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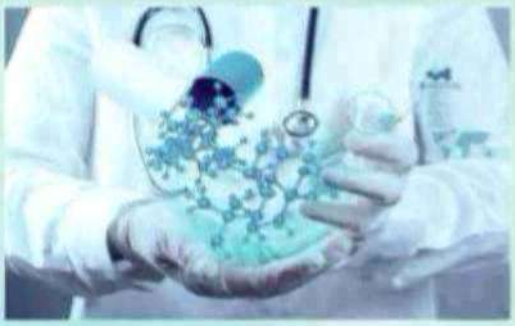

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NEW DAY IN MEDICINE

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EFFECTIVENESS OF TREATMENT FOR DRUG-RESISTANT PULMONARY TUBERCULOSIS *(Review)*

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✓ ***Resume***

This review critically evaluates advances in treating drug-resistant pulmonary tuberculosis (DR-TB), focusing on multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains. It synthesizes evidence from clinical trials (e.g., endTB, STREAM), observational studies, and 2025 guidelines (WHO, ATS/CDC/ERS/IDSA) to assess modern therapeutic strategies.

Paradigm shift from toxic, prolonged regimens (18–24 months) to shorter (6-month), all-oral therapies (e.g., BPaLM/BPaL), leveraging novel agents like bedaquiline, pretomanid, and delamanid. Cure rates now exceed 85% in trials, a dramatic improvement from historical rates (30–60%).

HIV coinfection, pediatric, and pregnancy-specific challenges are addressed, with evidence supporting early ART integration and pediatric bedaquiline use. Limited diagnostic access, drug stockouts, and infrastructure gaps in high-burden regions (e.g., Russia, Central Asia). Rising bedaquiline/linezolid resistance (4–8%) and inadequate safety data for pregnancy.

Cost and supply chain limitations despite price reductions. Universal drug susceptibility testing (DST), decentralized care models, and accelerated research into ultra-short regimens and pediatric formulations. Conclusion: While novel regimens mark a therapeutic breakthrough, achieving WHO End TB targets requires addressing implementation gaps and emerging resistance through coordinated global action.

Key words: treatment, drug-resistant, tuberculosis, effectiveness

ЭФФЕКТИВНОСТИ ЛЕЧЕНИЯ ЛЕКАРСТВЕННО-УСТОЙЧИВОГО ТУБЕРКУЛЕЗА ЛЕГКИХ *(обзор литературы)*

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✓ ***Резюме***

В этом обзоре критически оцениваются достижения в лечении лекарственно-устойчивого туберкулеза легких (ЛУ-ТБ), уделяя особое внимание штаммам с множественной лекарственной устойчивостью (МЛУ-ТБ) и широкой лекарственной устойчивостью (ШЛУ-ТБ). В нем обобщены данные клинических испытаний (например, endTB, STREAM), наблюдательных исследований и руководств 2025 года (ВОЗ, ATS/CDC/ERS/IDSA) для оценки современных терапевтических стратегий.

Смена парадигмы с токсичных, длительных схем (18–24 месяца) на более короткие (6 месяцев), полностью пероральные терапии (например, BPaLM/BPaL), с использованием новых препаратов, таких как бедаквилин, претоманид и деламанид. В настоящее время показатели излечения превышают 85% в испытаниях, что является резким улучшением по сравнению с историческими показателями (30–60%).

Решаются проблемы коинфекции ВИЧ, педиатрии и беременности, при этом приводятся данные, подтверждающие раннюю интеграцию АРТ и использование бедаквилина у детей. Ограниченный доступ к диагностике, дефицит лекарств и пробелы в инфраструктуре в регионах с высоким бременем (например, Россия, Центральная Азия). Рост резистентности к бедаквилину/линезолиду (4–8%) и неадекватные данные о безопасности для беременности.

Ограничения затрат и цепочки поставок, несмотря на снижение цен. Универсальное тестирование на лекарственную чувствительность (ТЛЧ), децентрализованные модели ухода и ускоренные исследования сверхкоротких схем и педиатрических формул. Вывод: хотя новые схемы знаменуют собой терапевтический прорыв, достижение целей ВОЗ по ликвидации туберкулеза требует устранения пробелов в реализации и возникающей резистентности посредством скоординированных глобальных действий.

Ключевые слова: лечение, лекарственная устойчивость, туберкулез, эффективность

ДОРИГА ТУРҒУН ЎПКА ТУБЕРКУЛЁЗИНИНГ ДАВО САМАРАДОРЛИГИ

(адабиётлар шарҳи)

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✓ ***Резюме***

Ушбу мақолада дори-дармонга чидамли ўпка туберкулёзини даволашда эришилган ютуқлар ва камчиликларни бахолаш хақида бўлиб, айниқса куп дори-дармонга чидамли ва кенг миқёсдаги дорига чидамлилик тўғрисида сўз олиб борилади. Мақола жорий терапевтик стратегияларни бахолаш учун клиник синовлар (масалан endTB, STREAM) кузатув тадқиқотлари ва 2025йил йўриқномалари далилларини (ЖССТ, ATS/CDC/ERS/IDSA) умумлаштирган.

Бедаквилин, претоманид ва деламанид каби янги дориларни қўллаш орқали заҳарли, узоқ давом етадиган режимлардан (18-24 ой) қисқароқ (6 ой), тўлиқ оғиз орқали даволаш усулларига парадигма ўзгариши содир бўлмоқда. Ҳозирда синовларда даволаниш ставкалари 85% дан ошади, бу тарихий кўрсаткичларга нисбатан кескин яхшиланиш (30-60%). АРТнинг ерта интеграциялашувини ва болаларда бедақуилинни қўллашни қўллаб-қувватловчи далиллар билан ОИВ билан биргаликда инфекция, педиатрия ва ҳомиладорлик масалаларига мурожаат қилади. Диагностика, дори заҳиралари ва инфратузилма бўшлиқлари юқори юк шароитида (масалан, Россия, Марказий Осиё) чекланган фойдаланиш имконияти. Бедаквилин/линезолидга (4-8%) қаршилик кучайиши ва ҳомиладорликда хавфсизлик маълумотларининг етарли эмаслиги.

Умумжаҳон дори-дармонларга сезувчанлик тести (ДСТ), марказлаштирилмаган парвариш моделлари ва ултра-қисқа режимлар ва педиатрик формулалар бўйича тезлаштирилган тадқиқотлар. Хулоса: Гарчи янги режимлар терапевтик ютуқ бўлса-да, ЖССТнинг сил касаллиги бўйича умрининг охиригача бўлган мақсадларига ерииши мувофиқлаштирилган глобал ҳаракатлар орқали амалга оширишдаги камчиликларни ва пайдо бўладиган қаршиликни бартараф етишни талаб қилади.

Калит сўзлар: даволаш, дориларга чидамлилик, туберкулёз касаллиги, самарадорлик

Relevance

Drug-resistant tuberculosis (DR-TB), particularly multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains, remains one of the most pressing global health challenges. In 2023, TB caused 1.25 million deaths worldwide, surpassing COVID-19 as the leading infectious disease killer, with DR-TB accounting for a disproportionate share of morbidity and mortality [4,11]. Historically, MDR-TB cure rates hovered around 50–60%, while XDR-TB treatments succeeded in

only 30% of cases, largely due to toxic, prolonged regimens and systemic gaps in healthcare infrastructure [2,8]. However, the therapeutic landscape has shifted dramatically since 2012, with the introduction of novel oral agents like bedaquiline, delamanid, and pretomanid. These advancements, coupled with updated WHO and ATS/CDC/ERS/IDSA guidelines, have redefined treatment paradigms, offering shorter, safer, and more effective regimens [5,12].

This review synthesizes recent clinical trial data, observational studies, and policy updates to critically evaluate the efficacy of modern DR-TB therapies and identify persisting challenges.

Results and discussion

Classification and Mechanisms of Drug Resistance DR-TB is stratified based on resistance profiles:

- MDR-TB: Resistance to isoniazid and rifampicin, the cornerstone first-line drugs [1,2].
- Pre-XDR-TB: MDR-TB with additional resistance to fluoroquinolones (e.g., moxifloxacin) or second-line injectables (e.g., amikacin) [1,8].
- XDR-TB: MDR-TB resistant to both fluoroquinolones and at least one second-line injectable, often compounded by resistance to newer agents like bedaquiline or linezolid [1,7].

Resistance arises via two pathways:

1. Primary transmission: Direct infection with resistant strains, driven by community spread and inadequate infection control. For example, Belarus reported 35% MDR-TB among new cases in 2011, highlighting unchecked transmission [2].
2. Acquired resistance: Mutations develop during inadequate treatment due to poor adherence, suboptimal dosing, or pharmacokinetic variability (e.g., drug-drug interactions in HIV coinfection) [1,8]. Molecular diagnostics, such as GeneXpert MTB/RIF, now enable rapid detection of rifampicin resistance, a proxy for MDR-TB [2,7].

Traditional Treatment Challenges

Prior to 2012, DR-TB management relied on 18–24-month regimens combining toxic injectables (e.g., kanamycin) and poorly tolerated oral agents. These therapies were fraught with:

Severe adverse effects: Deafness (20–60% of patients) and renal failure from aminoglycosides, alongside psychiatric effects from cycloserine [7,8].

Low adherence: Dropout rates exceeded 30% due to treatment duration and toxicity, perpetuating transmission and resistance amplification [2,8].

Comorbidity burdens: HIV coinfection reduced success rates to <50%, as seen in South Africa’s MDR-TB/HIV "perfect storm" [2,10].

Regional disparities exacerbated outcomes. A 2016–2018 Russian cohort reported 44% MDR-TB and 82% XDR-TB treatment failure, attributed to delayed diagnostics and limited access to second-line drugs [7,11].

Advancements in Treatment Regimens

1. Shorter, All-Oral Regimens

The 2012–2019 approvals of bedaquiline (a diarylquinoline), delamanid (a nitroimidazole), and pretomanid (a PA-824 analog) revolutionized DR-TB care. These agents target novel bacterial pathways, circumventing traditional resistance mechanisms [5,7]. Key regimens include:

BPaLM: Bedaquiline, pretomanid, linezolid, and moxifloxacin (6 months for MDR/RR-TB with fluoroquinolone susceptibility) [7,11].

BPaL: Bedaquiline, pretomanid, and linezolid (6 months for pre-XDR/XDR-TB) [7,8].

These regimens eliminate injectables, reduce pill burden by 50%, and shorten treatment to 6 months, achieving >85% cure rates [5,11].

2. Clinical Trial Evidence

endTB Trial (2024): Tested five bedaquiline/delamanid-based regimens across seven countries. Three oral regimens achieved 85–90% efficacy, outperforming the 81% success rate of older WHO therapies. Notably, the trial included high-risk populations (HIV, hepatitis C, pregnancy), demonstrating real-world applicability [5,11].

STREAM Trial: Validated the 9-month "Bangladesh regimen" (clofazimine, moxifloxacin, high-dose isoniazid), showing non-inferiority to 20-month regimens (87.9% vs. 84.5% success) with reduced toxicity [8,9].

Study 31/A5349: A UCSF-led trial demonstrated that a 4-month rifapentine/moxifloxacin regimen matched the efficacy of standard 6-month therapy for drug-susceptible TB, paving the way for ultra-short regimens in DR-TB [9].

Special Populations and Comorbidities

HIV Coinfection - Early antiretroviral therapy (ART) integration reduces mortality by 64%. The BPaLM regimen achieves 73–84% cure rates in HIV-positive patients, though outcomes lag behind HIV-negative cohorts due to immune dysfunction and drug interactions [4,10].

Pediatric TB - Bedaquiline is now approved for children ≥5 years, with studies supporting 4-month regimens for non-severe cases. Decentralized care models improve adherence in low-resource settings [10,11].

Pregnancy - Ethambutol and rifampicin remain first-line, but safety data for newer agents are limited. Pyridoxine supplementation is critical to prevent neurotoxicity from isoniazid [1,10].

Global Disparities and Regional Challenges

While high-income countries report >85% treatment success with novel regimens, regions like Russia and Central Asia face persistent barriers:

Diagnostic delays: Only 40% of MDR-TB cases are promptly diagnosed, perpetuating transmission [4,7].

Regimen accessibility: Stockouts of bedaquiline and pretomanid persist in high-burden countries despite price reductions to $500/course [5,11].

Community transmission: In Belarus, 75% of retreatment cases involved MDR-TB strains, underscoring the need for infection control [2,8].

Guidelines and Recommendations

The 2025 ATS/CDC/ERS/IDSA guidelines prioritize:

Universal DST: Mandatory drug susceptibility testing for all TB patients to guide regimen selection [7,11].

Oral regimens: BPaLM/BPaL as first-line for MDR/XDR-TB, with delamanid as an alternative [11].

Decentralized care: Task-shifting to community health workers and telehealth platforms to expand access in rural areas [1,10].

Remaining Challenges and Future Directions

Access and equity: Scaling up BPaLM/BPaL in high-burden countries requires addressing supply chain bottlenecks and training healthcare workers [5,11].

Resistance monitoring: Emerging bedaquiline resistance (4–8% in recent cohorts) necessitates genomic surveillance and DST standardization [7,8].

Research priorities:

Pediatric formulations of pretomanid and delamanid [10].

Pregnancy safety profiles for newer agents 1.

Ultra-short regimens (e.g., 4 months) for non-severe DR-TB [9,11].

Conclusion

The DR-TB treatment landscape has undergone a paradigm shift, with 6-month oral regimens achieving >85% cure rates and significantly reducing patient burden. However, equitable implementation remains hindered by diagnostic gaps, cost barriers, and emerging resistance. Sustained investment in drug development, diagnostics, and health system strengthening is imperative to meet the WHO's 2030 End TB targets.

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