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Tuberculosis Treatment and Drug Regimens

Giovanni Sotgiu[1], Rosella Centis[2], Lia D'ambrosio[2], and Giovanni Battista Migliori[2]

[1]Clinical Epidemiology and Medical Statistics Unit, Department of Biomedical Sciences, University of Sassari, Research, Medical Education and Professional Development Unit, AOU Sassari 07100, Italy

[2]World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate 21049, Italy

Correspondence: gbmigliori@fsm.it

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.

Medical treatment of tuberculosis, together with correct diagnosis, represents a cornerstone in the management and control of tuberculosis. It is relevant from a clinical and public health perspective, as tuberculosis is a serious contagious airborne disease.

Antibiotic treatment, reducing the bacterial load in the lungs, can be helpful to reduce the probability of transmission, along with other public health measures, such as isolation and cough etiquette.

The dramatic change of the epidemiological scenario during the last two decades, as a consequence of the increased incidence of the tuberculosis/HIV (human immunodeficiency virus) coinfection and of drug-resistant forms of tuberculosis, however, significantly complicated the clinical and public health management of the patients and of their contacts.

Currently, clinicians and public health specialists are facing daily problems related to the prescription of less effective and toxic second-line drugs, with frequent pharmacological interactions with antiretroviral drugs or medicines used to treat other comorbidities.

TUBERCULOSIS THERAPY: HISTORY AND RATIONALE

Tuberculosis is an ancient disease; nevertheless, effective drugs were not available for centuries. The preantibiotic therapy was initially repre-

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sented 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 (Rosenblatt 1973; Sakula 1983; Dheda and Migliori 2012).

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 (Goldsworthy and McFarlane 2002; Daniel 2006).

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 (Barry 1964; World Health Organization 2004; Migliori et al. 2011; Sotgiu et al. 2013).

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 (Table 1) (Schatz et al. 1944; Hinshaw and Feldman 1945; Wassersug 1946; Fox et al. 1954, 1999; World Health Organization 2004).

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 (Crofton 1960, 1969, 2006; Fox et al. 1999; World Health Organization 2004; Migliori et al. 2011; Sotgiu et al. 2013).

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 treat-

Table 1. 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
Ethionamide	15–20 mg/kg
Prothionamide	15–20 mg/kg
Cycloserine	500–1000 mg
Para-aminosalicylic acid	150 mg/kg
Linezolid	600 mg
Clofazimine	200–300 mg
Amoxicillin/clavulanate	875/125 mg BID or 500/125 mg TID
Clarithromycin	1000 mg
Terizidone	600–900 mg
Thiacetazone	150 mg
Thioridazine	75 mg
Bedaquiline	400 mg (for 2 wk) 200 mg TIW (for 22 wk)
Delamanid	200 mg

BID, twice a day; TID, thrice a day; TIW, thrice a week.

ment (East African/British Medical Research Council 1974; Sensi 1983; Fox et al. 1999; Migliori et al. 2011; Sotgiu et al. 2013).

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 (Table 2) (Dawson et al. 1966; Migliori et al. 2011; Sotgiu et al. 2013).

On the basis of the microbiological characteristics of *M. tuberculosis* (i.e., slow growth and dormancy of some of the bacilli belonging to the bacterial population), numerous scientific contributions showed the efficacy of a long-term and multidrug therapeutic approach to obtain a bacteriological eradication in pulmonary and extrapulmonary sites.

Other factors can contribute to the successful outcome of the antituberculosis therapy, including the chemical features of the infection site. An adequate combination of effective drugs can reduce the probability of failure, relapse, and selection of resistant strains. To achieve those clinical and public health outcomes, it is necessary to prescribe antituberculosis drugs with an adequate dosage, for a specific time of exposure, and whose efficacy has been proved in in vitro tests (i.e., drug-susceptibility testing). In particular, to avoid the emergence of resistant strains, it is necessary to prescribe at least two effective drugs.

Table 2. 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

Duration of drug exposure is different according to the susceptibility of the isolated strains. In general, two different steps in the treatment of tuberculosis can be recognized—initial (or bactericidal) phase and continuation (or sterilizing) phase. During the first step of treatment, mycobacteria with a high replication rate are killed, and, consequently, with the histological pulmonary restoration and the reduction of the inflammation process, symptoms and clinical signs resolve (clinical recovery). From a public health perspective, this phase is crucial because the treated patient becomes noninfectious and the probability of selection of drug-resistant strains decreases (it is directly correlated to the fast-growing bacteria). The continuation phase is oriented to the elimination of semidormant bacteria, whose size is significantly reduced if compared with that at the beginning of the antituberculosis therapy; this quantitative feature, related to the low replication rate, is associated with a low probability of emergence of drug-resistant mycobacteria. In cases of drug-susceptible tuberculosis, two potent medicines are sufficient (e.g., isoniazid and rifampicin) in this phase. On the other hand, the regimen prescribed during the initial phase is more complex: two bactericidal drugs (isoniazid with streptomycin or rifampicin), ethambutol to inhibit monoresistant strains and to reduce the mycobacterial burden, and pyrazinamide, whose action is mainly focused to the semidormant mycobacteria. The intensive phase has a duration of 4 mo, whereas the sterilizing phase has a duration of 2 mo.

On this basis, the choice of the antituberculosis drugs in the different phases is not random but is based on the epidemiology (e.g., resistance rate in a specific setting, probability of having been infected by a contact with drug-resistant tuberculosis) and on the specificity of action of the antituberculosis drugs. The antituberculosis drug armamentarium is characterized by molecules with two main different mechanisms of action—bactericidal effect and sterilizing effect. The first one is crucial in the intensive phase and allows a relevant reduction

of the bacterial load; the indirect consequence of this activity is the reduction of the probability of selecting drug-resistant strains. The most important drugs prescribed for that aim are isoniazid, pyrazinamide, rifampicin, and streptomycin. The sterilizing activity is relevant in the initial phase and in the continuation phase, but primarily in the continuation phase because it is oriented to kill mycobacteria in a dormancy state. Antituberculosis drugs deemed helpful in this phase are pyrazinamide and rifampicin.

These general principles are accepted worldwide, and the standardized regimens recommended by the World Health Organization in its guidelines have their roots in this biological rationale (World Health Organization 2004; Migliori et al. 2011; Sotgiu et al. 2013).

The World Health Organization classified antituberculosis drugs into five classes following several criteria, among them their efficacy and their chemical characteristics. The drugs usually prescribed for the drug-susceptible tuberculosis are included in the first class, whereas the drugs with unclear efficacy are included in the fifth class. In particular, the following drugs are integrated in the first class: ethambutol, isoniazid, pyrazinamide, and rifampicin. The second class includes amikacin, capreomycin, kanamycin, and streptomycin; old- and new-generation fluoroquinolones are included in the third class. The antituberculosis drugs in the fourth class are cycloserine, ethionamide, para-aminosalicylic acid, prothionamide, terizidone, and thioacetazone. The fifth class encompasses amoxicillin/clavulanate, clarithromycin, clofazimine, imipenem, and linezolid (World Health Organization 2010).

TREATMENT OF DRUG-SUSCEPTIBLE TUBERCULOSIS (WORLD HEALTH ORGANIZATION 2010)

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 (Table 3).

The World Health Organization recommends the prescription of an empiric regimen for those who are identified as relapsers or defaulters, in case of a low multidrug resistance prevalence—ethambutol, isoniazid, pyrazinamide, rifampicin, and streptomycin in the intensive phase, followed by ethambutol, isoniazid, pyrazinamide, and rifampicin for 30 d; the last 5-mo phase is characterized by ethambutol, isoniazid, and rifampicin, for a total duration of 8 mo (Table 4).

It was clearly shown that the 6-mo regimen is practically 100% effective; after a follow-up period of 2 yr, the relapse rate can range from 0% to 7%. Intermittent regimens proved a similar efficacy, with a slightly higher relapse rate at

Table 3. Main adverse events of the antituberculosis drugs

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

2 and 5 yr and a lower proportion of adverse events (World Health Organization 2004).

Extrapulmonary tuberculosis is a paucibacillary disease, and therapeutic regimens are the same as those prescribed for the pulmonary forms. Severe extrapulmonary disease, characterized by the neurological, abdominal, bilateral pleural, pericardial, bone, or joint or systemic involvement, needs four drugs in the intensive phase and sometimes a treatment duration of 9 mo (e.g., in case of neurological involvement). In case of relevant inflammation, the prescription of steroids is recommended. However, the prognosis strictly depends on the precocity of the administration of the antituberculosis drugs (World Health Organization 2004).

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 (Falzon et al. 2011; World Health Organization 2011b).

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

Table 4. Recommended antituberculosis regimens from World Health Organization

New tuberculosis cases				Previously treated tuberculosis cases			
Intensive phase		Continuation phase		Probability of multidrug-resistant tuberculosis			
					Medium or low (relapse, default)		
Drugs	Duration (mo)	Drugs	Duration (mo)	High (failure)	Drugs (duration, mo)	Drugs (duration, mo)	Drugs (duration, mo)
Ethambutol[a] Isoniazid Pyrazinamide Rifampicin	2	Isoniazid Rifampicin	4	Empirical multi-drug-resistant tuberculosis regimen[c]	Ethambutol Isoniazid Pyrazinamide Rifampicin Streptomycin (2)	Ethambutol Isoniazid Pyrazinamide Rifampicin (1)	Ethambutol Isoniazid Rifampicin[c] (5)
Ethambutol[a] Isoniazid Pyrazinamide Rifampicin	2[b]	Ethambutol Isoniazid Rifampicin	4				

[a]Only for noncavitary, smear-negative pulmonary tuberculosis or for extrapulmonary tuberculosis. In tuberculosis meningitis, streptomycin is suggested.
[b]Level of isoniazid resistance among new is elevated and in vitro isoniazid-susceptibility testing is not available.
[c]Changed once drug-susceptibility testing results are available.

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 (World Health Organization 2011a).

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 (World Health Organization 2008).

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 (Diacon et al. 2009, 2012a,b, 2013; Willyard 2012; Mahajan 2013; World Health Organization 2013b).

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 $\geq$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 (Diacon et al. 2011; Gler et al. 2012; Skripconoka et al. 2013).

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 (Diacon et al. 2012a,b; Migliori and Sotgiu 2012).

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 (Migliori et al. 2009; Sotgiu et al. 2009, 2012; Alffenaar et al. 2010; Koh et al. 2012; Srivastava et al. 2013).

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 (De Lorenzo et al. 2013). The latter was evaluated in vitro and in a few cases, and its efficacy needs to be proved in experimental, controlled studies (Forgacs et al. 2009; Huang et al. 2012; Vilchèze and Jacobs 2012). New experimental clinical trials are needed to assess the clinical profile of the new therapeutic options (Grosset et al. 2012; Pontali et al. 2013).

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 (Table 5).

A recent systematic review, enrolling 217 patients, whose CD4 cell counts were <200 μL in the majority of cases, showed that individuals exposed to antiretrovirals were more likely to survive (hazard ratio of 0.38) and have a longer median time to death (i.e., 37 mo vs. 11 mo among those not exposed to antiretrovirals). Furthermore, the prescription of antiretroviral drugs was associated with a higher probability of cure (hazard ratio, 3.4). It was proved that the level of immunodeficiency and the mycobacterial resistance pattern do not influence the above-mentioned risks (Arentz et al. 2012).

The concomitant prescription of anti-HIV and antituberculosis drugs does not depend on the severity of the immunodeficiency and then on the CD4 cell counts.

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

Table 5. 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
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 Prothionamide Para-aminosalicylic acid Terizidone Thiacetazone	Didanosine Protease inhibitors Stavudine Zidovudine	Gastrointestinal disorders
Cycloserine fluoroquinolones terizidone	Efavirenz	Psychosis

Data modified from Arentz et al. 2012.

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 healthcare 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 (World Health Organization 2004).

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 (Tuberculosis Coalition for Technical Assistance 2009).

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

CONCLUDING REMARKS

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 $\geq$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 loose the new drugs in much less than the time necessary to develop them.

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