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Review Article for Treatment of Tuberculosis

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Abstract

Tuberculosis is an airborne infectious disease treated with combination therapeutic regimens. Adherence to long-term antituberculosis therapy is crucial for maintaining adequate blood drug level. The emergence and spread of drug-resistant Mycobacterium tuberculosis strains are mainly favored by the inadequate medical management of the patients. The therapeutic approach for drug-resistant tuberculosis is cumbersome, because of the poor, expensive, less-effective, and toxic alternatives to the first-line drugs. New antituberculosis drugs (bedaquiline and delamanid) have been recently approved by the health authorities, but they cannot represent the definitive solution to the clinical management of drug-resistant tuberculosis forms, particularly in intermediate economy settings where the prevalence of drug resistance is high (China, India, and former Soviet Union countries). New research and development activities are urgently needed. Public health policies are required to preserve the new and old therapeutic options.

Keywords: Tuberculosis, Mycobacterium tuberculosis, Management, Alternatives

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Introduction

Tuberculosis (TB) is an infectious disease that is acquired by inhaling the bacteria that cause the disease. About 90 percent of those who become infected show no sign of disease (latent infection), but harbor the organism and have a risk of developing active TB later. Left untreated, a third to a half of those who do develop disease will die from it. The others with active disease will go into remission or have chronic symptoms. Those with active TB can infect others. Effective drugs have been available for more than half a century, and virtually all cases of TB should be curable, although the emergence of drug-resistant bacteria has made the treatment much longer, more difficult, and expensive.[1]

Tuberculosis (TB), the disease caused by Mycobacterium tuber- culosis, remains a major public health problem globally. In 2014, more than 9.6 million people are estimated to have fallen ill with TB while 1.5 million people died of the disease[2]. The disease is closely associated with poverty, which explains the high rates of TB in countries or in geographic areas within countries where poverty rates are high. The disease is also closely linked with HIV which has been the major driver for the high rates of TB in many countries of Sub –Saharan Africa [3–6]. TB is also associated with other immunosuppressive states such as diabetes mellitus and to- bacco smoking and it is currently postulated that the next wave of the global TB epidemic will be driven by these emerging health threats[7–9].

One-third of the world's population is infected with tuberculosis (TB) with nearly 2 million deaths occurring each year. Among those infected annually, more than 1.5 million occur in Sub- Saharan Africa [10]. In Ghana, about 46,000 cases are reported in health facilities yearly, but the treatment of the disease had been erratic since 1900 until the introduction of TB services in 1959[11]. Many infected people apply both homeopathic and allopathic medicines as treatment since 1900, but

the World Health Organization has recommended medicines for treatment[12, 13]. After diagnosing someone with the disease, chemotherapy is administered to interrupt transmission to others[12]. Ghana adopts the directly observed treatment strategy (DOTS) when a case is identified. Initially, multiple doses were given for treatment between eight and eighteen months until the introduction of fixed dose combination (FDC) in which two or more drugs are combined to form a single tablet. FDC involves the amalgamation of first-line drugs: ethambutol, isoniazid, rifampicin, and pyrazinamide into one dosage[3]. Initial treatment duration is six months for all new cases with intensive phase of twomonths and continuation phase of four months. Patients are usually assigned a treatment supporter who supervises the in-take of medication to prevent cases of default [6, 7]. From 1960 to 1990, programmes designed to combat TB in the country decreased. However, in 1994, a National TB Control Programme began with the aim of eradicating the disease from the country through set of related activities and services such as free supply of drugs to patients[10, 12, 15]. Over the last two decades treatment of TB has significantly im- proved and 61 million patients were successfully treated for TB globally since 1995[2]. However such successful treatment of TB based on either documentation of bacteriological clearance of My- cobacterium tuberculosis bacilli from the involved site or comple- tion of the prescribed drug dose does not assess structural and functional effects on the involved organ which is the hallmark of the pathology of TB[16] . While any part of the body may be affected by TB, pulmonary TB is the most common site of disease primarily because the Mycobacterium tuberculosis transmits through the respiratory route. Thus TB is a major contributor to the overall burden of lung disease in the world. It may be that the majority of patients with pulmonary TB, the resulting structural and functional damage is small and will not pose any significant long term lung health risk, however, for some patients an episode of pulmonary TB may herald the beginning of chronic respiratory disease and pose a significant risk of reduced longevity despite the "successful"treatment of their disease[17]. In this paper we ar- gue on the importance of a programmatic approach to address the long term complications of PTB and suggest mechanisms to pre- vent, rapidly identify and provide appropriate long term care for patients with post TB chronic lung disease.

Tuberculosis disease usually occurs when a latent infection becomes active. Disease may follow the initial infection if the immune response fails to contain the spread of the organisms from the lungs (see above), especially in young children (less than 5 years of age) or persons with compromised immune systems (such as HIV-infected persons). Most TB disease in the USA today represents re-activation of latent TB infection. Symptoms and signs of TB disease often are not specific and may be overlooked easily. Active pulmonary disease may present with a cough productive of sputum, fevers, weight loss, night sweats, and/or general fatigue. Tuberculosis of the lymphatic system may produce swollen lymph nodes; tuberculosis meningitis may present as a change in mental status[1].

Signs and symptoms

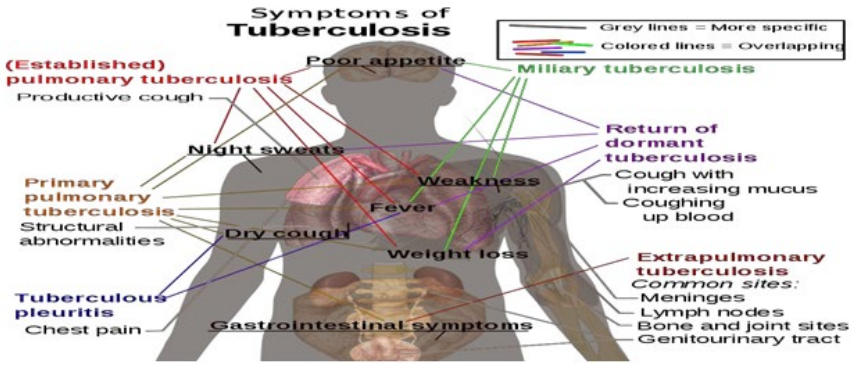
Tuberculosis may infect any part of the body, but most commonly occurs in the lungs (known as pulmonary tuberculosis). Extrapulmonary TB occurs when tuberculosis develops outside of the lungs, although extrapulmonary TB may coexist with pulmonary TB. General signs and symptoms include fever, chills, night sweats, loss of appetite, weight loss, and fatigue. Significant nail clubbing may also occur[18].

Pulonary

If a tuberculosis infection does become active, it most commonly involves the lungs (in about 90% of cases)[19, 20]. Symptoms may include chest pain and a prolonged cough producing sputum. About 25% of people may not have any symptoms (i.e. they remain "asymptomatic")[19]. Occasionally, people may cough up blood in small amounts, and in very rare cases, the infection may erode into the pulmonary artery or a Rasmussen's aneurysm, resulting in massive bleeding[18, 21]. Tuberculosis may become a chronic illness and cause extensive scarring in the upper lobes of the lungs. The upper lung lobes are more frequently affected by tuberculosis than the lower ones[18]. The reason for this difference is not clear. It may be due to either better air flow, or poor lymph drainage within the upper lungs.

Extrapulmonary

In 15–20% of active cases, the infection spreads outside the lungs, causing other kinds of TB[19]. These are collectively denoted as "extrapulmonary tuberculosis". Extrapulmonary TB occurs more commonly in people with a weakened immune system and young children. In those with HIV, this occurs in more than 50% of cases[22]. Notable extrapulmonary infection sites include the pleura (in tuberculous-pleurisy), the central nervous system (in tuberculous meningitis), the lymphatic system (in scrofula of the neck), the genitourinary system (in urogenital tuberculosis), and the bones and joints (in Pott disease of the spine), among others. A potentially more serious, widespread form of TB is called "disseminated tuberculosis", also known as miliary tuberculosis[18]. Miliary TB currently makes up about 10% of extrapulmonary cases[23].



[https://upload.wikimedia.org/wikipedia/commons/thumb/2/2f/Tuberculosis_symptoms.svg/800p x-Tuberculosis_symptoms.svg.png]

Tuberculosis Therapy: History and Rationale

Tuberculosis is an ancient disease; nevertheless, effective drugs were not available for centuries. The preantibiotic therapy was initially represented by isolation in sanatoria to reduce the probability of Mycobacterium tuberculosis transmission to healthy contacts, with rest, adequate nutrition, and sunlight exposure; then, the surgical approach represented the gold standard, after Carlo Forlanini's discovery of the beneficial effects of the artificially induced pneumothorax in 1927[24].

Only after the discovery of the etiological agent by Robert Koch in 1882 and the identification of the antibacterial activity of penicillin by Alexander Fleming did new experimental activities focused on the evaluation of the efficacy of natural and chemical compounds in animals start[25].

The first experimental evidence of the potential efficacy of new antituberculosis drugs was obtained in 1940 when a dapsone-derivative compound, known as promin, was administered to a sample of guinea pigs. However, that sulfonamide was never given to humans [26-29].

A different destiny awaited streptomycin, a natural substance isolated from Streptomyces griseus, which proved its efficacy in animals and then in humans. In 1944, Schatz and Waksman stated that the drug could be prescribed for the treatment of tuberculosis as a consequence of its bactericidal activity. In 1946, the United Kingdom Medical Research Council Tuberculosis Unit showed its short-term 6-mo efficacy in terms of mortality reduction (i.e., from 27% to 7%). However, after 5 yr, no differences were found between those exposed and not exposed to streptomycin as a consequence of the acquired antibiotic resistance[30-33]

Antituberculosis drugs

Drug	Mean daily dosage
Isoniazid	5 mg/kg
Rifampicin	10 mg/kg
Ethambutol	15–25 mg/kg
Pyrazinamide	30–40 mg/kg
Streptomycin	15–20 mg/kg
Amikacin	15–20 mg/kg
Kanamycin	15–20 mg/kg
Capreomycin	15–20 mg/kg
Ofloxacin	800 mg
Ciprofloxacin	1000 mg
Gatifloxacin	400 mg
Moxifloxacin	400 mg
Levofloxacin	1000 mg

Four years later, the discovery of streptomycin, a new synthetic drug, called para-aminosalicylic acid (PAS), was presented as an alternative drug for the treatment of tuberculosis. Following the poor results of the monotherapy, in 1952, the first regimen based on the combination of streptomycin, PAS, and isoniazid was proposed. Sir John Crofton with the "Edinburgh method," characterized by the prescription of at least two drugs, showed the efficacy of the combination therapy[28, 34-37].

In 1954, pyrazinamide was discovered, but at the prescribed dosages, the rate of hepatic toxicity was significantly high. Ethambutol and rifampicin were introduced in 1961 and 1963, respectively. The duration of therapy varied from 1 to 2 yr. In 1970, trials on regimens including rifampicin showed good results with a therapy of 9 mo, whereas in 1974, the inclusion of rifampicin and pyrazinamide at low dosages demonstrated the efficacy of a 6-mo treatment[28,36-39]

The Madras study started in India in 1956. It showed the efficacy of the ambulatory treatment and the crucial role of the directly observed treatment for the improvement of the patient's adherence [28, 37, 40].

Historical steps of the antituberculosis treatment

Year	Historical step
1940	Use of promin in guinea pigs
1944–1946	Discovery of streptomycin
1948	Discovery of para-aminosalicylic acid
1952	Streptomycin + para-aminosalicylic acid + isoniazid
1954	Discovery of pyrazinamide
1956	Madras study
1961	Discovery of ethambutol
1963	Discovery of rifampicin
1970	9-mo rifampicin-containing regimens
1974	6-mo rifampicin- and pyrazinamide-containing regimens
2012	Food and Drug Administration approval of bedaquiline
2013	Approval of delamanid by European Regulatory authorities

Treatment of Drug-Susceptible Tuberculosis

Individuals diagnosed with a pulmonary form of tuberculosis, not exposed to antituberculosis drugs for >1 mo (i.e., "new cases" of tuberculosis), have to be treated for 6 mo. During the 2-mo intensive phase, patients should be administered a combined regimen including ethambutol, isoniazid, pyrazinamide, and rifampicin. Only isoniazid and rifampicin are prescribed during the 4-mo continuation phase.

Patients should take drugs daily to obtain a clinical and a microbiological cure; however, during the second phase of treatment, thrice per week is allowed, but, in that case, adherence is crucial to avoid reduction of the drugs' blood level and, consequently, the risk of emergence of drugs' resistances.

As mentioned above, a higher efficacy of antituberculosis regimens longer than 6 mo for individuals both with and without HIV infection was not shown; a different scenario has been found in the treatment of the latent tuberculosis infection, in which the duration of the treatment is longer in HIV-infected patients.

Microbiological monitoring of the efficacy of the prescribed regimen is mandatory; sputum smear and culture conversion should be evaluated, particularly at the end of the intensive and continuation phases of treatment.

Previously treated cases (i.e., previous course of antituberculosis drugs for >1 mo) should be managed differently. To prescribe an effective regimen tailored on the phenotypic profile of the mycobacterial isolates, a rapid and conventional drug-susceptibility testing is required before the initiation of therapy. It is crucial to monitor the potential adverse events to avoid the interruption of the prescribed therapy.

Main adverse events of the antituberculosis drugs

Drug	Adverse event
Isoniazid Linezolid	Peripheral neuropathy
Bedaquiline Isoniazid Para-aminosalicylic acid Pyrazinamide Rifampicin	Liver dysfunction
Amikacin Amoxicillin/clavulanate Fluoroquinolones Isoniazid kanamycin Rifampicin Streptomycin Thiacetazone	Skin rash
Bedaquiline Pyrazinamide Thiacetazone	Arthromyalgia
Amikacin Capreomycin Kanamycin Streptomycin	Renal dysfunction
Amikacin Capreomycin Kanamycin Streptomycin	Vestibular and auditory dysfunction
Amoxicillin/clavulanate Bedaquiline Clarithromycin Clofazimine	Gastrointestinal disorders

Treatment of Drug-Resistant Tuberculosis

The clinical and public health management of drug-resistant tuberculosis is complicated. The therapeutic approach, as well as the prognosis, is significantly associated with the resistance pattern[41, 42]

It has been clearly shown that the multidrug resistance (i.e., the resistance in vitro to at least isoniazid and rifampicin) could represent a relevant clinical issue because of the poorest therapeutic armamentarium. The so-called second- and third-line antituberculosis drugs are less efficacious, more toxic, and more expensive than the first-line drugs.

It is straightforward that the adequate treatment of drug-resistant tuberculosis can prevent the emergence of new serious drug-resistant forms, which could have a worst prognosis and less alternative therapeutic options.

Furthermore, another relevant feature of an adequate and early treatment is the low probability of transmission of drug-resistant mycobacterial strains in a specific setting, such as a hospital or a community.

Nevertheless, to obtain a clinical and a microbiological cure, it is mandatory to treat individuals for a long period because of the lesser effectiveness of the second- and third-line drugs. The prolonged exposure to medicines, characterized by a poor safety and tolerability profile, reduces the adherence of the patient. This pathogenetic step could be crucial for the emergence of new drug-resistant mycobacterial strains and their spread in the community.

One of the most important points in the management of the drug-resistant strains is the prescription of an efficacious drug regimen, which should be based on the results of the drug- susceptibility testing. The current availability of rapid molecular tests, which can assess the resistances of mycobacterial strains to isoniazid and rifampicin, can allow the administration of an early tailored antituberculosis regimen. In particular, the World Health Organization recently approved an automated nucleic acid amplification test to diagnose tuberculosis disease and to assess mycobacterial resistance to rifampicin (Xpert MTB/RIF System). The rapid identification of a multidrug-resistant case can allow an immediate prescription of an empiric and specific antituberculosis drug regimen. This molecular method might avoid the administration of an inappropriate treatment and, consequently, indirectly favor the clinical recovery of patients and the reduction of their infectiousness[43].

The World Health Organization suggests the prescription of at least four active drugs during the intensive phase. In particular, the backbone of the administered regimen should include pyrazinamide, one of the injectable second-line drugs (amikacin, capreomycin, or kanamycin), a new-generation fluoroquinolone, ethionamide (or prothionamide), and cycloserine (or PAS). Other drugs should be prescribed in case of resistances to one or more of the backbone drugs. The duration of the first phase of the treatment should depend on the culture conversion, but it should last at least 8 mo, whereas the duration of the second phase should be longer than 20 mo.

The World Health Organization guidelines issued in 2011 (WHO 2011b) showed significant differences if compared with those issued in 2008; in particular, the suggested duration of the intensive phase is longer (i.e., 8 vs. 6 mo), as well as the total duration of therapy (i.e., at least 20 mo). If feasible, pyrazinamide should be added up to a backbone regimen of four second-line antituberculosis drugs, in which ethionamide and new-generation fluoroquinolones are the preferred medicines. Furthermore, monthly monitoring of the culture conversion is relevant to assess the efficacy of the prescribed therapy[44].

New therapeutic options have been proposed in recent years for the management of the drug- resistant mycobacterial strains, including new molecules and drugs prescribed for other diseases.

Several drugs, approved for infectious diseases other than tuberculosis, showed in vitro and in vivo antimycobacterial activity; among them, imipenem-cilastatin, linezolid, and meropenem- clavulanate have had a relevant role in individuals with drug-resistant tuberculosis in the last few years. The new molecules recently approved or in the last clinical trial phases are bedaquiline (a new diarylquinoline, previously called TMC 207), delamanid (previously called OPC-67683), sutezolid (PNU 100480), and PA-824.

Bedaquiline and delamanid have recently received a marketing approval. Bedaquiline-containing regimens increase by 12 times the probability of culture conversion in multidrug-resistant tuberculosis cases and prevent the emergence of further resistances to the drugs included in the backbone regimens. It reduces the time to culture conversion in the first 6 mo of exposure (hazard ratio: 2.3). The safety and tolerability profile is good if compared with other antituberculosis drugs (i.e., acne, bilateral hearing impairment, extremity and noncardiac chest pain). However, the frequency of nausea was significantly higher during some clinical trials if compared with that in the control group[45-49].

Delamanid-containing regimens showed a short- and long-term efficacy in terms of culture conversion. The positive microbiological features are associated with the relevant improvement of a strong epidemiological indicator-like mortality; the proportion of individuals who died after a ≥6-mo exposure to delamanid was 1% versus 8% in those not exposed or with a short-term exposure. The percentage of individuals who culture-converted at 2 mo was about 45% versus nearly 30% in the control group. The most important adverse event that occurred in patients exposed to this novel nitroimidazole was QT prolongation, although not associated to relevant cardiac events[50-52].

Other new promising drugs are currently being tested in the phase II and III clinical trials. In particular, sutezolid, belonging to the same chemical family of linezolid, showed its ability in the reduction of the colony forming units (Shaw and Barbachyn 2011; Wallis et al. 2012). The early bactericidal activity showed by PA-824, a new nitroimidazo-oxazine, was superior to that of bedaquiline in the first clinical trials[53, 54].

Antibiotics licensed for bacterial infections other than tuberculosis proved their efficacy in the treatment of the multidrug-resistant and extensively drug-resistant tuberculosis cases.

Linezolid is efficacious but is characterized by several hematological side effects (anemia and/or leucopenia and/or thrombocytopenia), peripheral nervous system problems, and gastrointestinal toxicity. However, it has been proved that the therapeutic monitoring of its blood levels (TDM) can allow a dosage adjustment, followed by the reduction of the probability of occurrence of adverse events. Several pharmacokinetic studies showed that a 600-mg dosage has the best cost/benefit ratio. TDM was helpful in understanding the best dosage to be administered to patients on the basis of the blood drug concentration. It was clear that a daily dosage of 1200 mg is toxic if compared with a 600-mg dosage. On the other hand, a 300-mg daily dosage is less efficacious[55-60].

Meropenem-clavulanate and cotrimoxazole showed their efficacy in some observational studies. The former favored sputum smear and culture conversion in >80% of the multidrug-resistant tuberculosis cases (88% and 84%, respectively, in a case-control study) and was associated with an optimal safety profile[61].

The latter was evaluated in vitro and in a few cases, and its efficacy needs to be proved in experimental, controlled studies, Vilchèze and Jacobs 2012). New experimental clinical trials are needed to assess the clinical profile of the new therapeutic options[62, 63].

The management of individuals with multidrug-resistant tuberculosis and HIV infection requires the involvement of tuberculosis/HIV specialists. Anti-HIV drugs should be prescribed within 8 mo from the first administration of the antituberculosis drugs. The pill burden is relevant and the adherence of the patients can be significantly affected; furthermore, the toxicity linked to the pharmacological interactions can contribute to reduce the compliance of the patients. In particular, the severity of the hepatic, gastrointestinal, hematological, renal, and central and peripheral nervous system toxicity could interrupt the treatment.

Main adverse events of the antituberculosis drugs and of the antiretrovirals

Antituberculosis drugs	Antiretroviral drugs	Adverse event
Isoniazid Linezolid	Didanosine Stavudine	Peripheral neuropathy
Bedaquiline Isoniazid Para-aminosalicylic acid Pyrazinamide Rifampicin	Efavirenz Etravirine Maraviroc Nevirapine Ritonavir/protease inhibitors	Liver dysfunction
Amikacin Amoxicillin/clavulanate Fluoroquinolones Isoniazid kanamycin Rifampicin Streptomycin Thiacetazone	Abacavir Efavirenz Etravirine Nevirapine	Skin rash
Thiacetazone Bedaquiline Pyrazinamide Thiacetazone	-	Arthromyalgia
Amikacin Capreomycin Kanamycin Streptomycin	Indinavir Tenofovir	Renal dysfuction
Amikacin Capreomycin Kanamycin Streptomycin	-	Vestibular and auditory dysfunction
Amoxicillin/clavulanate Bedaquiline clarithromycin Clofazimine Ethionamide fluoroquinolones linezolid	Didanosine Protease inhibitors Stavudine Zidovudine	Gastrointestinal disorders

Adherence to Antituberculosis Therapy

The efficacy of the combination regimens described above will determine, in addition to bacteriological conversion, a subjective improvement of the patient's clinical conditions. The latter feature may anticipate the microbiological conversion and could be paradoxically dangerous from an individual and a public health perspective; patients feeling better might decide to interrupt their treatment.

Several approaches have been proposed to increase patient's adherence. One of the most important is the so-called DOT (i.e., directly observed therapy). The patient takes the prescribed therapy in the presence of a health-care worker (physician or nurse), a social worker, or another person involved in agreement with the local tuberculosis program. The direct observation avoids all the problems associated with self-administration, including compliance with the dosages and time of administration affecting the pharmacokinetic curve of the drugs. In addition, DOT allows rapid management of adverse events related to the drug intake.

Another important tool to enhance adherence is represented by the fixed-dose combination of the antituberculosis drugs. They were introduced in clinical practice at the end of the 1980s, and several advantages were immediately recognized: easy management for the national tuberculosis program and for health staff not fully familiar with antituberculosis drugs and reduced probability of emergence of drug resistances because of the improved patient's adherence. The main disadvantages, intrinsically related to the fixed dose, are the risk of a nonadequate blood level (rare, and limited to patients characterized by a poor intestinal absorption or by a rapid metabolism) and the difficulty in attributing an adverse event to a specific drug.

Another strategic therapeutic approach to improve adherence is represented by the intermittent regimens, whose efficacy was shown in 1964 in Chennai, India. Antituberculosis drugs are administered at intervals of >1 d. The relapse rate is 8% after a follow-up of 2 yr [27].

An important role to increase adherence can be played by incentives and enablers (money, food, incentives for transportation, etc.), particularly in resource-limited countries. Poor patients living in rural areas can lose their job and their daily salary because of the medical visits in far urban settings. National tuberculosis programs should identify the geographical areas or the social groups where these nonmedical interventions could be crucial in improving adherence [64].

Last but not least, when health education is adequately provided by health services to the patients and their families, adherence tends to improve.

Result and Discussion

The current therapeutic management of drug-susceptible and drug-resistant strains needs to be further improved. The available regimens are characterized by a relevant pill burden, long duration, variable efficacy, safety, and tolerability. The overall treatment success rate is below the recommended World Health Organization proportion of 85%, and, consequently, the drug resistance level increases. The World Health Organization estimates that a suboptimal proportion of multidrug-resistant cases is presently diagnosed and treated. In 2010, 48% of the detected multidrug-resistant tuberculosis cases were successfully treated. Only 34 countries obtained a treatment success rate ≥75% (World Health Organization 2013a). Even in tuberculosis reference centers, the proportion of treatment success in multidrug-resistant cases does not exceed 50%.

Although the adherence, efficacy, safety, and tolerability profile of the newly available drugs (delamanid and bedaquiline, in particular) appear to be promising, we cannot predict, as of today, their long-term efficacy and the affordability of their use in resource-limited settings.

Further research efforts are necessary to identify the potentialities of the new drugs and to understand better how to use them in combination regimens. These new regimens are ideally able to treat tuberculosis sustained by both drug-susceptible and drug-resistant strains without interfering with antiretroviral drugs, thus allowing a more effective approach against HIV-infected cases.

The new approach adopted to test different drug combinations in parallel can improve the current situation, giving new insights in a shorter period of time. New research and development activities are requested, along with a preservation of the current therapeutic options. Training and educational activities focused on the rationale use of the antituberculosis drugs are necessary to avoid the dramatic increase of the drug-resistant forms. National and local public health programs should issue guidance, based on the local epidemiology, to prevent inappropriate management of the new and old antibiotics, as to ensure that all cases of tuberculosis diagnosed and correctly treated, complete their treatment. The risk is to lose the new drugs in much less than the time necessary to develop them.

Conclusion

TB is spread from person to person through the air. When people with lung TB cough, sneeze or spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected.About one-quarter of the world's population has latent TB, which means people have been infected by TB bacteria but are not (yet) ill with the disease and cannot transmit the disease.People infected with TB bacteria have a 5–15% lifetime risk of falling ill with TB. However, persons with compromised immune systems, such as people living with HIV, malnutrition or diabetes, or people who use tobacco, have a much higher risk of falling ill.When a person develops active TB disease, the symptoms (such as cough, fever, night sweats, or weight loss) may be mild for many months. This can lead to delays in seeking care, and results in transmission of the bacteria to others. People with active TB can infect 10–15 other people through close contact over the course of a year. Without proper treatment, 45% of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die.

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