subjects were subsequently given a reduced dose of 300 or 600 mg of linezolid, with the second dosage determined by patient body weight and tolerability. The linezolid group had a significantly higher treatment success rate compared to the non-linezolid group, and most adverse events experienced by the linezolid treatment group resolved after the linezolid dose was reduced.[12] A Korean clinical trial following a similar de-escalatated dosage strategy starting at 600 mg of linezolid daily also demonstrated promising results.[13]

The *endTB Clinical Guide* recommends a dose of 600 mg daily for the full duration of treatment, which is often 20-24 months for patients in the endTB Observational Study. All patients should be carefully monitored throughout their entire treatment for linezolid-related adverse events, and dose reduction is strongly recommended if the patient experiences such adverse events. In the endTB Clinical Trial, however, a different management strategy is used. All trial subjects are started at 600 mg of linezolid daily for a total of four weeks, followed by a reduction to 300 mg daily or 600 mg three times a week, regardless of whether or not the patient experiences adverse events.

1.4 Should pyridoxine be given to prevent adverse events due to linezolid?

The *endTB Clinical Guide* does not recommend prescribing pyridoxine to prevent linezolid-related adverse events such as peripheral neuropathy or myelosuppression. While pyridoxine has been shown to be effective in reducing the incidence of isoniazid-induced

[9] Agyeman AA, Ofori-Asenso R. Efficacy and safety profile of linezolid in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis: a systematic review and meta-analysis. Ann Clin Microbiol Antimicrob. 2016; 15(1): 41.

[10] Schecter GF, Scott C, True L, Raftery A, Flood J, Mase S. Linezolid in the Treatment of Multidrug-Resistant Tuberculosis. Clin Infect Dis. 2010; 50(1): 49-55.

[11] Xu H-B, Jiang RH. Li L, Xiao HP. Linezolid in the treatment of MDR-TB: a retrospective clinical study. Int J Tuberc Lung Dis. 2012; 16(3): 358-63.

[12] Tang S, Yao L, Hao X, Zhang X, Liu G, Liu X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J. 2015; 45(1): 161-170.

[13] Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, et al. Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis. N Engl J Med. 2012; 367(16): 1508-18.

neuropathy,[14] there is insufficient evidence to support the use of pyridoxine to reduce linezolid-induced neuropathy or myelosuppression.

There is minimal evidence to suggest that pyridoxine can help to reduce or relieve cases of myelosuppression during linezolid treatment. Administering pyridoxine helped to resolve linezolid-associated cytopenias in two patients that were being treated for *Mycobacterium abscessus* infections. However, no effect of using pyridoxine to treat peripheral neuropathy was found.[15] In a retrospective study of 75 septic patients with gram-positive cocci receiving linezolid treatment, patients who did not receive pyridoxine showed greater reductions in red blood cell counts, hemoglobin and hematocrit values, compared to those who were given pyridoxine. This study also found no impact of pyridoxine on instances of neuropathy.[16]

In an open-label, matched-control study of 31 cancer patients receiving pyridoxine in conjunction with their twice-daily linezolid treatment, matched to 62 control patients, there seemed to be a potential protective effect of pyridoxine against linezolid-induced anemia but no effect on linezolid-induced thrombocytopenia or leucopenia.[17] Similarly, in a retrospective observational study that included 38 patients admitted to a university hospital who received linezolid-containing treatment during a 6-month period, no protective effect of pyridoxine against hematological toxicity was observed.[18] In a retrospective study of 24 patients being treated for various infectious diseases using linezolid and pyridoxine, with planned treatment duration spanning 6-12 weeks, there was no protective effect of pyridoxine against linezolid-induced myelosuppression.[19] Similar results were found in an observational study of two consecutive cohorts (n=52) of patients infected with gram-positive cocci. One cohort received pyridoxine in conjunction with their linezolid, while the other did not. No difference in myelosuppression incidence between the two groups was observed.[20]

A published review of the medical literature reported that there may be some limited data to suggest that administering low doses of pyridoxine during linezolid treatment could prevent peripheral neuropathy. However, the review cautioned against supplementation at doses greater than 50 mg daily.[21]

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[14] Snider DE, Pyridoxine supplementation during isoniazid therapy. Tubercle. 1980; 61(4): 191-6.
[15] Spellberg B, Yoo T, Bayer AS. Reversal of linezolid-associated cytopenias, but not peripheral neuropathy, by administration of vitamin B6. J Antimicrob Chemother. 2004; 54(4): 832-5.
[16] Deng J, Su LX, Liang ZX, Liang LL, Yan P, Jia YH, et al. Effects of vitamin B6 therapy for sepsis patients with linezolid-associated cytopenias: a retrospective study. Curr Ther Res Clin Exp. 2013; 74: 26-32.
[17] Youssef S, Hachem R, Chemaly RF, Adachi J, Ying J, Rolston K. The role of vitamin B6 in the prevention of haematological toxic effects of linezolid in patients with cancer. J Antimicrob Chemother. 2008; 61(2): 421-4.
[18] Moraza L, Leache L, Aquerreta I, Ortega A. Linezolid-induced haematological toxicity. Farm Hosp. 2015; 39(6): 320-6.
[19] Plachouras D, Giannitsioti E, Athanassia S, Kontopidou F, Papadopoulos A, Kanellakopoulou K. No effect of pyridoxine on the incidence of myelosuppression during prolonged linezolid treatment. Clin Infect Dis. 2006; 43(9): e89-91.
[20] Soriano A, Ortega M, García S, Peñarroja G, Bové A, Marcos M, et al. Comparative study of the effects of pyridoxine, rifampin, and renal function on hematological adverse events induced by linezolid. Antimicrob Agents Chemother. 2007; 51(7): 2559–2563.
[21] Ghavanini AA, Kimpinski K. Revisiting the evidence for neuropathy caused by pyridoxine deficiency and excess. J Clin Neuromuscul Dis. 2014; 16(1): 25-31.

There has been only one published study of pyridoxine to prevent linezolid-related adverse events in MDR-TB patients. In a case series of 30 patients treated with linezolid for MDR-TB in California, USA, all patients were administered pyridoxine throughout their treatment. Five of the 30 patients developed peripheral neuropathy; three of these patients were able to continue their linezolid treatment with careful monitoring. The pyridoxine dosage was increased in the fourth patient, in an unsuccessful attempt to resolve the peripheral neuropathy. The fifth patient had to discontinue treatment due to the adverse event.[10]

1.5 How long should carbapenems be used in the treatment of MDR-TB?

A variety of carbapenems have been used to treat MDR-TB, including imipenem/cilastatin, meropenem, ertapenem and faropenem. *Mycobacterium tuberculosis* is thought to be completely unaffected by penicillins, but carbapenems are a class of extended-spectrum penicillins that are effective against a broad spectrum of bacteria. There have been case reports, case series and even larger studies of carbapenems being used to treat MDR-TB with some success, mostly from hospitals in eastern Europe and the former Soviet Union countries that have high rates of XDR-TB and the expertise and resources to administer these drugs for extended periods of time.[22,23] There are several early bactericidal activity studies currently underway which should provide more evidence about the potency of the carbapenems against TB.[24] Currently, though, there is no consensus about very basic questions, such as the dosing, duration of treatment or whether these drugs should always be administered with clavulanic acid.

Previous studies have reported a variety of treatment durations in patients treated with carbapenems for MDR-TB. Most clinicians aim for at least six months of treatment, but some clinicians have administered carbapenems for much longer, even the entire length of treatment. Practically, the need for IV access greatly complicates the use of carbapenems. The optimal method of administration is a Port-A-Cath, which is more comfortable for the patient and allows carbapenems to be administered as an outpatient service. However, this is not feasible for all countries or sites. Midline or even peripheral catheters are used in some sites, but these have their own difficulties for both the patient and clinician. Given the difficulty of administration, the *endTB Clinical Guide* recommends that the carbapenems be administered for at least eight months, which is the usual duration of treatment for the intramuscular injectables (aminoglycosides or capreomycin), recognizing that shorter durations of treatment may be required in some settings or patients due to non-clinical reasons.

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[22] Jaganath D, Lamichhane G, Shah M. Carbapenems against *Mycobacterium tuberculosis*: a review of the evidence. Int J Tuberc Lung Dis. 2016; 20(11): 1436-1447.

[23] Payen MC, Muylle I, Vandenberg O, Mathys V, Delforge M, Van den Wijngaert S, et al. Meropenem-clavulanate for drug-resistant tuberculosis: a follow-up of relapse-free cases. Int J Tuberc Lung Dis. 2018; 22(1): 34-39.

[24] Sotgiu G, D'Ambrosio L, Centis R, Tiberi S, Esposito S, Dore S, et al. Carbapenems to treat multidrug and extensively drug-resistant tuberculosis: A systematic review. Int J Mol Sci. 2016; 17(3): 373.

1.7 Can bedaquiline and delamanid be used more than six months?

One of the most common misunderstandings among clinicians is that bedaquiline and delamanid can only be prescribed for 24 weeks.[25] WHO guidelines do not expressly prohibit the use of these two drugs for more than 24 weeks, but neither do they recommend extending treatment with these drugs beyond 24 weeks. Rather, the WHO guidelines simply acknowledge the fact that in Phase II clinical trials, the use of these drugs has been limited to 6-9 months.

Many endTB patients have been previously treated with second-line TB drugs multiple times and are infected with extensively drug-resistant strains for which it is difficult to design an effective regimen. There is no need to stop bedaquiline or delamanid after 24 weeks if these are the only safe and effective drugs. Stopping these drugs after 24 weeks of treatment, in fact, increases the risk of reversion even after culture conversion.[26] In such patients, it is clinically prudent to prescribe bedaquiline and delamanid for the entire length of treatment.

At sites participating in the endTB Observational Study, patients are routinely treated with bedaquiline or delamanid for longer than 24 weeks and have tolerated this well. This is consistent with other studies of compassionate use patients that have shown good safety of prolonged use of bedaquiline.[27] The endTB experience also shows that these two drugs are tolerated better than many other TB drugs that are routinely prescribed for more than 24 weeks, such as linezolid. For this reason, the *endTB Clinical Guide* does not recommend any arbitrary limit to the use of bedaquiline and delamanid. The duration of treatment should depend on the judgement of the responsible physician, just as for other TB drugs.

1.8 Can high-dose moxifloxacin be used to treat quinolone-resistant TB?

High-dose moxifloxacin is generally considered to be 800 mg once daily, in contrast to the normal dose of 400 mg once daily. High-dose moxifloxacin and gatifloxacin were first used in the context of the "Bangladesh regimen" that was used for the treatment of fluoroquinolone-susceptible TB. In fact, many clinicians thought that the use of high-dose moxifloxacin or gatifloxacin was the reason for the high cure rates initially reported in the field with the Bangladesh regimen.

Other clinicians subsequently began using high-dose moxifloxacin for fluoroquinolone-resistant TB. There is very little scientific evidence about whether this

[25] Furin J, Lessem E, Cox V. Recommending prolonged bedaquiline use for the treatment of highly resistant strains of tuberculosis. Eur Respir J. 2017; 50(5).

[26] Sinha A, Tassew Y, Khusainova Z, Khaidarkhanova Z, Vasilyeva I, Herboczek K, et al. Effectiveness of TB treatment regimens containing bedaquiline with repurposed drugs for drug-resistant tuberculosis in the Chechen Republic, Russian Federation. Abstract OA-3036. [Online]. 2016 [Cited 2017 May 16].

[27] Guglielmetti L, Jaspard M, Le Dû D, Lachâtre M, Marigot-Outtandy D, Bernard C, et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. Eur Respir J. 2017; 49(3).

practice is effective, however. Some clinicians and laboratory experts think that high-dose moxifloxacin is effective only against strains that have low-level resistance to moxifloxacin—defined as resistant at 0.25 mg/L and susceptible at 1.0 mg/L (MGIT).[28] Testing at two breakpoints for moxifloxacin is currently available at some supranational laboratories. In vitro studies have shown, however, that even "low-level" resistance mutations will reduce the activity of all fluoroquinolones against *Mycobacterium tuberculosis*.[29]

Given the lack of evidence for the use of high-dose moxifloxacin in patients infected with fluoroquinolone-resistant strains, we cannot make any recommendations about how high-dose moxifloxacin should be used. Given the known adverse event profile of moxifloxacin, however, we do recommend that patients receiving high-dose moxifloxacin be monitored closely for adverse events, including QT prolongation if prescribed at the same time as other QT-prolonging drugs.[30]

2. Screening Tools

2.1 Why use hemoglobin A1c for diabetes screening?

Diabetes mellitus, a chronic metabolic disease that impairs the body's ability to produce or use insulin normally, is becoming increasingly prevalent in low-income and middle-income countries with high TB burdens. Various studies have suggested that diabetes triples a person's risk of developing active TB. In 2012, 15% of global TB cases were estimated to be linked to diabetes. Individuals suffering from chronic diseases such as diabetes have weakened immune systems and are therefore more prone to progress from latent to active TB if infected. In addition, diabetes patients with uncontrolled hyperglycemia maintain a higher risk of TB infection than those with controlled blood glucose levels, which suggests hyperglycemia is a significant determinant in co-infection.[31] On the other hand, TB has been found to temporarily impair glucose tolerance, a main risk factor for developing diabetes, suggesting that TB infection may also heighten a person's risk of developing diabetes.

The association between diabetes and an increased risk of developing active TB has been thoroughly supported by various case-control and cohort studies. Cohort studies have shown a pooled random effect relative risk of diabetic patients developing active TB of 2.52 (95% CI 1.53 – 4.03). An additional ten case-control studies demonstrated an odds ratio (OR) range between 1.16 – 7.81, with a random effects summary OR of 2.2. There have also been

[28] World Health Organization and Foundation for Innovative New Diagnostics. Technical report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis (WHO/CDS/TB/2018.5). Geneva: World Health Organization; 2018.
[29] Maitre T, Petitjean G, Chauffour A, Bernard C, El Helali N, Jarlier V, et al. Are moxifloxacin and levofloxacin equally effective to treat XDR tuberculosis? J Antimicrob Chemother. 2017; 72(8): 2326-2333.
[30] Yew WW, Chang KC. Management of adverse reactions to high-dose moxifloxacin used in multidrug-resistant tuberculosis treatment programmes. Respirology. 2018. doi: 10.1111/resp.13452.
[31] Harries, AD, Kumar AM, Satyanarayana S, Lin Y, Zachariah R, Lönnroth K, et al. Addressing diabetes mellitus as part of the strategy for ending TB. Trans R Soc Trop Med Hyg. 2016; 110(3): 173-9.

studies that have stratified diabetes by glycemic control and found higher blood glucose levels to be associated with a higher risk of TB infection. Various screening studies have additionally demonstrated that TB infection is more frequent among diabetic patients who are insulin-dependent as compared to diabetic patients who do not require insulin therapy.[32]

TB patients co-infected with diabetes have also been found to have an increased risk of death, treatment failure and TB relapse.[33] One factor that may contribute to undesirable outcomes is hepatic toxicity; diabetes has been shown to potentially increase a person's risk of developing hepatic toxicity, particularly while undergoing treatment with anti-TB medications. As a result, diabetic patients may receive lower concentrations of anti-TB medications. This, in combination with increased levels of hepatic toxicity, can lead to recurrent TB infection and increased mortality rates among diabetes and TB co-infected patients.[33]

Thus, it is critical that diabetes be detected as early as possible in TB patients. The *Collaborative Framework for Care and Control of TB and Diabetes* published by WHO and the IUATLD recommends that all TB patients be screened for diabetes at the start of TB treatment, especially in high-burden countries. The type of screening test may be adapted to local health systems' capacities, and numerous studies researching the association between diabetes and TB have used a diverse range of screening methods to detect diabetes in TB patients, including fasting blood glucose (FBG), random blood glucose (RBG), two-hour postprandial glucose (2hPG), urine glucose, performance of glucose tolerance test (GTT), and Hemoglobin A1c (HbA1c). There currently is not one specific preferred screening method for diabetes.

Nevertheless, the *endTB Clinical Guide* recommends measuring HbA1c to screen for diabetes at every patient's baseline visit, with repeated screening every three months if levels of HbA1c at baseline are elevated. HbA1c, or glycated hemoglobin, is a form of hemoglobin that is measured mainly to identify a diabetic patient's average plasma glucose concentration over 8 to 12 weeks. When blood glucose levels are high (hyperglycemic), glucose molecules bind to the hemoglobin in red blood cells. The longer blood is hyperglycemic, the more glucose binds to hemoglobin in red blood cells. Thus, higher levels of HbA1c indicate poor control of blood glucose levels, which can indicate diabetes.[34] The endTB Clinical Guide recommends measuring HbA1c because it has been shown to provide a significantly better indication of long-term glycemic control than blood and urinary glucose measurements. Additionally, HbA1c testing is not prone to rapid, temperamental changes that can occur during random and fasting blood glucose measurements.

[32] International Union Against Tuberculosis and Lung Disease and World Health Organization, Collaborative framework for care and control of tuberculosis and diabetes (WHO/HTM/TB/2011.15). Geneva: World Health Organization, 2011.

[33] Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Med. 2011; 9: 81.

[34] Mayo Clinic Laboratories. Hemoglobin A1c, Blood. 2016.

2.2 Why screen for hepatitis B and C with HBsAg and HCVAb?

The prevalence of hepatitis B and C in TB patients, particularly in MDR-TB patients, is largely unknown in most countries because screening is often not part of routine practice. In a few settings where it has been studied, the prevalence of viral hepatitis in MDR-TB patients has often been higher than expected.[35,36] Chronic active viral hepatitis appears to be an independent predictor of drug-induced liver injury during TB treatment. Thus, it is important to identify patients with chronic active hepatitis, since they will require additional monitoring and, mostly likely, specific treatment.[37,38,39] It is important to note that direct-acting antivirals (DAA), which are used to treat hepatitis C (HCV) infection, are well tolerated when given concomitantly with MDR-TB treatment.

The preferred test for initial screening for chronic active hepatitis B (HBV) is the test for HBV surface antigen (HBsAg). There are multiple tests for detecting HBV, but HBsAg is the first marker detectable in the blood following infection, and its production continues even in cases of chronic HBV infection. The presence of HBsAg indicates active infection with a high level of sensitivity and specificity. HBsAg can become positive during a "flare" and become negative after an episode of HBV has resolved. A positive HBsAg test should be followed by a HBV DNA test to measure the HBV viral load if treatment is deemed necessary.

The initial screening for HCV infection is HCV antibody (HCVAb). HCVAb will become positive after initial infection and will remain positive even if the patient spontaneously clears the infection, so a positive/reactive HCVAb result should be followed by an HCV RNA test to confirm chronic HCV infection and to determine if DAA is necessary.

2.3 What is the Household Hunger Scale?

The Household Hunger Scale (HHS) is an indicator used to assess the degree of household hunger experienced by populations in food-insecure settings. The HHS consists of three questions and three frequency-of-occurrence responses that are aim to measure the scale of food deprivation among specific populations. Typically employed as a population-based household survey, the HHS is used to estimate the percent of households that experience

[35] Richards DC, Mikiashvili T, Parris JJ, Kourbatova EV, Wilson JC, Shubladze N, et al. High prevalence of hepatitis C virus but not HIV co-infection among patients with tuberculosis in Georgia. Int J Tuberc Lung Dis. 2006; 10(4): 396-401.

[36] Sirinak C, Kittikraisak W, Pinjeesekikul D, Charusuntonsri P, Luanloed P, Srisuwanvilai LO, et al. Viral hepatitis and HIV-associated tuberculosis: Risk factors and TB treatment outcomes in Thailand. BMC Public Health. 2008; 8: 245.

[37] Chang TE, Huang YS, Chang CH, Perng CL, Huang YH, Hou MC. The susceptibility of anti-tuberculosis drug-induced liver injury and chronic hepatitis C infection: A systematic review and meta-analysis. J Chin Med Assoc. 2018; 81(2): 111-118.

[38] Kwon YS, Koh WJ, Suh GY, Chung MP, Kim H, Kwon OJ. Hepatitis C virus infection and hepatotoxicity during anti-tuberculosis chemotherapy. Chest. 2007; 131(3): 803-808.

[39] Kim WS, Lee SS, Lee CM, Kim HJ, Ha CY, Kim HJ, et al. Hepatitis C and not Hepatitis B virus is a risk factor for anti-tuberculosis drug induced liver injury. BMC Infect Dis. 2016; 16: 50.

each of three degrees of household hunger severity: 1) little to no household hunger; 2) moderate household hunger; and 3) severe household hunger.[40,41]

The HHS has been validated across various cultures and settings, allowing it to be effectively used cross-culturally and within a variety of food-insecure contexts. A validation study conducted by the Food and Nutrition Technical Assistance Project (FANTA II) suggested that the HHS is likely to be sensitive to successful program interventions and recommends that the HHS be used for assessment, geographic targeting, and monitoring and evaluation in settings affected by substantial food insecurity.[41] Since this study, the HHS has been used in many countries, particularly in conjunction with USAID programs, as part of routine monitoring and evaluation for programs focused on nutrition and food security.

The use of the HHS in contexts other than nutrition and food security programs, and on a more individualized basis, can also be important. This information is critical, as insufficient access to food, and particularly nutritious food, can impede TB treatment success. Individuals from food-insecure settings who receive nutritional supplementation have been shown to adhere better to their treatment.[42] Additionally, inadequate intake of essential vitamins, minerals and other essential nutrients have been shown to negatively impact the pharmacokinetics of certain anti-TB medications,[43] which also leads to a greater risk of treatment failure. In gathering information on each patient's food security, it is possible for endTB physicians to more appropriately account for nutritional challenges and counsel patients on eating habits.

2.4 What is the Brief Peripheral Neuropathy Screen?

Peripheral neuropathy is one of the most common adverse reactions during MDR-TB treatment. A number of anti-TB drugs are commonly associated with peripheral neuropathy, including cycloserine, ethambutol, ethionamide, fluoroquinolones, isoniazid, linezolid, and streptomycin.[44] Peripheral neuropathy induced by treatment with anti-TB drugs may be irreversible if not diagnosed in its early stages.

The Brief Peripheral Neuropathy Screen (BPNS) was originally developed and validated by the AIDS Clinical Trial Group (ACTG) for assessing HIV-related sensory

[40] Deitchler M, Ballard T, Swindale A, Coates J. Introducing a Simple Measure of Household Hunger for Cross-Cultural Use. Washington, D.C.: Food and Nutrition Technical Assistance II Project, AED, 2011.

[41] Ballard T, Coates J, Swindale A, Deitchler M. Household Hunger Scale: Indicator Definition and Measurement Guide. Washington, DC: Food and Nutrition Technical Assistance II Project, FHI 360. 2011.

[42] Claros JM, de Pee S, Bloem MW. Adherence to HIV and TB care and treatment, the role of food security and nutrition. AIDS Behav. 2014; 18(5): S459-64.

[43] Karyadi E, West CE, Schultink W, Nelwan RH, Gross R, Amin Z, Dolmans WM, et al. A double-blind, placebo-controlled study of vitamin A and zinc supplementation in persons with tuberculosis in Indonesia: effects on clinical response and nutritional status. Am J Clin Nutr. 2002; 75(4): 720-7.

[44] Shin S, Hyson A, Castañeda C, Sánchez E, Alcántara F, Mitnick C, et al. Peripheral neuropathy associated with treatment for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2003; 7(4): 347-53.

neuropathies.[45,46] To perform the BPNS, a trained healthcare worker asks the patient whether they have experienced any of the main symptoms of neuropathy. The screen is done on both sides of the feet and legs. The healthcare worker grades the severity of the symptoms reported and uses a reflex hammer to test the patient's ankle reflexes and a tuning fork to measure any loss of sensitivity to vibrations in the patient's great toe. If any of these bilateral neuropathic symptoms are found in addition to either decreased ankle reflexes or vibration sense, a clinical diagnosis of sensory neuropathy is made. The BPNS is inexpensive, simple, practical to administer and yields quick results.

While the BPNS has been used mostly in HIV patients, especially in resource-limited settings,[47,48] it has also been used in TB patients. A clinical trial studying the use of linezolid to treat chronic XDR-TB in patients in South Korea used the subjective portion of the BPNS to screen for peripheral neuropathy and to monitor progression.[13] The NiX-TB clinical trial studying the efficacy of a linezolid-including MDR-TB regimen in South Africa also used the BPNS to screen for peripheral neuropathy. Likewise, in the endTB Observational Study, the BPNS is recommended for peripheral neuropathy screening. Many MDR-TB drugs can cause peripheral neuropathy, so it is important to use the BPNS both at baseline and at follow-up visits.

2.5 How should patients be monitored for optic neuritis caused by linezolid?

Linezolid has been recommended by the WHO for the treatment of MDR-TB since 2006 and was officially incorporated into the WHO Model List of Essential Medicines as a reserve second-line drug for MDR-TB treatment in 2015. However, a common side effect associated with taking linezolid is optic neuritis; cases of toxic optic neuritis are well described across studies on the efficacy and safety profile of linezolid.[49,50,51]

A systematic review and meta-analysis that included 12 studies found optic neuritis occurred in 13.2% of all cases (n=121 individual patients with a definite treatment

[45] Cherry CL, Wesselingh SL, Lal L, McArthur JC. Evaluation of a clinical screening tool for HIV-associated sensory neuropathies. Neurology. 2005, 65 (11): 1778-1781

[46] Simpson DM, Kitch D, Evans SR, McArthur JC, Asmuth DM, Cohen B, et al. HIV neuropathy natural history cohort study: assessment measures and risk factors. Neurology. 2006; 66(11): 1679-87.

[47] Luma HN, Tchaleu BC, Doualla MS, Temfack E, Sopouassi VN, Mapoure YN, et al. HIV-associated sensory neuropathy in HIV-1 infected patients at the Douala General Hospital in Cameroon: a cross-sectional study. AIDS Res Ther. 2012; 9(1): 35.

[48] Tumusiime DK, Venter F, Musenge E, Stewart A. Prevalence of peripheral neuropathy and its associated demographic and health status characteristics, among people on antiretroviral therapy in Rwanda. BMC Public Health. 2014; 14: 1306.

[49] Lee E, Burger S, Melton C, Mullen M, Warren F, Press R. Linezolid-associated toxic optic neuropathy: a report of 2 cases. Clin Infect Dis. 2003; 37(10): 1389-91.

[50] Fortún J, Martín-Dávila P, Navas E, Pérez-Elías MJ, Cobo J, Tato M, et al. Linezolid for the treatment of multidrug-resistant tuberculosis. J Antimicrob Chemother. 2005; 56(1): 180-5.

[51] McKinley SH, Foroozan R. Optic neuropathy associated with linezolid treatment. J Neuroophthalmol. 2005; 25(1): 18-21.

outcome).[52] Linezolid-induced toxic optic neuropathy appears to be dependent on treatment duration: Rucker et al. described 3 cases of metabolic optic neuropathy caused by treatment with linezolid and noted another 9 possible cases, all of which experienced symptoms after a treatment duration of 5 to 11 months (mean 9 months).[53]

Linezolid-induced toxic optic neuropathy, or metabolic optic neuropathy, consists of symmetric, painless decreased central vision manifested as decreased visual acuity and color vision; bilateral central or cecocentral scotomas; and normal maculae with normal, swollen, or pale optic nerves. These effects are thought to be related to the inhibition of mitochondrial protein synthesis.[13]

The first sign of optic neuritis is dyschromatopsia, or difficulty perceiving colors normally. Therefore, to monitor for optic neuritis, patients in the endTB study are screened for visual acuity and colorblindness at baseline and monthly visits thereafter. For colorblindness, the endTB study uses the concise (11-plate) version of the Ishihara pseudoisochromatic test. This version was used by the Optic Neuritis Treatment Trial—a randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis (from a variety of causes, but mostly multiple sclerosis)—to measure the presence of color defects in 488 enrolled patients.[54] It is also common for optometrists and ophthalmologists in high-burden TB settings to recommend this 11-plate version to screen for colorblindness in patients undergoing TB treatment.

2.6 What is the Golovin–Sivtsev visual acuity table?

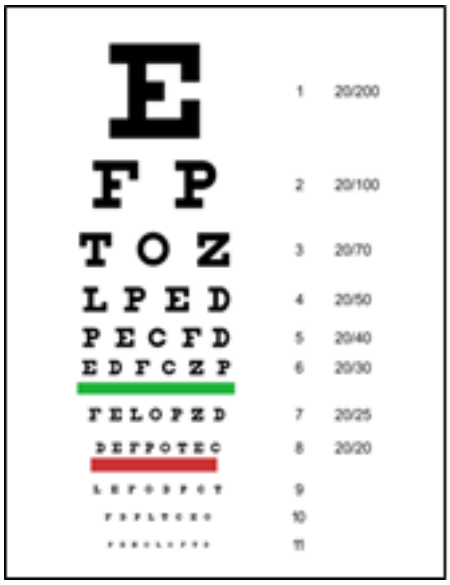
The Snellen chart is the most commonly used vision-testing chart in clinical practice dating back to its introduction in 1862. The Snellen chart uses letters from the Roman alphabet, while the corresponding Tumbling E chart uses a series of the letter “E”, shown in various positions, to measure visual acuity in patients who are unable to read the Roman alphabet.

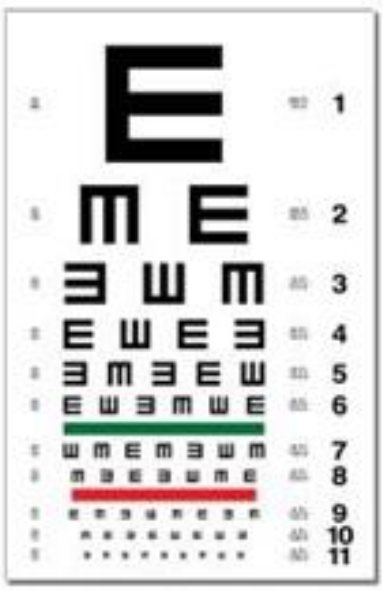
Snellen and Tumbling E charts

[52] Sotgiu, G, Centis, R, D'Ambrosio, L, Alffenaar JW, 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. Eur Respir J. 2012;40(6): 1430-42.

[53] Rucker JC, Hamilton S, Bardenstein D, Isada CM, Lee MS. Linezolid-associated toxic optic neuropathy. Neurology. 2006; 66(4): 595-8.

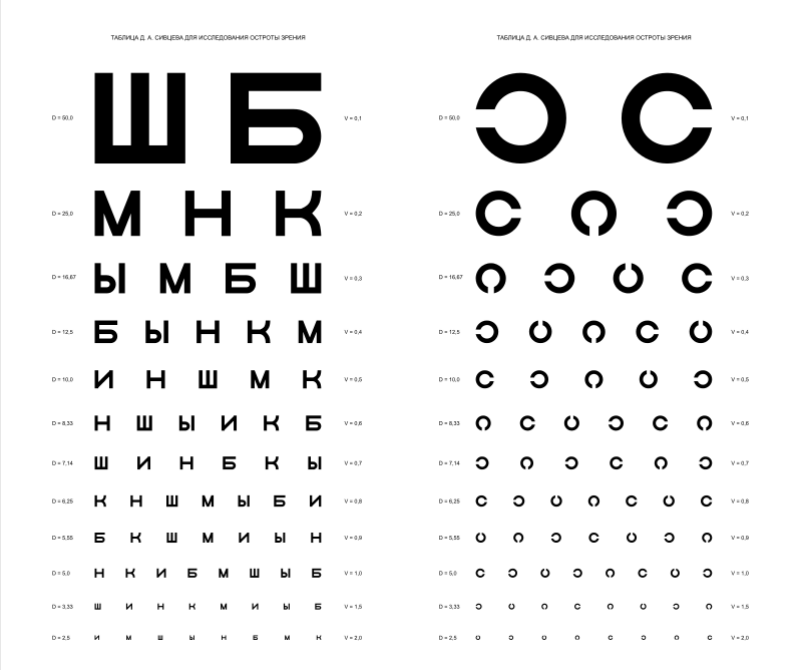
[54] Beck RW, Cleary PA. Optic neuritis treatment trial. One-year follow-up results. Arch Ophthalmol. 1993; 111(6): 773-5.





The Snellen and Tumbling E charts are generally used in populations that are familiar with the Roman alphabet. For populations unfamiliar with the Roman alphabet, the Golovin-Sivtsev table is another option. This standardized vision-testing was developed in 1923 by ophthalmologists Sergei Golovin and D.A. Sivtsev. It was the most commonly used table for testing visual acuity in the USSR and continues to be widely used in post-Soviet countries.[55]

Golovin-Sivtsev table



The Golovin-Sivtsev table is comprised of two parts: the left part of the table shows a series of the Cyrillic letters Ш, Б, М, Н, К, ы, and И, and the right part displays a series of

[55] Wikipedia. Golovin-Sivtsev Table. 2018. Available from https://en.wikipedia.org/wiki/Golovin%E2%80%93Sivtsev_table.

Landolt C symbols.[55] Each part consists of 12 rows: *D* values to the left of each row indicate the distance in meters from which a person with a visual acuity of 1.0 can read the corresponding row, while *V* values to the right of each row indicate the minimum visual acuity needed to read each row from a distance of 5 meters.[55] The rows represent visual acuity values between 0.1 and 2.0. Characters in the first row are 70 mm, 35 mm in the second row, and 7 mm in the last row, with the width of each character equaling its height.[55]

In the endTB Observational Study, the Kazakhstan sites routinely use the Golovin-Sivtsev table to measure visual acuity. All other sites use the standard Snellen chart to measure visual acuity among enrolled patients.

2.7 How should patients receiving injectables be monitored for possible hearing loss?

The injectable anti-TB drugs (capreomycin and the aminoglycosides: amikacin, kanamycin and streptomycin) are commonly used to treat MDR-TB. The conventional wisdom is that once-daily dosing of AGs, which is commonly used in TB treatment, is less toxic than multiple-daily dosing, which is used for treatment of other bacteria.[56]

A case review of 100 consecutively treated MDR-TB patients at four health centers in the U.K. revealed that 40% of patients stopped their injectable due to hearing loss, though, that hearing loss was significantly lower in patients receiving capreomycin in place of an aminoglycoside. Mean treatment time with the injectable agent in this population was 178 days.[57] A retrospective cohort study in Botswana in 2014 showed that prolonged amikacin therapy and higher dosages per kilogram were associated with a higher incidence of hearing loss. Of the 437 patients included in the cohort, 70% developed hearing loss over the course of treatment using amikacin, and hearing loss was found to be independently associated with amikacin duration and dosage. Such high rates may still be an underestimate, particularly given that hearing loss in this study was measured at conversational level without the availability of audiograms; by the time hearing loss was diagnosed, patients likely had already experienced high-frequency hearing loss.[58]

There is little guidance or expertise available on the use of audiograms for patients being treated for MDR-TB. Additionally, audiograms can be challenging to conduct in resource-poor settings. For example, it is usually recommended that screening be conducted in a sound-proofed booth, which are unavailable in many resource-limited settings.

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[56] Peloquin CA, Berning SE, Nitta AT, Simone PM, Goble M, Huitt GA, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis. 2004; 38(11): 1538-44.

[57] Arnold A, Cooke GS, Kon OM, Dedicoat M, Lipman M, Loyse A, et al. Adverse effects and choice between the injectable agents amikacin and capreomycin in multidrug-resistant tuberculosis. Antimicrob Agents Chemother. 2017; 61(9): pii: e02586-16.

[58] Modongo C, Sobota RS, Kesenogile B, Ncube R, Sirugo G, Williams SM, et al. Successful MDR-TB treatment regimens including amikacin are associated with high rates of hearing loss. BMC Infect Dis. 2014; 14: 542.

Nevertheless, the *endTB Clinical Guide* recommends performing monthly audiograms from the beginning of treatment with any injectable until the time that the injectable is suspended. Most of the endTB Observational Study sites use hearScreen—a fully-automated screening audiometer that uses a smartphone connected to a calibrated set of headphones, making the device portable with minimal training required. In a clinical validation study, 1,070 school-age children were screened twice for hearing loss: once using conventional audiometry methods, and once using the hearScreen device. Researchers found no statistically significant difference in performance between the two techniques, with hearScreen demonstrating equivalent sensitivity (75.0%) and specificity (98.5%) to conventional screening audiometry methods.[59] In sites where audiologists are available, if hearing loss is detected, patients can be referred to an audiologist for further evaluation. If audiologists are not available, the responsible MDR-TB clinician can use the results of serial screening audiograms to determine if the injectable should be suspended.

2.8 How often should ECGs be done to monitor for QT prolongation?

The QT interval represents electrical depolarization and repolarization of the ventricles. A prolonged QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

According to the *Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis*, "an ECG should be obtained before initiation of treatment with bedaquiline or delamanid, and at least 2, 4, 8, 12 and 24 weeks after starting treatment. Monitoring ECGs should be done monthly if taking other QT prolonging drugs (i.e. moxifloxacin, clofazimine)".[60]

As the majority of endTB patients have been treated with regimens containing multiple QT prolonging drugs, the *endTB Clinical Guide* stipulates that an ECG should be conducted at the baseline and 2-week follow-up visits, with monthly ECGs conducted thereafter for the duration of treatment with bedaquiline or delamanid.

The *endTB Clinical Guide* also notes that some patients may require closer monitoring. Patients who experience QT prolongation during treatment should undergo ECG testing on a weekly basis until the QT has returned to a grade 1 level or below, as defined by the endTB Severity Grading Scale. Additionally, it is recommended that patients with QT-prolonging co-morbidities (e.g. hypokalemia) undergo more frequent ECG testing. Patients who are receiving multiple QT-prolonging drugs should also be closely monitored. Keep in mind that QT-prolonging drugs include TB drugs (e.g. clofazimine, bedaquiline, moxifloxacin, delamanid), and also non-TB drugs (e.g. antipsychotics, many antibiotics).

[59] Mahomed-Asmail F, Swanepoel de W, Eikelboom RH, Myburgh HC, Hall J 3rd. Clinical validity of hearScreen™ smartphone hearing screening for school children. Ear Hear. 2016; 37(1): e11-7.
[60] World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2014.11). Geneva: World Health Organization; 2014.

2.9 What formula should be used for correcting the QT interval?

QT interval shortens with faster heart rates and lengthens with slower heart rates. For accurate interpretation of this interval, it is necessary to correct the QT interval by standardizing it to a heart rate of 60 beats per minute (bpm). There are several formulas available to correct the QT interval, including the Bazett, Fridericia, Framingham, Hodges, and Rautaharju formulas. A 2016 study conducted at the University Hospitals of Leuven (Leuven, Belgium) compared these different formulas and their rate correction performance. The study included all ECGs conducted during a 2-month period in patients 18 years or older with sinus rhythm, normal QRS duration and a heart rate of 90 or greater bpm. A total of 6,609 patients were included. The researchers found that the Fridericia and Framingham formulas performed best in terms of rate correction. Further, they reported that using these formulas led to better ability to predict patient mortality (both 30-day and 1-year).[61]

The Fridericia formula is generally considered to be the best method to correct when the heart rate is high, which is commonly the case in TB patients. TB clinical trials mostly use the Fridericia method for correcting the QT interval, and WHO also recommends the Fridericia method for monitoring TB patients receiving potentially QT-prolonging drugs.

2.10 What chest X-ray data is collected and analyzed?

There are three types of X-ray data that are collected for each patient in the endTB Observational Study: cavitary disease (< 5 cm or ≥ 5 cm), extent of disease (unilateral or bilateral), and fibrosis (≤ 1 lobe or > 1 lobe).

Cavitary disease has long been known to be associated with a poor response to TB treatment. Multiple clinical studies have shown this in drug-resistant TB. For example, a study of 167 Latvian MDR-TB patients found that the presence of bilateral cavitations on chest radiography was associated with a longer time to initial sputum culture conversion.[62] A meta-analysis of 9,153 MDR-TB patients adjusted for the extent of disease factor (AFB smear positive, or cavitation on chest X-ray) in assessing the effect of treatment.[63] In the Phase II trial of delamanid, patients were stratified at randomization by the existence of cavitary disease. In addition, unilateral or bilateral cavitation was investigated as a potential covariate associated with poor outcome. In the Phase IIb trial of bedaquiline, patients were stratified by the existence of cavities greater than 2 cm in diameter. For this reason, in most clinical trials of new TB drugs the presence and size of cavities are assessed at baseline.

The extent of TB disease has also been associated with poor response to TB treatment. In the endTB Observational Study, extent of TB disease is simply classified as

[61] Vandenberk B, Vandael E, Robyns T, Vandenberghe J, Garweg C, Foulon V, et al. Which QT correction formulae to use for QT monitoring? J Am Heart Assoc. 2016; 5(6): e003264.
[62] Holtz TH, Sternberg M, Kammerer S, Laserson KF, Riekstina V, Zarovska E, et al. Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. Ann Intern Med. 2006; 144(9): 650-9.
[63] 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): e1001300.

unilateral or bilateral. There are a number of more complicated classification systems that have been used and validated in other studies to estimate the proportion of lung affected (i.e. 0-100%). For example, Ralph et al. found that a scale that included the proportion of lung affected and the presence of cavitation significantly predicted outcome.[64] However, we judged these scales as too difficult and cumbersome to implement in the endTB Observational Study sites.

A prospective cohort study of 135 pulmonary TB patients in South Korea showed a significant association between fibrosis and poor radiographic response in a multiple regression model.[65] Fibrotic lesions are common amongst MDR-TB patients, particularly in chronic patients with a history of multiple failed treatments.

3. Variable definitions

3.1 Why is smoking defined as more than one cigarette a day?

In the endTB Observational Study, a person is considered to be a smoker if they smoke at least one cigarette per day. This cutoff of one cigarette per day was chosen for this project given the evidence showing that light and intermittent smoking results in many of the same substantial health effects as daily smoking.

Evidence has shown that light and intermittent smoking carries a substantial risk for developing lung cancer. Women between the ages of 35 and 49 years who smoke 1-4 cigarettes per day have five times the risk of developing lung cancer, while men in the same age range have three times the risk of developing lung cancer compared to non-smokers.[66,67] Light smoking has also been linked to other lung diseases, including lower respiratory tract infections, and has been shown to cause prolonged duration of respiratory symptoms such as cough.[66] Furthermore, light and intermittent smoking carries nearly the same risk for cardiovascular disease as daily smoking: adults who smoke 1-4 cigarettes per day have nearly three times the risk of developing ischemic heart disease than a non-smoker.[67]

Given that MDR-TB patients are already afflicted with a severe form of lung disease, it is important for attending physicians to be aware of behaviors such as smoking that increase the patient's risk for additional health challenges and poor treatment outcomes. In terms of treatment success, studies have demonstrated a significant relationship between tobacco smoking and treatment outcomes for TB and MDR-TB patients. One study found

[64] Ralph AP, Ardian M, Wiguna A, Maguire GP, Becker NG, Drogumuller G, et al. A simple, valid, numerical score for grading chest x-ray severity in adult smear-positive pulmonary tuberculosis. Thorax. 2010; 65(10): 863-9.

[65] Heo EY, Chun EJ, Lee CH, Kim YW, Han SK, Shim YS, et al. Radiographic improvement and its predictors in patients with pulmonary tuberculosis. Int J Infect Dis. 2009; 13(6): e371-6.

[66] Schane, RE, Ling, PM, Glantz, SA. Health effects of light and intermittent smoking: a review. Circulation. 2010; 121(13): 1518-22.

[67] Bjartveit K, Tverdal A. Health consequences of smoking 1–4 cigarettes per day. Tob Control. 2005; 14(5): 315-20.

current smokers to be 70% more likely to experience a poor TB treatment outcome than TB patients who never smoked cigarettes;[68] MDR-TB patients specifically were found to be three times more likely to experience a poor treatment outcome than patients being treated for other forms of TB.[68] In defining "smoking" as smoking one or more cigarettes per day, physicians are more likely to be aware of the majority of patients who smoke to some degree—daily or intermittently—so as to document an accurate medical history that can inform appropriate clinical monitoring throughout treatment for MDR-TB.

3.2 Which AEs are captured as part of the endTB Observational Study?

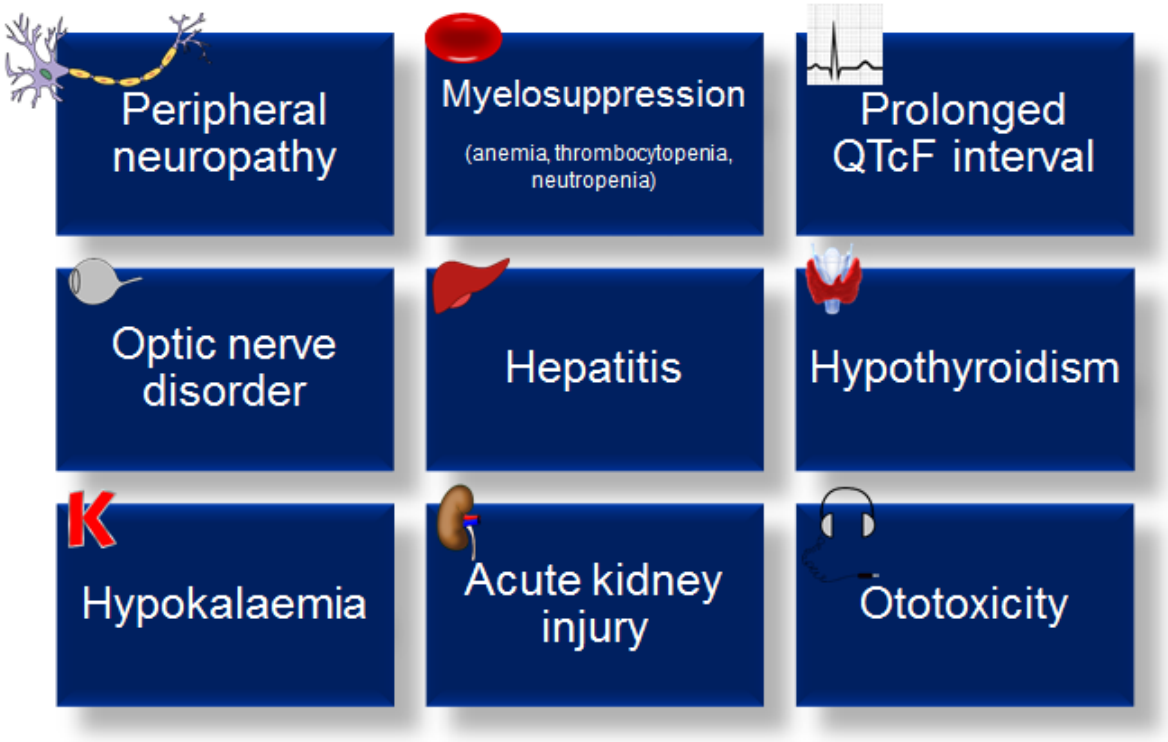
Collecting and analyzing data related to adverse events (AEs) is an important activity of the endTB Observational Study. When initially discussing the types of AEs to be captured, the investigators recognized two points. First, the endTB Observational Study is not a clinical trial. Treatment is delivered under program conditions, and while additional resources were provided for research activities, the AE monitoring schedule could not approach the intensity of the endTB Clinical Trial. Second, the endTB Observational Study should not focus only on the potential AEs caused by bedaquiline and delamanid. Rather, the Observational Study should capture all AEs that impact the patient, irrespective of the causal drug.

The endTB Observational Study captures four major categories of AEs. **Serious Adverse Events (SAEs)** are defined in the traditional manner, as any untoward medical occurrence that, at any severity level: results in death; requires hospitalization or prolongation of hospitalization; results in persistent or significant disability/incapacity; is life-threatening; is a congenital anomaly or a birth defect; is otherwise medically significant. SAEs should be captured as part of routine programmatic management according to WHO's active tuberculosis drug-safety monitoring and management (aDSM) framework.[69]

AEs of interest are defined as all AEs irrespective of their seriousness, severity or causal relationship to the MDR-TB treatment, pertaining to the following medical conditions:

[68] Gegia M, Magee MJ, Kempker RR, Kalandadze I, Chakhaia T, Goulb JE, et al. Tobacco smoking and tuberculosis treatment outcomes: a prospective cohort study in Georgia. Bulletin of the World Health Organization. 2015; 93: 390-99.

[69] World Health Organization. Active tuberculosis drug-safety monitoring and management (aDSM): Framework for implementation (WHO/HTM/TB/2015.28). Geneva: World Health Organization. 2015.



These nine AEs of interest were chosen because they were known to be related to the new or repurposed drugs, common AEs related to other MDR-TB drugs, or often managed without stopping the drug and therefore not captured in the following category.

AEs leading to treatment discontinuation or change in drug dosage, are any AE, regardless of severity or causal relationship to the MDR-TB treatment, leading to a discontinuation of MDR-TB treatment. This includes permanent and temporary treatment interruption or changes in drug dosage(s) or drug regimen, as decided by the endTB clinician. This category was included because any AE that required discontinuation of the offending drug was likely to be clinically significant. On the other hand, common AEs such as nausea or headache that did not require discontinuation of the causal drug were unlikely to be clinically significant. Some AEs such as hypothyroidism or hypokalemia, however, are routinely treated with replacement therapy without discontinuation of the offending drug—these were included in the previous category.

Adverse events judged as otherwise clinically significant, included any AE, regardless of severity or causal relationship to the MDR TB treatment, not pertaining to one of the above-mentioned categories, but considered of clinical significance by the treating endTB clinician.