REVIEW / DERLEME

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Recent and New Strategies for Extensively Drug-resistant Tuberculosis

Yaygın İlaca Dirençli Tüberküloz için Son ve Yeni Stratejiler

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Abstract

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) are very problematic clinical conditions due to the few therapeutic options and long course of treatment. It is a global public health problem for countries because of its socio-economic characteristics and difficult and long treatment period. It is not easy to evaluate recent treatment options as well as to manage new strategies. In this paper, recent treatment options, new strategies for coping with drug-resistant forms of TB including new drugs and repurposed agents, surgery, nutritional support, laser therapy, host-directed therapies, immunomodulation, gene therapy, cellular therapy, and phage therapy are reviewed.
Keywords: Host-directed therapies, immunomodulation, gene therapy, cellular therapy, phage therapy

Öz

Çok ilaca dirençli tüberküloz (ÇİD-TB) ve yaygın ilaca dirençli TB (YİD-TB) az sayıda tedavi seçenekleri ve uzun tedavi süresi nedeniyle çok sorunlu klinik durumlardır. Hem zor ve uzun tedavi süreci nedeniyle hem de sosyo-ekonomik özelliklerinden dolayı global bir halk sağlığı sorunudur. Son tedavi seçeneklerini değerlendirmek kadar yeni stratejileri idare etmek de kolay değildir. Bu yazıda son tedavi seçenekleri, TB'nin ilaca dirençli formları ile baş edebilmek için yeni ilaçlarla birlikte yeni stratejiler, başka amaçla kullanılan ilaçların bu hastalık için değerlendirilmesi, cerrahi, beslenme desteği, lazer tedavisi, konakçı merkezli tedaviler, immünomodülasyon, gen tedavileri, hücresel tedaviler ve faj tedavisi gibi bazı tamamlayıcı teknikler derlenmiştir.
Anahtar Kelimeler: Konakçı merkezli tedaviler, immünomodülasyon, gen tedavileri, hücresel tedaviler, faj tedavisi

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Introduction

Tuberculosis (TB) is one of the most important infectious causes of morbidity and mortality[1]. In 2016, the World Health Organization (WHO) reported an estimated 10.4 million new cases and 1.3 million TB deaths among HIV-negative (Human Immunodeficiency Virus-HIV) people[2]. In 2015, the number of patients with TB living with HIV reached 1.2 million (11% of new cases). The emergence of drug-resistant forms is the principal challenge in the treatment of TB. Multidrug-resistant TB (MDR-TB) is described as *Mycobacterium tuberculosis* (MTB) strains with resistance to isoniazid and rifampicin (RIF). The global distributions of new and previously treated MDR-TB cases are shown in Figure 1 and 2[1]. Extensively drug-resistant TB (XDR-TB) is also described as MDR-TB with additional resistance to fluoroquinolones and one or more second-line injectable drug (kanamycin, amikacin, and capreomycin). Totally drug-resistant TB has also been reported in India and South Africa[1-3].

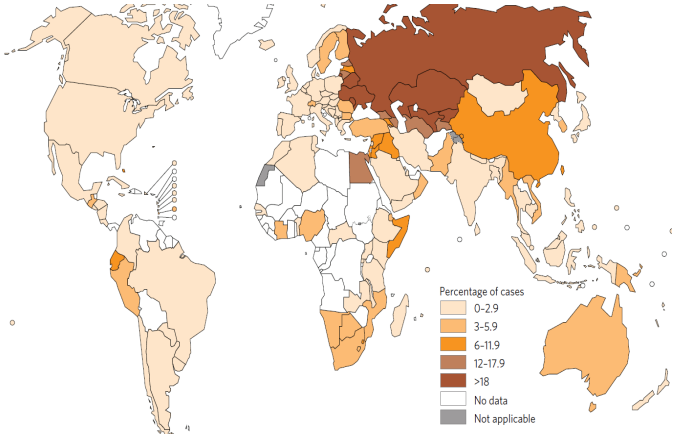

Figure 1. Percentage of new tuberculosis cases with multidrug-resistant tuberculosis[1]

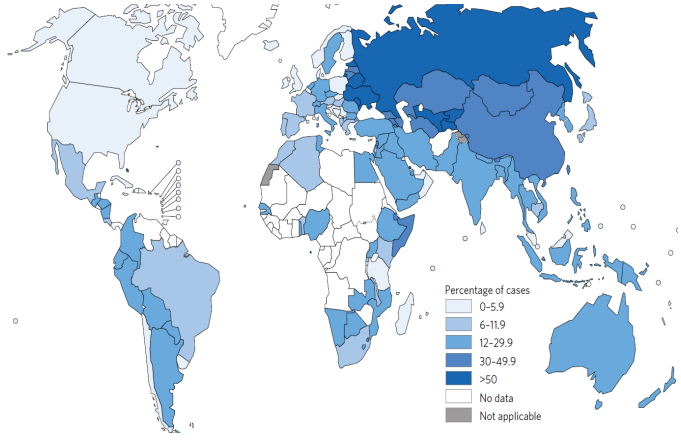

Figure 2. Percentage of previously treated tuberculosis cases with multidrug-resistant tuberculosis[1]

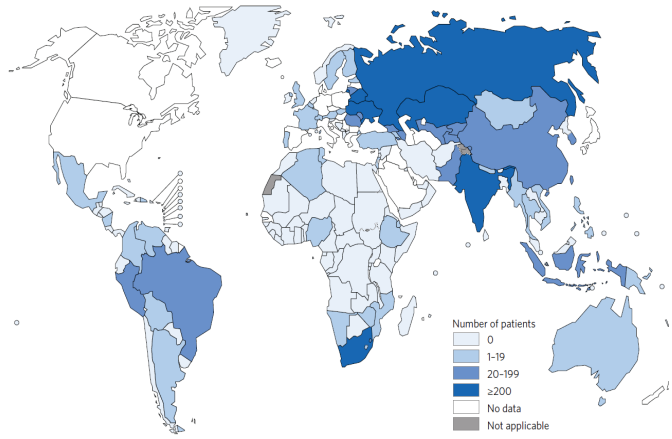

Figure 3. Number of patients with laboratory-confirmed extensively drug-resistant tuberculosis started on treatment in 2015[1]

According to the Global Tuberculosis Report 2016 issued by the WHO, the estimated number of new MDR-TB cases in 2015 was 480,000 (9% of which met the XDR-TB criteria) and these cases existed in more than 100 countries[1]. The number of patients with laboratory-confirmed XDR-TB started on treatment in 2015 is shown in Figure 3[1]. Multidrug-resistant TB and even laboratory-confirmed XDR-TB have become a healthcare problem in Turkey as well as most countries of the world. Komurcuoglu et al.[4] reported that the rates of MDR among new, re-treated, and chronic cases in Turkey were 2.16%, 11.3%, and 92.3%, respectively in 387 male patients with pulmonary TB[5]. According to the 2017 National Tuberculosis Control Report of Turkey, 18 cases of XDR-TB were reported between 2010 and 2015[6]. In this paper, recent treatment options, new strategies for coping with drug-resistant forms of TB including new drugs and repurposed agents, surgery, nutritional support, laser therapy, host-directed therapies, immunomodulation, gene therapy, cellular therapy, and phage therapy are reviewed.

Drug Susceptibility Testing (DST)

More effective MDR-TB treatment requires earlier diagnosis. It is estimated that approximately 50% of MDR-TB patients are not identified due to limited TB culture and DST skill and laboratory requirements. Molecular tests such as Xpert MTB/RIF (Cepheid, CA, USA) and line probe assays enable more rapid detection of RIF and isoniazid resistance. Xpert MTB/RIF ultra has recently been introduced to the market and provides higher sensitivity and faster diagnosis (<80 minutes). Fluoroquinolone resistance, especially acquired-resistance during therapy is also associated with poor prognosis. Thus, second-line drug (SLD) resistance is important in the selection of treatment regimens[7-9].

Strengthening of the laboratory arm is an essential need. The 'Expanding Access to New Diagnostics for Tuberculosis Project'

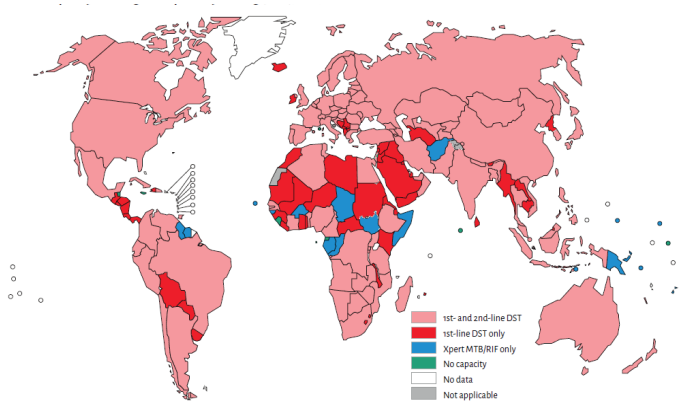

Figure 4. Global capacity for drug-susceptibility testing, 2014[1]
[a]Data for 2013 were used if data for 2014 were not reported (n=6)

is aimed at diagnosing more than 100,000 patients with MDR-TB by supporting 103 TB laboratories in 27 countries which carry approximately 40% of the estimated global burden of MDR-TB[10,11]. WHO 2014 Global Tuberculosis Report defined some improvements in DST standards, including rapid RIF resistance testing with Xpert MTB/RIF systems. The WHO and national TB programs must closely track all patients receiving new drugs to monitor the development of resistance. Global capacity for DST is shown in Figure 4. Following new treatments will be helpful in limiting the spread of new MDR strains, and will also make it possible to collect the strains for researchers and diagnostic companies to identify emerging resistance mutations and develop more effective diagnostic tests relevant to the new drugs[10].

Multidrug-resistant Tuberculosis Treatment

Second-line drugs for treating MDR-TB and XDR-TB are very costly and not easily accessible[7]. In the 2016 Global Tuberculosis Report, the WHO stated that treatment success rates for MDR- and XDR-TB were 52% and 28%, respectively[1].

The grouping of TB drugs has recently been updated. Current WHO guidelines classify anti-TB drugs into five groups and give the basics for the MDR-TB treatment regimens[7]. Conventional and updated drug categories are given in Tables 1 and 2[3].

Treatment is implemented in two main phases. The conventional regimen consists of at least 5 drugs including pyrazinamide and 4 core SLDs, 1 chosen from group A, 1 from group B, and at least 2 from group C. If TB drugs cannot be combined as described, an agent from group D2 and other agents from group D3 could be added to achieve the sufficient number of drugs. The regimen could be strengthened with high-dose isoniazid and/or ethambutol in some cases. This is followed by a continuation phase consisting of a minimum of 4 oral drugs continued until completing at least 20 months of treatment in total[3,7]. Complete treatment increases the long-term cure rate without relapse, but introduces some difficulties. Injections require prolonged hospitalization or daily outpatient visits. Aminoglycosides used for parenteral therapy cause nephrotoxicity and ototoxicity. Drugs that are taken orally and have better safety profiles are preferable[11].

Table 1. Conventional groups of anti-tuberculosis drugs

Group 1	First-line drugs	Isoniazid Rifampicin Ethambutol Pyrazinamide
Group 2	Injectable agents	Amikacin Capreomycin Kanamycin Streptomycin
Group 3	Fluoroquinolones	Levofloxacin Moxifloxacin Ofloxacin Gatifloxacin
Group 4	Oral second-line drugs	Ethionamide/prothionamide Cycloserine/terizidone P-aminosalicylic acid
Group 5	Agents with unclear efficacy	Bedaquiline Delamanid Linezolid Clofazimine Imipenem-cilastatin Meropenem Amoxicillin-clavulanate High-dose isoniazid Thioacetazone Clarithromycin

Table 2. Recommended drugs for the treatment of drug-resistant tuberculosis

Group A	Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin
Group B	Second line injectable agents	Amikacin Capreomycin Kanamycin Streptomycin
Group C	Other core second-line agents	Ethionamide/prothionamide Cycloserine/terizidone Linezolid Clofazimine
Group D	D1	Pyrazinamide Ethambutol High-dose isoniazid
	D2	Bedaquiline Delamanid
	D3	P-aminosalicylic acid Imipenem-cilastatin Meropenem Amoxicillin-clavulanate

TB control programs are successful in the intensive phase of therapy; however, due to the long treatment periods, loss-to-follow-up is a problem during the continuation phase[7].

In Ukraine, a tertiary care facility reported that of 484 MDR-TB patients who were treated between 2006 and 2011, 67% had completed injectable treatment; however, only 22% had successful results at 20 months[12]. Another study in India indicated that factors associated with poor treatment compliance amongst MDR-TB patients were thought to be lack of service provider support and financial limitations[13]. These findings show that more practical and shorter treatment is required.

Patients coinfected with HIV and drug-resistant TB have an increased risk of death[14]. There are more drug interactions between SLDs and antiretroviral therapy (ART) compared to first-line anti-TB drugs. Side effects can overlap, and all of the drug interactions between new anti-TB drugs and antiretrovirals are not known.

New MDR-TB treatment regimens are required to have oral delivery, a good side-effect profile, shorter duration regimens, and minimal interaction with antiretrovirals[15].

Programmatic Management of Drug-resistant (PMDT) Tuberculosis

Programmatic management of drug-resistant TB is a TB control program. The strategy is designed to treat MDR-TB in developing countries by SLDs with the Directly Observed Treatment, Short Course (DOTS) chemotherapy strategy.

DOTS would be prioritized above DOTS-Plus since DOTS aims to decrease the occurrence of MDR-TB, and thus, is a requirement for DOTS-Plus. Directly Observed Treatment, Short Course Plus (DOTS-Plus) was developed as a comprehensive initiative that was to build upon the elements of DOTS. However, it would take into account specific issues such as the use of second line anti-TB drugs, which are needed to be used in resource limited settings where there are significant levels of MDR TB. Multidrug-resistant TB patients under this program receive a standardized treatment, known as Category IV regimen, consisting of 6 drugs (kanamycin, levofloxacin, ethionamide, cycloserine, pyrazinamide, and ethambutol) for 6-9 months as the intensive phase and 4 drugs (levofloxacin, ethionamide, cycloserine, and ethambutol) during the 18 months of the continuation phase. Para-aminosalicylic acid is substituted if any bactericidal drug (kanamycin, levofloxacin, pyrazinamide and ethionamide) or any 2 bacteriostatic (ethambutol and cycloserine) drugs are not tolerated[16]. This regimen is very convenient for high TB-prevalent and low-income countries. Injectable agents should be administered for at least six months and treatment duration should be a minimum of 18 months after sputum conversion. Standardized second-line treatment has been shown to be applicable and cost-effective in MDR-TB[16,17].

According to the 2016 updated version of the WHO treatment guideline for drug-resistant TB, patients receiving shorter MDR-TB treatment regimens had a significantly higher chance of treatment success than those who received longer regimens (90% vs. 78% when success was compared with treatment failure/relapse/death and 84% vs. 62% when compared with treatment failure/relapse/death/loss to follow-up). The number of relapses was very low, although this may be due to the relatively small number of patients followed. As expected, treatment success was lower among patients with additional resistance to pyrazinamide and/or fluoroquinolones on shorter MDR-TB regimens, as well as higher in patients on longer regimens (although the differences were not statistically significant)[3].

Shorter, simpler, and more successful new regimens for the treatment of TB are needed. At the same time, adjunctive treatment options such as immunotherapy and TB surgery should be considered.

Shortening Therapy with Existing Drugs

Short-term treatments are aimed at increasing compliance rates. Different combinations of drugs from existing anti-TB agent groups have been used to shorten MDR-TB treatment. The "Bangladesh regimen" was framed as 7 drugs [kanamycin, clofazimine, gatifloxacin or moxifloxacin, ethambutol, high-dose isoniazid, pyrazinamide, and prothionamide (Pto)] for four months and the following five months with 4 drugs (gatifloxacin, ethambutol, pyrazinamide and clofazimine)[7]. Two different studies were carried out with this regimen. Cure rates of 81% and 82% were achieved[18,19]. Another approach for short therapies was carried out in Cameroon. A cure rate of 88% was reported[20]. A difference from the Bangladesh regimen was that the quinolone dosage was standard. In both short regimens, the intensive phase was prolonged until sputum smear conversion. All short-course treatments were very successful with almost no relapse and low death rates (0.6%)[20]. However, short MDR-TB regimens are recommended by authorities only if the treatment is administered under research conditions and under close monitoring. Those regimens have not been evaluated for the treatment of XDR-TB and high-level fluoroquinolone resistance[7,21].

Repurposed Agents

Linezolid (LZD), fluoroquinolones, clofazimine, and meropenem-clavulanate are considered for the treatment of drug-resistant TB in general[16,22].

Clofazimine and meropenem-clavulanate are not preferable drugs in the management of difficult drug-resistance cases[23,24].

High-dose isoniazid in the treatment of MDR-TB needs further analysis[25].

Linezolid

Oxazolidinones are another drug class in MDR-TB management. Outcomes improved when LZD was included in MDR-TB and XDR-TB regimens[26,27]. These drugs can be administered via oral route and are considered one of the most effective group 5 anti-TB drugs. As with other SLDs, side-effects must be weighed against expected anti-TB efficacy. In a study from South Korea, 31/39 (87%) pulmonary XDR-TB patients who had previously failed chemotherapy achieved sputum culture conversion within six months of adding LZD to their regimens[7,28] and only four (10%) had reported LZD failure. However, severe side effects such as myelosuppression and peripheral or optic neuropathy were encountered in 82% of patients within the first 24 weeks[7,29]. Similar results were seen in a clinical trial in China[7,30]. Linezolid toxicity is generally dose-dependent and the optimal dose in TB patients has not been established. The standard dose is 600 mg twice daily for non-TB bacterial infections; daily doses of 300-600 mg once daily would be recommended for TB[7,31]. Studies are needed to establish whether reduction of LZD dose in multidrug regimens longer than six months (especially in XDR-TB when other alternatives are not possible), causes amplification of bacterial resistance to LZD.

Linezolid safety is especially important for countries with high rates of HIV infection, because HIV disease and ART can already cause bone marrow toxicity and neuropathic complications. Some data from MDR-TB and XDR-TB cases in South Africa and India suggest that HIV infection increases the risk of LZD side-effects, such as neuropathy and myelosuppression, but no better outcomes from using the drug[7,32].

Linezolid is an expensive drug; thus, access to LZD in low-resource countries is not easy outside the context of clinical trials (e.g., Nix-TB and PRACTECAL)[7]. Nonregistered drugs can be provided by funds and may help reduce costs, as long as quality can be assured[7,27].

Sutezolid and posizolid are newer oxazolidinones currently in phase 2 clinical assessment. If they are efficient with lower toxicity than LZD, they may have greater importance for MDR-TB treatment[7]. Tedizolid is another second-generation oxazolidinone and has a good intracellular mycobactericidal activity. Its safety and tolerability seem comparable to LZD. However, further analysis is needed to confirm these findings[33].

Fluoroquinolones

Later generation fluoroquinolones are promising agents with potential sterilizing effects. A number of studies, many of which are randomized controlled trials, have been conducted to investigate whether fluoroquinolones can be used to shorten the duration of TB treatment[34].

Both levofloxacin and moxifloxacin are generally used to treat MDR-TB. Levofloxacin is more commonly available than moxifloxacin, but is more expensive. An advantage of levofloxacin is its availability in suspension form.

Gatifloxacin is a more affordable drug that was commonly used in TB treatment programs. However, its dysglycemic effects emerged as a major side effect. If the manufacturers could resolve this problem, gatifloxacin may be a good alternative to more costly fluoroquinolones. Its only commercially available form is an ophthalmic solution[3].

Other Repurposed Drugs

Several additional antibiotics are listed in WHO group 5 anti-TB drugs. Clofazimine is a fat-soluble rhiminophenzine dye used in the treatment of leprosy. It does not demonstrate rapid bactericidal effect in the first two weeks of treatment, but it is supposed to improve long-term outcomes[7,23]. Clofazimine is an important component of the Bangladesh regimen[7].

There is weak clinical evidence supporting the use of meropenem-clavulanic acid,[35] imipenem, or macrolides[7,36] for TB treatment. The use of these drugs is limited due to extensive resistance, toxicity, or poor supply.

In a double-blind, placebo-controlled trial, pulmonary MDR-TB subjects were given metronidazole (500 mg three times daily) or placebo for eight weeks in addition to a background regimen[16]. In the metronidazole arm, sputum smear conversion (p=0.04) was achieved in more subjects at one month, but this difference was lost by two months. Overall, 81% showed clinical success six months after stopping therapy, with no differences. Newer nitroimidazoles may increase the sterilizing potency of future treatment regimens[16,17,37].

New Anti-TB Drugs

New drugs have refreshed hopes of treating MDR-TB. However, access to these drugs is very limited, particularly in countries with the highest TB burden and low resources[7]. Ideally they should be affordable, safer, and more effective. The development pipeline of TB drugs is given in Figure 5.

Bedaquiline (BDQ)

Bedaquiline is the first new anti-TB drug in over four decades. It is a diarylquinoline that interferes with mycobacterial adenosine triphosphate synthesis and has a significant early bactericidal activity[38,39].

Bedaquiline is an orally administered drug. World Health Organization approved BDQ for the first 24 weeks of pulmonary MDR-TB treatment. Bedaquiline is also allowed to be used during the 'intensive phase' of prolonged regimens for XDR-TB[7].

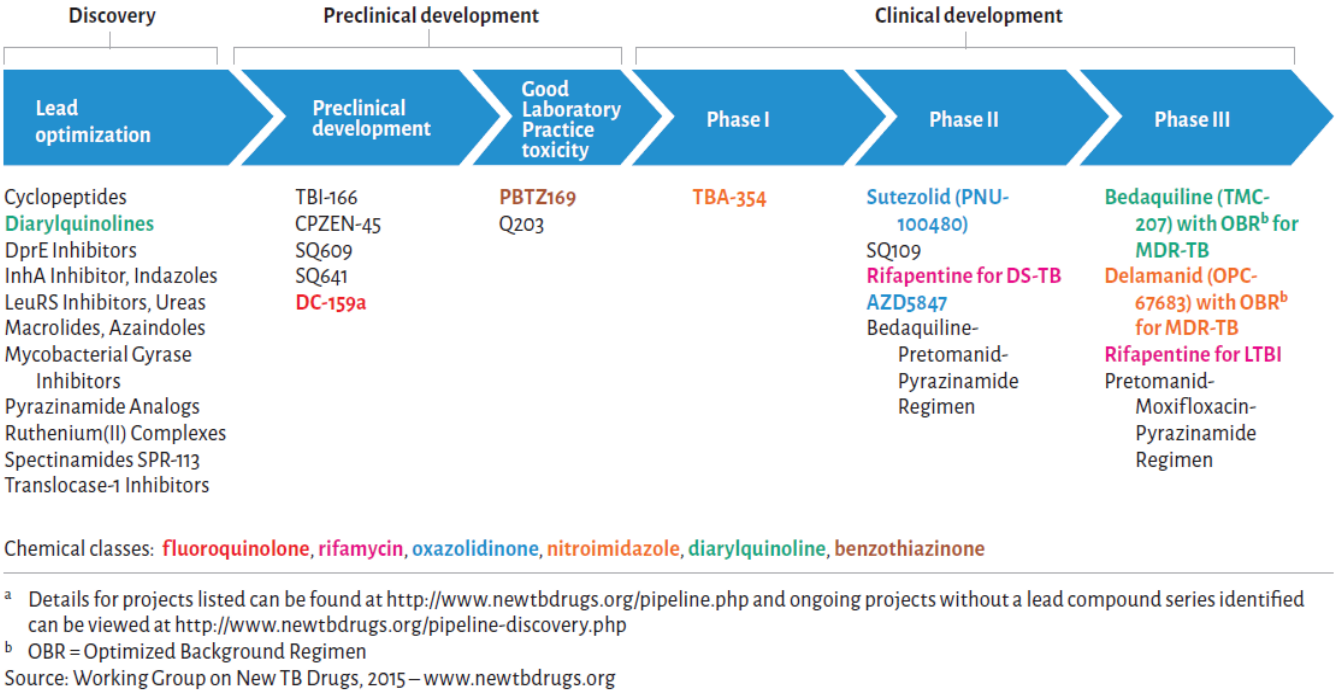

Figure 5. Development pipeline for new tuberculosis drugs[2]

DS-TB: Drug susceptible tuberculosis,

LTBI: Latent tuberculosis infection

Successful results with BDQ also suggested that it inhibited the development of mycobacterial resistance to the other drugs in the regimen[40]. A trial of six-months BDQ treatment demonstrated reduced culture conversion time (83 days vs. 125 days), higher culture conversion rates at 24 (79% vs. 58%) and 120 weeks (62% vs. 44%), and higher cure rate at 120 weeks (58% vs. 32%) compared to a regimen not including BDQ[41].

There are some safety concerns regarding BDQ. Bedaquiline creates QTc prolongation. It has a terminal half-life of 5.5 months and is extensively distributed and accumulated in the peripheral tissues. Its long-term effects must be demonstrated for more complete toxicity data[7].

Mortality was reported to be 5-fold higher in patients taking BDQ compared to those who were not [10/79 (13%) in BDQ group and 2/81 (2%) in placebo group][41]. These deaths are under investigation, but BDQ is known to prolong the QT interval in some patients[42].

There are no current data on the use of BDQ in special patient groups such as children, those with extrapulmonary TB, pregnant and breastfeeding women, or HIV-infected persons on antiretroviral therapy.

In low-resource settings, drug cost is an important issue. Bedaquiline is too expensive for many high-burden countries. Solutions such as donation by manufacturers to low-resource countries or differential pricing strategy are being investigated[43].

The NExT trial is an ongoing open-label randomized controlled trial of a six-nine month injection-free regimen containing BDQ, LZD, levofloxacin, ethionamide/high-dose isoniazid, and pyrazinamide for the treatment of MDR-TB. It was launched in South Africa in October 2015 and will be completed in 2019. The drug regimen includes a combination of strategic drug classes, a fluoroquinolone, a repurposed agent, and a new drug. As the regimen consists completely of oral drugs, it is especially suitable for MDR-TB patients with HIV coinfection[34].

Nitroimidazoles

There are two new nitroimidazole drugs under clinical evaluation for the treatment of MDR-TB: delamanid (DLM) and pretomanid (PTM). These drugs exert their effects by inhibiting mycolic acid synthesis in the mycobacterial cell wall[7,44]. They are both oral drugs.

Delamanid has been studied much more than PTM. Delamanid was found to be more effective compared to placebo in terms of rates of sputum culture conversion at 2nd month (45.4% vs. 29.6%, p=0.008) in a phase 2b randomized controlled trial in adults with pulmonary MDR-TB[7,45]. An open-label extension of this trial showed that patients who were administered DLM for 2-6 months had higher rates of cure or treatment completion (75% vs. 55%, p<0.001) and lower mortality (1% vs. 8%, p<0.001) than those who took DLM for ≤2 months. Low mortality was also seen in XDR-TB (0% vs. 25%, p<0001)[7,46]. These phase 2 data led to regulatory approval in Europe and Japan.

Table 3. Ongoing and planned phase 3 trials of delamanid, bedaquiline, prothionamide, and linezolid in pulmonary tuberculosis patients[7]

Study	Locations	Participants	Regimens	Planned number of participants	Due to report
STREAM stage 2	Ethiopia Mongolia South Africa Vietnam	MDR-TB	OBR 4Km-CFZ-MFX-E-Hh-Z-Pto → 5MFX-E-Z-CFZ 6BDQ-Km-LFX-CFZ-Z 9BDQ-LFX-CFZ-Z-Hh-Pto	1155	2021
Nix-TB	South Africa	MDR-TB XDR-TB	6BDQ-Pa-LZD (single-arm study)	200	2021
NEXT	South Africa	MDR-TB	OBR 6-9BDQ-LFX-LZD-ETO-Z 6-9BDQ-LFX-LZD-ETO-H 6-9BDQ-LFX-LZD-ETO-Trd	300	2019
NCT01424670	Estonia, Latvia, Lithuania, Moldova, Peru, Philippines, South Africa	MDR-TB	6OBR-DLM 6OBR-Placebo	511	2017
STAND	Brazil, China, Georgia, Haiti, Kenya, Malaysia, Mozambique, Peru	DS-TB MDR-TB XDR-TB	6Pa-MFX-Z 2HRZE → 4RH (control arm in DS-TB only)	1500	2018
PRACTECAL	Uzbekistan Swaziland	MDR-TB XDR-TB	BDQ-Pa-LZD-MFX BDQ-Pa-LZD-CFZ BDQ-Pa-LZD	630	2020
endTB (part 1)	Kazakhstan, Kyrgyzstan, Lesotho, Peru, Georgia	MDR-TB	BDQ-LZD-Hh-MFX-Z BDQ-CFZ-LZD-LFX-Z DLM-LZD-Hh-MFX-Z DLM-CFZ-LZD-LFX-Z DLM-CFZ-MFX-Z OBR (may include DLM or BDQ)	600	2019

Numbers preceding drug regimens indicate planned months of therapy.
TB: Tuberculosis, BDQ: Bedaquiline, CFZ: Clofazimine, DLM: Delamanid, DS-TB: Drug-sensitive-TB, E: Ethambutol, ETO: Ethionamide, H: Isoniazid, Hh: High-dose isoniazid, Km: Kanamycin, LFX: Levofloxacin, LZD: Linezolid, MDR-TB: Multidrug-resistant-TB, MFX: Moxifloxacin, OBR: Optimized background regimen, Pa: Pretomanid, Pto: Prothionamide, R: Rifampicin, T: Terizidone, XDR-TB: Extensively drug-resistant-TB, Z: Pyrazinamide

World Health Organization interim guidance has been published to inform programmatic use[7,47]. Planned or ongoing phase 3 trials of DLM, BDQ, Pto, and LZD in adult pulmonary TB patients are summarized in Table 3. The endTB trial will evaluate 9-month BDQ or DLM-containing regimens at certain time points for prevention of poorer outcomes[48].

Delamanid prolongs the QTc interval on electrocardiograms[7]. Its metabolite, DM-6705, was found to cause toxicity. Serum albumin regulates the formation of DM-6705 and use of DLM is contraindicated in patients with hypoalbuminemia. However, excessive mortality has not been reported in patients receiving DLM[7].

Experience with DLM use in low-resource settings is more limited than BDQ due to lack of regulatory approval and the cost of the drug[7]. The prices of DLM and BDQ are approximately 1,700 USD and 24,000 USD per course, respectively[49].

For national TB programs wishing to provide DLM, the WHO advises that MDR-TB patients should be appropriately informed and provide consent to receive an experimental drug and that a secure infrastructure for pharmacovigilance should be in place[7,47].

There are reports of BDQ and DLM being used in the same regimen. Manufacturers and WHO currently do not recommend this. Due to the long half-life, patients who have previously received BDQ must wait six months before DLM is administered. The half-life of DLM is much shorter (38 hours). It is advised to wait a minimum of five days before replacement with BDQ[7,49].

Other New Drugs

Studies are ongoing to evaluate the clinical effectiveness of new drugs. One of them, a US National Institutes of Health-sponsored study (ACTG 5343), was planned to be launched in South Africa to assess the coadministration of BDQ and DLM. Depending on the results of this study, the second part of the endTB trial will be assessed in terms of clinical utility for patients with fluoroquinolone-resistant TB[7].

The other nitroimidazole, PTM, is not licensed yet. However, it has displayed good bactericidal activity in combination with moxifloxacin and pyrazinamide during the initial 2-8 weeks of therapy according to phase 2 studies in drug-susceptible TB[7,26,27]. Phase 3 of the Shortening Treatments by Advancing New Drugs Trial will demonstrate its possible efficacy at 50 sites worldwide.

A combination of BDQ-PTM-LZD has been studied in phase 2a assessment. The open-label, single-arm phase 3 Nix-TB trial in South Africa is planned to estimate its efficacy as a rescue therapy in XDR-TB[33]. Pretomanid is also being studied in the randomized, open-label phase 2/3 TB-PRACTECAL trial to collect data regarding several PTM-containing regimens in Uzbekistan and Swaziland. Combined PTM-moxifloxacin-pyrazinamide seems to be promising for the treatment of TB[7,26,27].

Side Effects of Second-line Drugs

Contrary to general belief, in clinical practice, the rates of adverse drug reactions attributed to SLDs are not very high[16]. In a study among 98 MDR-TB patients treated with a modified strategy of PMDT TB, formerly known as DOTS-Plus, it was reported that nausea and vomiting occurred in 24.5%, hearing disorders in 12.3%, dizziness/vertigo in 10.2%, and arthralgia in 9.2% of patients[16]. Other side effects were gastrointestinal intolerance, hypothyroidism, and hepatitis. Agents responsible for these adverse effects were believed to be kanamycin, cycloserine, ethionamide, and pyrazinamide (ototoxicity, headache/psychosis, gastrointestinal intolerance/hypothyroidism, arthralgia/hepatitis, respectively[16,50]. Another study conducted with 39 MDR-TB patients reported that 41% of patients expressed some complaints, but only 21.1% of patients needed to stop or drug change. Thus, it was concluded that MDR-TB patients could be treated with these drugs in the clinical setting[16,17].

Surgery

Surgery may be added to chemotherapy, especially for drug-resistant but anatomically localized disease[7,51]. It is a treatment approach adjunct to chemotherapy. Resection is the most preferred surgical procedure. Chemotherapy should be given for at least two months prior to surgery and should be continued for 12-24 months after resection. This approach is indicated in patients who remain sputum-positive despite appropriate drug treatment and have localized pulmonary disease[52]. There are also different reversible surgical methods for cavitary disease, such as collapsing the lung by artificial pneumo-peritoneum or pneumothorax by compression of the cavity, that change the local environment and inhibit mycobacterial growth. Therefore, artificial pneumo-peritoneum and pneumothorax may be recommended in selected cases[53]. Controlled studies are needed to support the utility of surgical treatment of MDR-TB.

Possible New Approaches to Improving Outcomes of Drug-resistant TB

High-dose Fluoroquinolones

Fluoroquinolones at high doses can be effective even in fluoroquinolone-resistant MDR-TB and XDR-TB[54]. Gatifloxacin has been used in high doses for this purpose[34].

The Bangladesh regimen is based on high-dose gatifloxacin, up to 800 mg once daily, combined with clofazimine, ethambutol, and pyrazinamide for nine months and the addition of kanamycin, Pto, and high-dose isoniazid (10 mg/kg/day) for a minimum of four months. This is a shortened version of the MDR-TB treatment regimen given to patients who were previously untreated with SLD[55]. This regimen might support the dose-dependent bactericidal and sterilizing effect of the new generation fluoroquinolones[54], and high-dose fluoroquinolone would also decrease the risk of resistant mutants of *M. tuberculosis* strains emerging. Fluoroquinolones in the treatment of bacterial infections, especially those related with the lower respiratory tract, should be mimimized to constrain the development of bacillary resistance to fluoroquinolones[56].

Major adverse reactions were less common than expected (<10%) with the Bangladesh regimen[55]. Unfortunately, gatifloxacin supply is decreasing worldwide and other new fluoroquinolones are more expensive. Furthermore, efficacy and safety issues require further research. For this purpose, there are two ongoing studies, the STREAM and the Opti-Q trials, which are investigating efficacy of moxifloxacin[50] and levofloxacin (NCT01918397), respectively. The STREAM trial has recently included an additional arm to evaluate the utility and security of BDQ. Levofloxacin was used as the fluoroquinolone in this arm. The side-effects of new generation fluoroquinolones, especially the additive risks of cardiotoxicity due to the addition of BDQ, are under close scrutiny[57].

Nutritional Support

Adequate nutritional support is a crucial aspect of TB treatment. Food support may upgrade treatment compliance in settings with food insecurity[58]. Vitamin B6 (pyridoxine) should be given to all patients receiving cycloserine, terizidone, high-dose isoniazid, and LZD to prevent adverse neurological effects. Vitamins (especially A and D) and mineral supplements (zinc, selenium) can be given to patients who have relevant deficiencies[16].

Timing of administering multivitamins and minerals (zinc, iron, calcium, etc.) is important so as not to interfere with drug absorption[7]. For example, they should not be given within three to four hours of administering fluoroquinolones[59].

Laser Therapy

In some countries, such as Russia, laser therapy has also been tested as an adjunct to chemotherapy[16]. The main purpose is its potential efficacy in multicavitary disease with heavy bacterial loads when there is a higher risk of failure with medical treatment. The treatment aims to kill bacteria quickly by increasing and improving penetration of anti-TB drugs through the walls of cavitary lesions[16]. There is proven benefit in cases of tracheal and bronchial stenosis due to endobronchial lesions[60].

Host-directed Therapies (HDTs)

Host-directed therapies (HDTs) have arisen as a new and promising development against drug-sensitive and resistant forms of TB[61]. When antibiotic choices are restricted, augmenting host immunity has also been considered to support TB treatment. Host-directed therapies modify pathological immune responses by directly modulating host cells. In TB, HDTs may neutralize excessive inflammation in organs and limit *M. tuberculosis* proliferation[62,63]. Host-directed therapies target autophagy prevention, regulation of the vitamin D pathway and anti-inflammatory modulation. Nevertheless, trials of vitamin D supplementation have not demonstrated significantly improved outcomes as expected[7,64]. Host-directed therapies are not likely to be a good alternative for clinical use in the near future[65]. Some immunomodulatory agents for the treatment of MDR-TB are given in Table 4.

Mycobacterium vaccae vaccine has been suggested as an adjunctive therapy agent to improve results when given to drug-resistant TB patients who previously received unsuccessful chemotherapy[66]. Vaccination with *M. vaccae* modulates immune responses by increasing proinflammatory cytokines like interleukin-2 (IL)-2, IL-12, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α), inhibiting anti-inflammatory cytokines like IL-4, IL-5, IL-10, raising levels of some another humoral factors, or converting destructive Th2 immune reactions to the beneficial Th1 response[16]. Although the benefits of these therapies must be confirmed in randomized controlled trials, successful results have been reported in some cases of drug-resistant TB[67].

As another HDT, granuloma-targeted therapy, may benefit in treatment and prevention of TB. Transforming growth factor-β (TGF-β) is a major fibroblast growth factor that stimulates the granuloma formation. Inhibition of TGF-β in particular has been proposed as a good therapeutic target to minimize the negative effect on protective immune responses. Transforming growth factor-β gene polymorphisms have been related to *M. tuberculosis* susceptibility in humans.

Table 4. Some immunomodulatory agents for the treatment of multidrug-resistant tuberculosis. The aim of the therapeutic modulation of the immune system is to support the host immunity to control tuberculosis disease and to reduce the duration of chemotherapy. Some partial success has been achieved. Mesenchymal stromal cells represent a population of tissue-resident non-hematopoietic adult progenitor cells[62-64]

Immunomodulatory agent	Host target	Currently licensed indication(s)	Biological activity
Metformin	AMPK activator	Diabetes	Augments mitochondrial activity, intracellular *M. tuberculosis* killing
Zileuton	5-lipoxygenase inhibitor	Asthma	Inhibits 5-lipoxygenase and decrease formation of leukotrienes
Ibuprofen	COX inhibitor	Pain and fever relief	Inhibits COX2 and COX1; reduces lung pathology and *M. tuberculosis* load
Aspirin (acetylsalicylic acid)	COX inhibitor	Pain and fever relief	Inhibits COX1, lessen TNF-α-induced over inflammation; aids tissue repair and control of *M. tuberculosis* load
Valproic acid	HDAC inhibitor	Epilepsy and bipolar disorder	Increased CD8 T cell activity; can induce autophagy and apoptosis
Carbamazepine	GABA receptor agonist and sodium channel stabilizer	Epilepsy and neuropathic pain	Induces autophagy, potentiating killing of intracellular *M. tuberculosis*; improves immune responses
Vorinostat	HDAC inhibitor	Cutaneous T cell lymphoma	Inhibits HDAC I, II and IV to block histone deacetylation; can induce autophagy and apoptosis;
Cyclophosphamide	DNA alkylating agent	Lymphomas and pre-transplant preconditioning	Beneficial immune responses in severe pulmonary TB
Prednisone	Glucocorticoid receptor agonist	Immunosuppressant used in cancer and inflammatory diseases	Activated downstream signaling of the GC receptor; results in TB patients inconclusive and requires further validation
Vitamin D3	Innate immune response activator	Dietary supplement	Kills intracellular *M. tuberculosis*; activates innate immune responses in macrophages; augments IL-32 and IL-15-mediated immune responses in clinical TB
Interleukin 15	Involved in CD8 memory T cells maintenance	In clinical trials for various cancers	Increases mitochondrial mass and fatty acid oxidation in memory CD8 T cells; augments IFN-γ and vitamin D3-mediated immune responses in human TB

Adopted from https://wwwnc.cdc.gov/eid/article/22/3/15-1228-t1

COX: Cyclooxygenase, HDAC: Histone deacetylase, TB: Tuberculosis, TNF-α: Tumor necrosis factor-alpha, IL: Interleukin, IFN: Interferon, AMPK: Adenosine mono phosphate-activated protein kinase, CD4: (cluster of differentiation 4), CD8: (cluster of differentiation 8), GABA: gamma-aminobutyric acid

Inhibition of TGF-β expression has been shown to be an effective immumunomodulatory approach *in vitro* and *in vivo*.[68] .

Thalidomide inhibits the release of TNF-α from peripheral blood monocytes[16]. Significant weight gain has been observed in patients with active TB[16,69]. However, further studies are needed to determine whether thalidomide agents can facilitate recovery from tissue injury in TB[70,71].

The potential role of various agents such as transfer factor, indomethacin, and levamisole has been studied, but the outcomes are not yet certain[16]. More rapid radiological clearing was reported in a levamisole-treated group, but it has not been associated with a significant clinical effect[17,72,73].

Mycobacterium w vaccine is another vaccine that shares common antigens with *M. leprae* as well as *M. tuberculosis,* suggesting possible benefit via its application in the treatment of TB. *Mycobacterium w* vaccine is as an effective immunomodulator in the treatment of leprosy. It increases bactericidal activity and reduces the lesions when used as an adjuvant treatment for leprosy[16]. A randomized-controlled study demonstrated that duration of therapy may be shortened, but sputum conversion rate was unchanged compared to traditional short-course chemotherapy in both new and re-treatment cases of TB[16,17,74,75].

Gene Therapy

Decoding and identifying genes has enabled the development of drugs that target these specific mycobacterial genes in future therapeutic interventions[16,76].

Cellular Therapy

Bone marrow-derived mesenchymal stromal cells and antigen-specific T cells have been studied as potential therapeutic options for treating drug-resistant TB[77]. Mesenchymal stromal cells act as immune effector cells in the treatment of infectious diseases. Their therapeutic target is reduction of inflammation and improved tissue regeneration. When tissues are injured, bronchoalveolar stem cells proliferate and restore lung epithelium. Mesenchymal stromal cells have been shown to be immune-modulating and have anti-inflammatory action via cell-cell contacts and soluble factors[78].

Antigen-specific T cells are currently used in cancer immunotherapy and are successfully used to treat post-transplantation opportunistic viral infections. It has been suggested that antigen-specific T cells can be used as TB therapy by targeted killing of *M. tuberculosis*-infected host cells[79].

Cellular therapy could offer salvage therapy options for patients with drug-resistant TB and possibly shorten the duration of anti-TB therapy[79].

Phage Therapy

Mycobacteriophage therapy is another potential alternative treatment for *M. tuberculosis* infection. Mycobacteriophages are bacteriophages that are able to infect and kill *M. tuberculosis*. The mycobacteriophages Bo4 and TM4 in particular are shown to have the ability to infect and lyse mycobacterial strains. They are effective on viable intracellular bacilli, even those harbored in macrophages. It has been indicated that these phages do not contain any harmful genes that increase mycobacterial virulence or decrease human immunity. Though phages have treatment potential in TB therapy, the technology is still in the *in vitro* and animal study stages, and requires further research[80,81].

Challenges for New Treatment Strategies

There are some important obstacles facing all new therapeutic strategies. Among these are safety and financial issues. These are relevant to diagnosis and treatment options. Ongoing trials will provide insight into the safety profiles and effectiveness of new approaches. However, data from those trials will become available over the coming years. In the meantime, healthcare providers need guidance. The European Respiratory Society/WHO has established a platform for an international consilium[82] through which clinicians may present and discuss complex cases[7]. Data collected by that consilium may help standardize and improve knowledge about the reliability of new treatments.

An improved drug-resistant TB control program may require new drugs, which are very expensive. Diagnostic tests, hospitalization, direct expenses to the patient, and follow-up monitoring should be considered from this point of view[7,83-87].

Argument for Restricting New Drugs

Prescription of inadequate or inappropriate drug regimens results in treatment failure. Due to evidence of poor prescribing practices worldwide, it has been argued that restricting the use of new TB drugs to central hospitals, public clinics, or authorized providers may help promote correct prescribing. A study reported that 89.3% of private physicians in the Philippines gave inappropriate treatment to TB patients[17,88].

Some countries have already applied limitations on TB drug prescribing to reduce inaccurate treatment practices. Tuberculosis drugs are only available from government institutions in these countries[89]. A similar system is also in place in Turkey. Although Brazil is one of the 22 highest TB burden countries worldwide, the incidence of MDR-TB is relatively low[21]. These restrictions are not implemented in most other countries with a high TB burden. For example, Médecins Sans Frontières made an emergency call for the regulation of the TB

drug supply in India in order to impede the rising rates of TB drug resistance[17,90].

One of the potential benefits of restricting the use of new drugs to skilled centers is enabling closer monitoring of adverse drug reactions and interactions. Some new anti-TB medications have severe toxicity profiles that may not be fully recognized by inexperienced healthcare providers[91,92]. It is expected that the risks of treatment and the benefit expected from the new treatment options will balance each other in terms of saving lives. Restricting the use of new drugs may interrupt global efforts to expand the delivery of needed MDR-TB care.

The Green Light Committee (GLC) was established in 2000 by the Stop TB Partnership[17]. It was created to supply low-cost, quality-assured SLDs. The GLC carries out programs funded by the Global Fund to Fight AIDS, TB and Malaria according to WHO guidelines. Although the GLC successfully supplied drugs and ensured their appropriate use, only 29,000 MDR-TB patients were started on treatment in ten years[17,93], a very small proportion of patients worldwide. The committee reconsidered their approach to regulation and the GLC has been repurposed into a less centralized program for improving drug accessibility[17,94]. The GLC decided to give assistance and education to countries that did not meet eligibility criteria to enable them to import specific SLDs.

Regulations that restrict new drugs to referral centers may obstruct access to care. In some countries, such as Ethiopia, Malaysia, and Argentina, TB treatment adherence has worsened due to the long distances and transportation costs[95-97]. Countries have reported numerous problems related to limited usage, such as long waiting lists, loss to follow-up, and the exclusion of critical populations such as refugees, prisoners, and migrants[17,98].

Curing patients with MDR-TB and reducing their infectiousness are the main objectives of TB control programs. However, while some argue for restricting new TB drugs to hinder their misuse, recent data suggest that primary transmission of drug-resistant TB, as opposed to treatment failure, may be an increasing cause of drug-resistant TB cases[99]. Providing new drugs may help reduce resistance rates through more effective treatment regimens. Therefore, the management of MDR-TB cases should be decentralized to the community level[17].

Other beneficial measures may include training healthcare providers for monitoring patients for treatment compliance, administering injectable SLDs, and referring cases with poor treatment response or severe drug-related side-effects to a higher level of care[17]. They may be trained to use new technologies and mobile telecommunication devices to monitor compliance[17,100-102], collect patient data, and share questions or concerns with providers[101]. Communication via text message and video-based directly-observed therapy may help improve adherence to treatment in developing countries[102-105]. More regulations like these may be possible without limiting access to treatment. Finally, local community-based organizations can be involved to help educate patients regarding TB prevention and treatment and to reinforce positive messages that TB is curable and that treatment is free[17].

Treatment Monitoring

Monitoring of treatment is essential and should include bacteriological, radiological, and clinical methods. Sputum specimens should be examined by smear and culture monthly starting from the third month of the intensive phase of therapy. Sputum conversion is defined as two sets of consecutive negative smears and cultures from samples collected at least 30 days apart[16,68]. If monthly smears and cultures are not possible, at least five smears and cultures must be done for follow-up (at months 4, 6, 12, 18 and 24) and X-rays should be done every six months. Clinical evaluation is recommended on a monthly basis[16,17].

In Turkey, implementation of the family medicine system over the last decade had negatively affected the TB control program. Experienced medical staff were transferred to other medical areas and the number of special TB control clinics was reduced. It is hoped that this situation will be rectified with the new regulations recently put into effect. Tuberculosis high-risk groups should be followed closely. Laboratory infrastructure, early diagnostic systems, and the notification system should be strengthened[106].

Conclusion

In summary, the increased burden of MDR-TB threatens TB control. New therapeutic strategies may gradually reduce dependence on injectable agents, lessen toxicity, and shorten treatment duration. However, trials seeking the most effective regimens are still ongoing. Meanwhile, advantages and disadvantages must be weighed to access new drugs without impairing safety. Novel treatments should be integrated in coordination with TB control programs. Drug susceptibility testing should become a standard and widely accessible. Patient support and monitoring systems should be improved.

Ethics

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