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REVIEW ARTICLE

A holistic approach to the treatment of drug-resistant tuberculosis

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Drug-resistant tuberculosis (DR-TB) is associated with lengthy, poorly tolerated, and less effective treatment compared with drug-susceptible TB, as well as high rates of mental health disorders and socioeconomic vulnerability. The aim of this article is to describe the potential of a holistic treatment approach as a complementary strategy to the chemotherapy of DR-TB. At the specialized TB hospital Serveis Clínics in Barcelona, Spain, a multidisciplinary team has implemented a holistic, person-centered approach using comprehensive clinical and psychosocial assessments that address patients' main needs, rather than focusing solely on airborne isolation and observed therapy, thereby improving adherence and outcomes. However, our experience may be difficult to extrapolate to other settings, where limited access to novel drugs, insufficient funding of national TB programs, and poor multisectoral coordination remain significant barriers. In conclusion, future clinical studies should evaluate the integration of malnutrition treatment, pulmonary rehabilitation, and psychological interventions within DR-TB care models.

Keywords: Holistic treatment. Multidrug-resistant tuberculosis. Psychosocial support. Equity.

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INTRODUCTION

Tuberculosis (TB) is one of the most ancient diseases of humankind, with morphological and molecular evidence dating back about 9000 years in a human skeleton from the Eastern Mediterranean[1]. Yet, despite recent advances in diagnosis and treatment, it remains the leading cause of death from a single infectious agent worldwide[2]. One possible explanation for the continued spread of *Mycobacterium tuberculosis* (MTB) is its airborne transmission and remarkable ability to persist without clinical manifestation as TB infection, awaiting immune suppression to progress into active disease[3]. Even in its active form, TB can mimic other conditions, thereby complicating early diagnosis. These biological features, together with social determinants such as war[4], poverty, and migration[5], further facilitate its transmission on a global scale. Moreover, MTB has demonstrated a rapid capacity to develop resistance to antimicrobial agents, including recently introduced anti-TB drugs such as bedaquiline (Bdq), and to disseminate resistant strains within communities[6].

In 2023, the estimated number of rifampicin-resistant TB (RR-TB) or multidrug-resistant TB (MDR-TB, defined as RR-TB with additional resistance to isoniazid [H]) cases was 400,000 (95% uncertainty interval: 360,000-440,000) with annual increases observed in most low- and middle-income countries[2]. Europe is a region where approximately 60% of all TB cases are estimated to be RR/MDR-TB, requiring more complex and costly treatment regimens[2]. In nearly 13% of patients in Europe, TB recurs even after apparently successful treatment[7], underscoring that current pharmacological interventions alone are insufficient to eliminate the disease. Notably, retreatment is associated with a twofold higher rate of RR/MDR-TB compared with new TB cases in the European Region[7], underscoring the urgent need for complementary preventive and therapeutic strategies.

A holistic approach – treating the whole person and not just a part[8], grounded in a comprehensive understanding of patient needs during and after treatment – is a growing trend in other areas of respiratory medicine[9] and oncology[10]. At Serveis Clinics, a specialized TB hospital in Barcelona, Spain, a multidisciplinary team has implemented this principle over the past decade in managing drug-resistant TB (DR-TB), consistently updating practices based on emerging evidence. Apart from conventional strategies that focus primarily on etiological anti-mycobacterial therapy, we consider it beneficial for our patients to address nutrition, emotional well-being, social needs, some adjunctive treatments, and respiratory rehabilitation as integral components of DR-TB care.

The aim of this article is to share our TB management experience and review the potential for a holistic treatment approach as a complementary strategy to chemotherapy for DR-TB.

WHY TACKLING DR-TB IS SO CHALLENGING

TB is a curable disease, but after being largely neglected for more than 50 years, the need for new medicines has become crucial. For

decades, DR-TB treatment relied mainly on repurposed drugs such as clofazimine (Cfz) and off-label use of antibiotics, including linezolid (Lzd), fluoroquinolones (FQs), and carbapenems[11]. When high MDR-TB burden countries in Eastern Europe were facing a growing number of incurable cases due to the lack of effective drug combinations[12], new hope emerged with the accelerated approval of Bdq in 2012 and delamanid (Dlm) in 2014. However, as demonstrated by recent analyses, only 68% of pre-extensively DR-TB (pre-XDR-TB, defined as resistance to rifampicin [R] and FQs) and 40% of extensively DR-TB (XDR-TB, defined as pre-XDR-TB with additional resistance to Bdq and/or Lzd) cases were successfully treated in Europe[13]. Before 2016, conventional treatments for DR-TB required combinations of drugs that often caused debilitating adverse effects, such as hearing loss (from second-line injectables [SLIs]) and neuropsychiatric disturbances (from cycloserine [Cs]), administered over nearly 2 years[14]. These regimens significantly affected treatment tolerability and led to non-adherence[15], prompting healthcare providers worldwide to implement additional support interventions beyond directly observed therapy (DOT). However, not all adherence-promoting technologies demonstrated sufficient evidence of effectiveness; for example, medication event reminder monitors failed to prove cost-effective, highlighting the need for strategic changes in patient management[16].

In 2016, the first shorter regimen lasting 9-11 months was introduced. This regimen consisted of 4-6 months of kanamycin (Km), moxifloxacin (Mfx), prothionamide (Pt), Cfz, pyrazinamide (Z), high-dose isoniazid (Hh), and ethambutol (E), followed by 5 months of Mfx-Cfz-Z-E[14]. Despite being twice as short as conventional therapy, this regimen was not applicable to the majority of MDR-TB patients in Europe[17]. Moreover, it was widely criticized due to its high pill burden, questionable dosing of Mfx and H in cases with low-level resistance, and limited access to Km in many countries. The regimen was later modified to become the first all-oral regimen, replacing SLIs with Bdq for 6 months[18], thereby reducing the need for hospitalization and making treatment less painful, especially for children. Recently, as a result of the endTB trial[19], clinicians were provided with three new options for 9-month all-oral regimens for RR/MDR-TB, with Bdq-Lzd-Mfx-Z suggested as the priority regimen (Fig. 1).

Thanks to long-awaited investments in TB research, as of 2025, we have two 6-month treatment regimens that can be tailored based on detected resistance patterns. As a result of recent clinical trials[20-22], evidence was collected supporting a new standard of care for DR-TB, based on the combination of Bdq, pretomanid (Pa), Lzd, and Mfx – abbreviated as BPaLM[18]. The introduction of the BPaLM regimen has revolutionized the treatment of DR-TB, bringing the length and efficacy of its treatment in line with those of regimens for DS-TB. However, only about half of the countries in Europe had access to all components of these regimens in 2023, whereas just 14% had access to drug susceptibility testing (DST) for all the drugs[23]. Moreover, the BPaLM regimen is not indicated for patients younger than 14 years, or for pregnant or breastfeeding women, for whom a 6-month Bdq-Dlm-Lzd-Lfx-Cfz regimen is recommended[24]. This regimen can be further adjusted depending on FQ resistance[25].

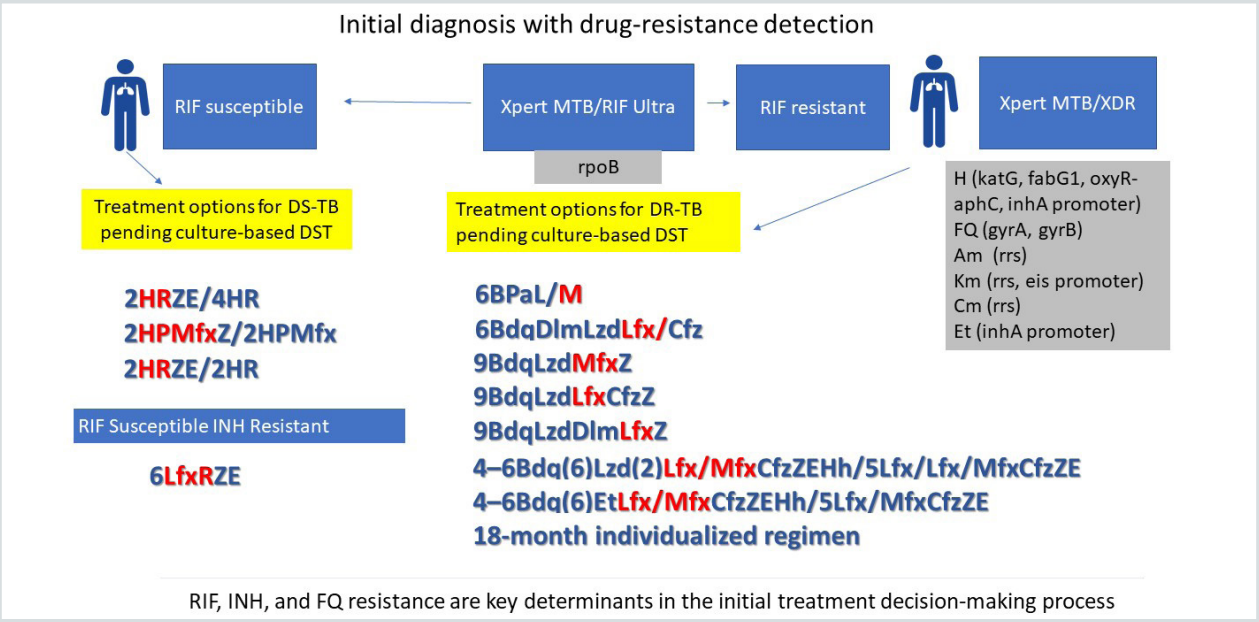


Figure 1. Illustrative summary of the 2025 World Health Organization consolidated guidelines on drug-resistant tuberculosis: initial diagnosis and treatment. Xpert Mycobacterium tuberculosis (MTB)/rifampicin (RIF) Ultra: an automated nucleic acid amplification test that simultaneously detects Mycobacterium tuberculosis complex and mutations in the rpoB gene associated with rifampicin resistance, providing results in < 80 min. RIF susceptible: a patient with bacteriologically confirmed tuberculosis and no detected mutations associated with rifampicin resistance. RIF resistant: a patient with bacteriologically confirmed tuberculosis and detection of mutations in the *rpoB* gene associated with rifampicin resistance. Xpert Mycobacterium tuberculosis/drug-resistant: a rapid molecular test that simultaneously detects resistance to several drugs, including isoniazid, fluoroquinolones, ethionamide, and second-line injectable drugs. H (INH): isoniazid; R (RIF): rifampicin; Z: pyrazinamide; E: ethambutol; Am: amikacin; Bdq (B): bedaquiline; Cm: capreomycin; Cs: cycloserine; Cfz: clofazimine; Dlm: delamanid; Et: ethionamide; Hh: high-dose isoniazid; Lfx: levofloxacin; Lzd (L): linezolid; Mfx (M): moxifloxacin; Pa: pretomanid.

Currently, individualized 18-month regimens remain the treatment of choice for extensive pulmonary and severe extrapulmonary forms of DR-TB, such as osteoarticular TB and TB meningitis, as well as for XDR-TB patients. Nevertheless, prolongation of the intensive phase of treatment is no longer recommended for any form of pulmonary DS-TB, as reflected in the World Health Organization consolidated guidelines[18]. Meanwhile, shorter regimens, such as 4 months rifapentine-based therapy with Mfx, have shown promising results in patients with extensive pulmonary lesions[26], offering potential future options for trials recruiting individuals with extensive pulmonary DR-TB. Regarding the shortening of treatment for severe extrapulmonary forms of DR-TB, this can be partially addressed using agents with improved tissue penetration, such as Lfx, Et, meropenem-clavulanic acid, and Lzd[27-29]. Notably, Et has already demonstrated the capacity to reduce treatment duration for TB meningitis to 6 months in children, replacing E[18]. On the other hand, the absence of standardized clinical criteria for defining cure in extrapulmonary TB complicates both treatment decisions and the design of clinical trials. According to the 2022

WHO definitions, for extrapulmonary TB, the only available classification for successful treatment outcomes is "treatment completed," defined as a patient who completed therapy in accordance with national treatment guidelines but whose outcome does not meet the criteria for either cure or treatment failure[30]. This definition implies that an appropriate alternative to the "bacteriological response" should be established, based on clinical recovery assessment and supported by radiographic (magnetic resonance imaging/computed tomography) or ultrasound (for pleurisy) criteria, representing a comprehensive, patient-oriented approach.

RIGHT DIAGNOSIS-RIGHT TREATMENT: GUIDING PRINCIPLES IN DR-TB CARE

Early point-of-care detection of drug resistance using molecular assays is crucial for the timely and appropriate initiation of treatment. However, the current diagnostic algorithm – based on initial TB testing with R resistance detection, followed by automated nucleic acid amplification tests for second-line resistance in RR-TB cases – no longer adequately reflects actual treatment needs[31]. As demonstrated in figure 1, the Xpert MTB/XDR cartridge detects molecular markers of resistance to second-line injectables, two of which (Km and capreomycin [Cm]) are no longer recommended for routine use, whereas amikacin (Am) remains a last-resort option. This highlights an opportunity to expand the panel by including rpoB mutations and developing a single-step assay capable of guiding initial treatment decisions for both DS- and DR-TB. An effective community campaign has already demonstrated that reducing the cost of Xpert cartridges is feasible[32]. It is now time to advocate for minimizing unnecessary laboratory workload and plastic waste. Furthermore, aligning diagnostic practices with current clinical needs – where information on resistance to H, R, and FQ is crucial for both RIF-susceptible and RIF-resistant TB – would represent a more rational and sustainable approach to TB diagnosis and management. Implementation of the suggested testing strategy could provide clearer insights into the prevalence of H resistance co-occurring with FQ resistance and inform evidence-based approaches to managing this resistance pattern.

Updated DR-TB guidelines further emphasize the importance of molecular resistance testing for Lzd, Dlm, Bdq, and Pa. Although WHO does not currently recommend low-complexity tests for these agents, targeted next-generation sequencing is suggested as a valuable tool[31]. Another, more expensive option is whole genome sequencing (WGS). In addition to providing comprehensive resistance information, this technology offers valuable insights that help clinicians distinguish between reactivation of MTB from a previous treatment episode and reinfection with a new strain[33]. A detailed analysis of the reasons for TB recurrence is valuable for understanding the determinants of this phenomenon and for planning appropriate preventive measures. In our retrospective study, which employed genotyping protocols based on restriction fragment length polymorphism, we found that the highest rate of TB recurrence occurs within 3 years after the previous episode of the disease[34]. Among the contributing factors, HIV infection emerged as particularly important, as it not only predisposes

individuals to relapse but also increases susceptibility to new infection and the development of active TB disease due to compromised immunity. Resistance to at least one anti-TB drug was associated with a threefold increase in the risk of TB recurrence (adjusted hazard ratio = 2.91; 95% confidence interval [CI]: 1.11-7.65) in our patient cohort[35]. Nevertheless, the implementation of such molecular typing methods, including WGS, remains limited in settings with a high burden of DR-TB, where scarce resources and a shortage of trained personnel further restrict access to these technologies, thereby exacerbating inequalities in TB diagnosis and management between low- and high-income countries[36].

MULTIDISCIPLINARY TEAM AT A SPECIALIZED TB CLINIC: COMMITTED TO HOLISTIC PATIENT CARE

Between 1993 and 2024, a total of 303 TB patients with various drug resistance profiles were admitted to Serveis Clinics (mean age: 38.6 years; 95% CI: 37.0-40.2), of whom 243 (81.5%) were male. Among these, 134 had RR/MDR-TB, and 11 had XDR-TB, reflecting substantial institutional experience in the management of DR-TB in a low-prevalence country such as Spain (Table 1). The majority of our patients belong to vulnerable populations, such as migrants with limited access to social and healthcare systems from Morocco, Pakistan, Romania, Senegal, and Eastern European countries. As shown in figure 2, between 5% and 10% of patients with TB admitted to Serveis Clinics in recent years had concomitant mental health disorders. These patients often require interdisciplinary and psychosocial support to enhance treatment adherence. Perceived stigma, which is strongly correlated with both depressive and anxiety symptoms, represents a major emotional risk factor for patients with DR-TB[37-39]. Many patients report discrimination, social rejection, and exclusion both within their communities and families, leading to social isolation and the loss of support networks. Reduced social support further moderates the impact of stigma: low social support increases vulnerability to depression and anxiety, whereas strong social support can help mitigate these effects[37]. Meta-analyses and multicenter studies indicate that depression affects 25-65% of patients with MDR-TB, anxiety 24-57%, and psychosis up to 10%, with considerable variation depending on country of origin, social context, and demographic profile[40]. Our multidisciplinary team at the specialized TB center is dedicated to providing comprehensive, patient-centered care, offering stigma-free services and supporting social reintegration (Fig. 3).

The model relies on the structured coordination of diverse professional roles – medical doctors, nurses, pharmacists, psychologists, social workers, social education specialists, and physiotherapists – working together to enhance treatment adherence, recovery, and reintegration into the community for patients with DR-TB. Social workers address socioeconomic vulnerability, promote self-care, and facilitate social and cultural adaptation. They identify key healthcare barriers – including transportation, food insecurity, and direct or indirect treatment-related costs – and facilitate patients' access to social protection schemes. The medical team ensures safe and effective pharmacological management, continuous clinical monitoring, and health education. Physiotherapists focus on respiratory

Table 1. Treatment outcomes of patients with drug-resistant tuberculosis treated at Serveis Clinics, 1993-2024

Variable	Type of resistance n (%)					
	Hr-TB (n = 65)		RR/MDR-TB (n = 134)		XDR-TB (n = 11)	
Treatment outcome	Pulmonary 61 (93.8)	Migrants 46 (70.8)	Pulmonary 120 (89.6)	Migrants 104 (77.6)	Pulmonary 11 (100)	Migrants 11 (100)
Successful treatment	49 (75.4)		98 (73.1)		8 (72.7)	
Unfavorable treatment	9 (13.8)		25 (18.7)		3 (27.3)	
Transferred out of Catalonia	7 (10.8)		11 (8.2)		-	

Hr-TB: tuberculosis with mono-resistance to isoniazid; RR/MDR-TB: tuberculosis with resistance to rifampicin/multidrug-resistant tuberculosis, with additional resistance to isoniazid; XDR-TB: extensively drug-resistant tuberculosis; defined since 2021 as tuberculosis resistant to rifampicin, a fluoroquinolone, and either bedaquiline or linezolid (WHO 2021 definition). Before January 2021, XDR-TB was defined as MDR-TB with additional resistance to any fluoroquinolone and at least one second-line injectable agent (Am, Km, or cm). A successful treatment outcome includes patients who were cured or completed treatment. Unfavorable treatment outcome includes treatment failure, loss to follow-up, and death. Transferred out refers to patients who were transferred out of Catalonia and for whom the final outcome was not evaluated.

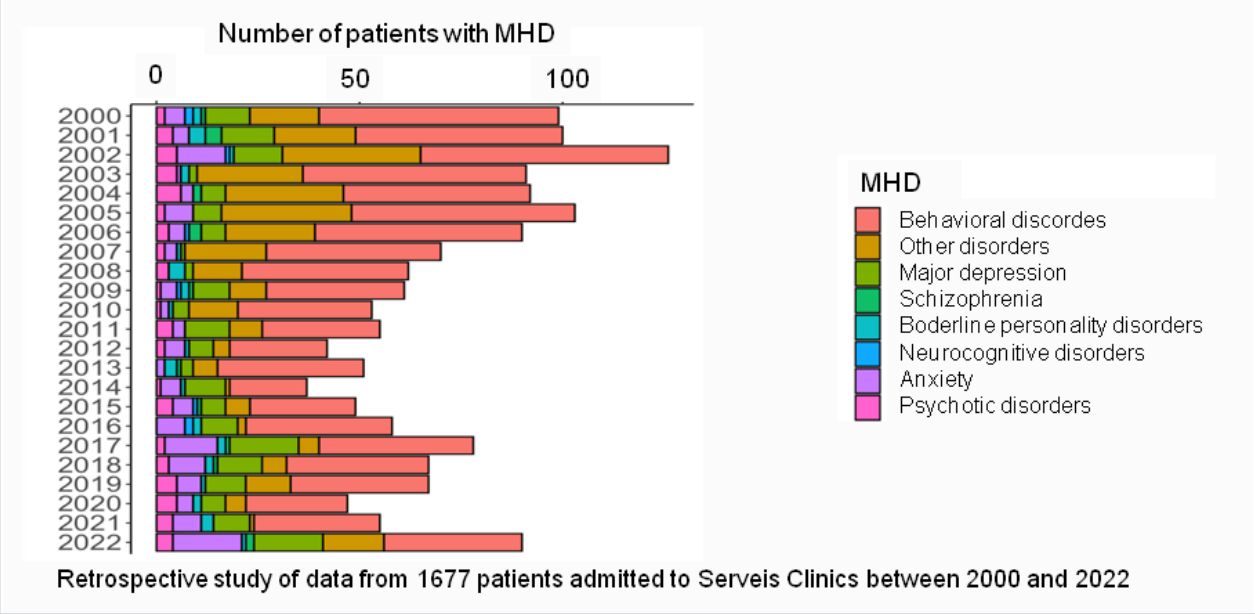
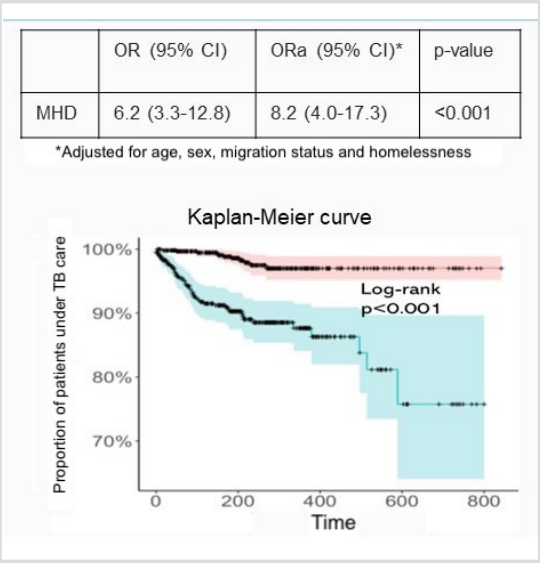


Figure 2. Annual distribution of mental health disorders among patients hospitalized at Serveis Clinics. MHD: mental health disorders.

rehabilitation to improve functional recovery and quality of life, whereas psychologists provide emotional support and integrative interventions to strengthen coping strategies. Community health agents bridge the gap between hospital and community, ensuring cultural mediation, social inclusion, and continuity of care after discharge. The shared

Figure 3. Principles of holistic drug-resistant tuberculosis treatment at Serveis Clinics, Barcelona.



	OR (95% CI)	ORa (95% CI)*	p-value
MHD	6.2 (3.3-12.8)	8.2 (4.0-17.3)	<0.001

*Adjusted for age, sex, migration status and homelessness

Figure 4. Impact of mental health disorders (MHD) on the probability of loss to follow-up during tuberculosis treatment compared to patients without MHD.

goal across all disciplines is to anticipate and understand patient behaviors through collaborative, interdisciplinary practice – minimizing non-adherence and other factors that contribute to treatment interruptions or increase relapse risk.

Results from a qualitative study reveal that patients with DR-TB experience intense emotional distress following diagnosis and throughout treatment, characterized by feelings of hopelessness, fear, shame, isolation, and both social and familial stigma[41]. Fear of permanent disability from residual physical changes, functional impairment, and adverse effects – such as aminoglycoside-induced hearing loss or cycloserine-associated neuropathy – further contributes to patients' psychological distress[42,43]. Based on our internal data analyses, we found that the presence of a mental health disorder may increase the likelihood of loss to follow-up by up to eightfold among TB patients admitted to Serveis Clinics (Fig. 4). Active drug safety monitoring and timely management of adverse events enhance treatment tolerance and adherence. For those who prefer to continue treatment at home, we offer video-supported or ambulatory DOT. Offering free language courses helps patients overcome social isolation, communicate their needs more effectively, and improve their employment opportunities.

The clinical setting at Serveis Clinics also functions as a patient-centered environment of coexistence, where diverse social, cultural, and clinical realities intersect. Patients often live side by side for extended periods, sharing spaces, experiences, and problem-solving strategies. This context calls for a framework of DR-TB care that is not only biomedical but also social and relational. An intersectional perspective – taking into account factors such as gender, migration, socioeconomic status,

mental health, and substance use – is essential for understanding patient behavior and sustaining coexistence as a key condition for adherence. Within this framework, harm reduction policies are implemented to address substance use, recognizing it as a health and social issue rather than a moral failing. This approach fosters trust, prevents relapses, and can shorten treatment duration by promoting responsibility and self-care within a non-punitive environment. By embracing diversity and cultivating mutual respect among patients, the clinic becomes a space that promotes adherence, accelerates recovery, and strengthens social reintegration.

Implementing holistic care in TB treatment programs for patients with DR-TB includes several structured phases: initial psychosocial assessment, risk categorization, intervention, and continuous follow-up. It begins with a systematic screening of depressive and anxious symptoms using brief tests such as the Patient Health Questionnaire-9 for depression, anxiety scales (e.g., Hopkins Symptom Checklist), stigma scales, and structured interviews to identify risk factors (comorbidities, substance use, and psychiatric history). We practice regular sessions of psychological counseling (individual or group), brief cognitive-behavioral therapy adapted to TB, emotional support for severe physical symptoms, proactive follow-up via phone calls or messaging, and psychoeducation for family members to reduce stigma and improve adherence. Group interventions and peer support are particularly valued for enhancing motivation and resilience.

Lifestyle interventions and rehabilitation are key pillars of our clinic's holistic approach. Educating patients and involving them in decision-making enhances motivation and treatment adherence. Our approach includes promoting adapted physical activity, explaining the benefits of pulmonary rehabilitation, supporting smoking cessation, encouraging reduced alcohol consumption, enhancing self-care, providing individualized nutritional assessment, and recommending appropriate supplementation. It is particularly important in individuals with comorbidities such as HIV co-infection and diabetes mellitus, as both increase mortality, the therapeutic complexity of DR-TB, and the risk of treatment failure[44,45]. These patients require multidisciplinary management, including concomitant antiretroviral therapy and glucose-control medications.

Respiratory rehabilitation is essential for patients with chronic pulmonary illnesses, including TB, as it helps to improve lung function, reduce dyspnea, prevent complications, increase exercise capacity and quality of life, and decrease the number of hospitalizations[46]. TB can cause both restrictive and obstructive pulmonary function impairments[47]. Even in new TB cases, without a history of obstructive disease, airflow obstruction is detected in 30% during the initial phase of treatment[48]. Pulmonary rehabilitation during the initial phase of TB treatment is considered safe, recommended, and clinically beneficial[49,50]. Moreover, patients with a history of TB and reduced FEV_1 have a significantly higher risk of mortality (odds ratio 4.59; 95% CI: 2.86-7.37) compared with those without a history of TB[51].

The implementation of rehabilitation programs for patients diagnosed with DR-TB represents an innovative, multidisciplinary

healthcare service aimed at preventing chronic sequelae, organ dysfunction, and mortality. It is based on a comprehensive and individualized patient-centered approach that combines muscle training, smoking cessation, respiratory physiotherapy, disease education, and psychological and nutritional assessment, with the goal of optimizing functional recovery and improving quality of life[52]. At our hospital, we are developing a rehabilitation program integrated with pharmacological treatment, which helps to counteract the negative effects of clinical symptoms and prevent the long-term consequences of lung damage in TB patients. We believe that it will have a rapid and positive impact on patients' well-being, improving daily functioning and providing long-term benefits by preventing residual changes.

RESEARCH PRIORITIES TO ENABLE A PARADIGM SHIFT

TB is a preventable disease; however, at present, 6 months of daily Lfx remains the only available option for contacts exposed to MDR-TB as preventive therapy[53]. Individuals with extended DR-TB often need to access newer agents as part of effective therapy through compassionate use or expanded access programs before regulatory approval, as was the case with Bdq at the start of its implementation[54]. The Spanish Society of Pneumology and Thoracic Surgery and the Spanish Society of Infectious Diseases and Clinical Microbiology have proposed certain medicines that could be effective, but currently lack sufficient evidence for routine use, such as faropenem and ceftazidime-avibactam[55]. There is also limited evidence supporting the use of adjunctive gamma-interferon therapy, which has been associated with successful treatment of life-threatening mycobacterial infections[56]. DR-TB regimens are associated with a higher frequency of adverse effects, particularly myelosuppression, neuropathy, hepatotoxicity, and cardiac abnormalities, and require intensive drug safety monitoring. We hope that adjusting doses based on pharmacokinetic studies and therapeutic drug monitoring will help minimize side effects for many patients.

Complementary host-directed therapies may play an adjunctive role in managing DR-TB. According to the Stop TB Partnership Working Group on New TB Drugs Clinical Biologics Pipeline, one adjunct immunotherapy – immunoxel honey lozenges – is currently in phase III for patients with pulmonary TB[57]. In addition, phase II clinical trial suggests that CC-11050 (type 4 phosphodiesterase inhibitor with anti-inflammatory properties) or everolimus (inhibitor of serine/threonine-protein kinase) in adults with pulmonary TB may improve recovery of FEV_1[58]. Other phase II candidates for host-directed therapy include metformin, imatinib, and pravastatin[59]. We also have a positive experience of using tumor necrosis factor antagonists, infliximab, for patients with severe TB of the central nervous system, who showed marked neurological improvement after the first infliximab dose[60].

The use of inhaled Am and inhaled Cfz suspension to treat non-tuberculous mycobacterial lung disease strongly suggests that inhalation therapy could play a major role in the future of TB treatment[61]. This approach

may help minimize the impact on the gut microbiota, particularly in patients receiving broad-spectrum antibiotics such as Mpn-Clv, Mfx, and Lzd, or those undergoing prolonged DR-TB treatment regimens[62].

Future research should prioritize randomized controlled trials of host-directed therapy, psychosocial interventions, and pulmonary rehabilitation, as well as qualitative research on cultural and gender-related barriers.

CONCLUSIONS

A holistic, person-centered approach to the treatment of DR-TB is a feasible and effective model. The core components of this model include engaging patients in treatment decisions, providing psychological support, offering social assistance, implementing pulmonary rehabilitation, and, when appropriate, administering adjunctive medications to enhance treatment outcomes and overall well-being. Prioritizing individual patient needs over simple bacteriological and clinical parameters or healthcare statistical indicators improves treatment adherence, reduces interruptions, and enhances patient satisfaction as well as overall quality of life.

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CONFLICTS OF INTEREST

None.

ETHICAL CONSIDERATIONS

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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