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Health Interventions to Improve the Medication Efficacy in Tuberculosis Treatment

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1. Introduction

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. According to the World Health Organization (WHO), there are an estimated of 8.8 million new cases annually -including 200.000 HIV-infected individuals- and 1.6 million deaths (WHO, 2008). Despite some reports demonstrates reduction of new cases, it is extensive in literature data showing the problem of drug-resistance and the consequence of this one to the effective treatment (FAUCI, 2008). The drug resistance can be caused by several factors such as: 1) antibiotic selective pressure characterized by inadequate selection or dosage; 2) immune status of the individuals; 3) No compliance by patients; 4) natural selection or any pre-existing resistances in the infecting clone, among others (Figure 1).

Nowadays, HIV co-morbidity treatment is a challenge. It has been reported that HIV is a potent risk factor to TB disease development. Some studies showed that HIV/TB co-infection increase 100 times the risk to develop TB disease when compared to people infected only with TB (HAVLIR & BARNES, 1999; PITCHENIK et al., 1988). In addition, the probability to develop drug resistance is higher in patients under HIV infection treatment due mainly drug related problems (Frieden et al. 1993; Gordin et al., 1996).

One of the first randomized studies about antitubercular drug was performed with streptomycin. This drug reduces 50% the mortality of infected patients after 6 months of treatment. However, it was observed high rate of resistance in cases of monotherapy. The combination of drugs reduces the resistance to TB drugs, therefore the current treatment of tuberculosis involves multidrug therapy (Herzog, 1998).

WHO recommends the use of rifampicin (or rifabutin), isoniazid, pyrazinamide and ethambutol by two months followed by rifampicin and isoniazid for four months. The first phase of the treatment aims eliminates the bacilli in mutiplicate and semi dormant stage. The second stage called the maintenance phase aims eliminate dormant bacilli reducing the number of failures and relapses (Bisaglia, 2003). The scheme of treatment is prolonged (6 months) contributing to no-therapy compliance by some patients.

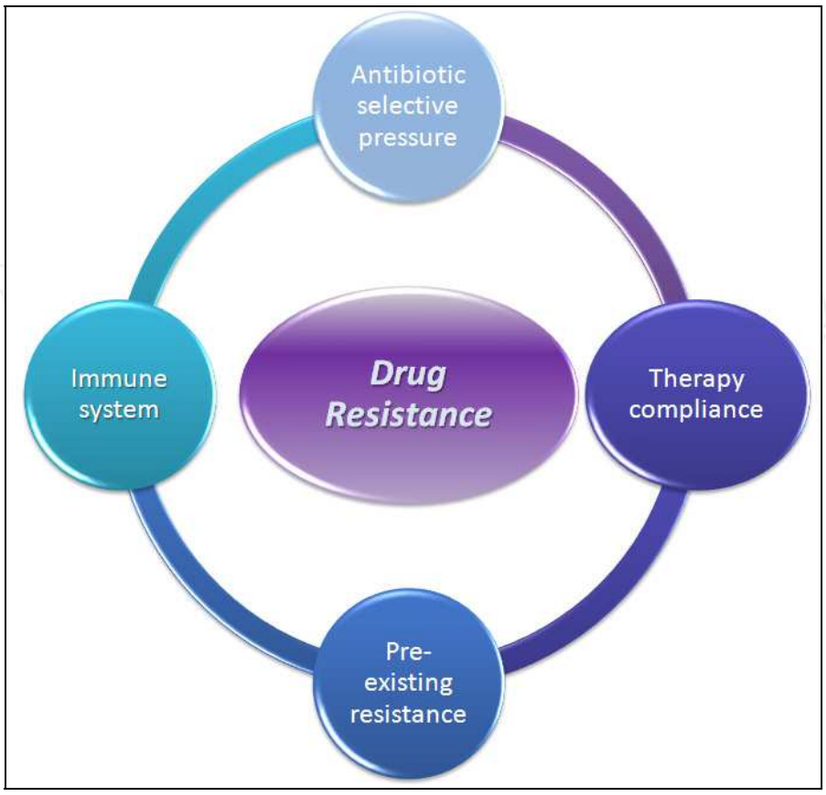

Fig. 1. Some causes of TB drug resistance.

The lack of therapy adherence is a serious problem to eliminate TB mainly in developing countries. Several aspects are related to this problem such as: adverse effects of TB drugs, long-term therapy, damage to certain organs (i.e. liver), lack of available drugs and co-morbidities.

Another important aspect to be considered in tuberculosis treatment is the unavailability of new drugs. The last discovery drug to TB was rifampicin in the 60's. Despite TB drug development efforts have emerged in the last years few advances were reached. Currently, there are some drugs, obtained by molecular modification, being evaluated in clinical trials. An ideal drug against TB must possess some characteristics that include: broad spectrum of action with possibility to be use in resistant strains; adequate pharmacokinetic profile increasing the concentration in some tissues target and reduce drug-drug interaction; adequate and shorten treatment duration reducing pill burden in order to reduce numbers of pills taken increasing the patients compliance (Koul et al, 2011).

The combination of all these factors discussed above makes difficult TB treatment. Not only strategies to discovery new drugs, but rational approach to improve the use of old drugs are essential to improve the efficacy of the treatment. This chapter aiming discusses some factors to improve medication efficacy in tuberculosis treatment. Some aspects of TB such as disease development, resistance and treatment will be discussed. Furthermore therapeutical aspects such as drug-drug interaction, patient compliance and some health interventions will be present.

TB Treatment

According to WHO new patients is recommended the treatment to receive a daily intensive phase of the two months of the isoniazid (H), rifampicin (R), pyrazinamid (P) and ethambutol (E); followed by 4 months for the maintenance phase of the H and R [2HRZE/4HR] (WHO, 2009). This treatment is highly efficient for the drug-susceptible TB patients, but, the questions is what about the latent and MDR (multi-drug resistant) or XDR (extremely drug-resistant) TB treatment?

Latent tuberculosis is individuals infected with M. tuberculosis but has no active disease. Although this state not is completely clear, there are two main hypothesis to explain this condition: 1) M. tuberculosis persists in a lazy state within granulomatous lesions, but periodically recrudesces; 2) the bacterium persisting in a dormant state resides within alveolar epithelial cells in the lung apices and adipocytes (Ma et al., 2010). Epidemiologically latent infection is responsible to contaminated 1/3 of the world population, and there is no specific treatment for it (Koul et al., 2011). However H has been used as preventive therapy (IPT) has long been known to markedly reduce the risk of reactivation of latent M. tuberculosis infection, but this affirmation not is completely proved and clear (Golub et al., 2008).

MDR-TB occurs when the TB mycobacteria are resistant to at least H, R and XDR-TB occur when the mycobacteria has the same resistant characteristic than MDR-TB plus resistant to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin, and amikacin). The resistant bacteria are selected due to mainly to failure of the treatment. Failures attributed mainly to the desistance of treatment by the patient. To understand how the bacteria become resistant is not completely understood, but various biochemical pathways to escape the lethal action of drugs can be assigned: (i) decreased intracellular accumulation of the antibiotic by an alteration of outer membrane permeability, diminished transport across the inner membrane, (ii) alteration of the target by mutation or enzymatic modification; (iii) enzymatic detoxification of the drug; and (iv) bypass of the drug target. The coexistence of several of these mechanisms in the same host can lead to MDR and XDR-TB. (Piddock et al., 2006; De Rossi et al., 2006). Another important question that needs to be highlighted is the association of these biochemical resistant pathways with the efflux pump system. Efflux is a ubiquitous mechanism responsible for intrinsic and acquired drug resistance in prokaryotic and eukaryotic cells. M. tuberculosis presents one of the largest numbers of putative drug efflux pumps compared with its genome size. Antimicrobial resistance in an efflux mutant is due to one of two mechanisms: (i) expression of the efflux pump protein is increased or (ii) the protein contains an amino acid substitution(s) that makes the protein more efficient at export (Piddock, 2006).

MDR treatment, anti-TB drugs are grouped according to efficacy, experience of use and drug class. There are five groups and only the group 1 can receive the first line drugs, all others groups will receive the second-line drugs namely: kanamycin (Km), amikacin (Am), capreomycin (Cm), streptomycin (S), Levofloxacin (Lfx), Moxifloxacin (Mfx), Ofloxacin (Ofx), para-aminosalicylic acid (PAS), cycloserine (Cs), terizidone (Trd), ethionamide (Eto), protionamide (Pto), clofazimine (Cfz), linezolid (Lzd), amoxicillin/clavulanate (Amx/Clv), thioacetazone (Thz), imipenem/cilastatin (Ipm/Cln), clarithromycin (Clr) (WHO, 2009).

2. TB therapy problems

TB treatment presents several challenges to be overcome. The treatment abandonment is one of them which contribute to development of resistance by mycobacterium to available drugs. The abandonment or lack of adherence occurs when the patient does not attend to receive medication for a month or more (Pablós-Méndez et al., 1997). Several factors contribute to this situation such as socio-economic factors, adverse effects of drugs, co-morbidities, environmental factors (familiar, social behavior). In developing countries the access to adequate health system is one of the most problems to TB therapy. It is very common situation that the population has not medical service neither education level to comprehend the therapy. There is a relation between poverty and predisposition to disease difficult the TB control. Malnutrition, increased expensive to take medicines and stigmatization are some intrinsic factors related to the inadequate control of TB in poor countries (Cegielski & McMurray, 2004; Atre et al., 2009; Dhingra et al., 2010; WHO, 2005; Hargreaves et al., 2011). Educational levels and employment are conditions related to abandonment of therapy. It has been reported that a worker, provider of family without adequate financial support present high abandonment rate (64%). An interesting relation is also observed when someone analyses the educational level of the patients. Those which possess higher education (university) demonstrate high level of adherence despite those with low educational level. Low level of knowledge is directed relate to inadequate treatment (Grace & Chenhall, 2006). The Table 1 shows the main reasons related to treatment abandonment.

The adverse effect of antitubercular drugs is one the main causes of therapy abandonment. Some adverse effects of antitubercular drugs are described above:

Socio-economic	Worker, a provider of family, lack of financial sources for feeding and locomotion: 64% abandonment. Unemployed: 36% abandonment (finantial problems and low self steem) Education: illiteracy (20% abandonment), less than 8 years of study (72 % abandonment), between 8 and 12 years of study (8% abandonment) and more than 13 years (0% abandonment).
Therapeutical	Adverse effects relate to antitubercular drugs: nausea, vomiting, hyperthermia and edema. Denial and oblivion. Regimens: - 2 months: R/I/P + 4 months R/I = 88% abandonment; - 6 months: S/P/E/Et = 8% abandonment; - 6 months S/I/Et = 4% abandonment. R – rifampicin; I – isoniazid; P- pyrazinamide; S- streptomycin; E – ethambutol; Et – ethionamide.

Disease related problems	Non-acceptance of diagnosis, riot with the illness. No knowledge of the existence of extra-pulmonary forms. No symptoms after initial treatment interpreted by patients as a cure (Uplekar et al 2001).
Health related problems	Fractures, improvement of symptoms, mental Illness; Hepatitis (do not show tolerance to treatment); *Patients with co-morbidity* Diabetes / TB = TB infections have more severe, with treatment failure rate of 8.5 x higher, which generates most abandoned, because this patient needs a longer treatment (Gupta et al, 2011). HIV / TB: The patient focuses on the treatment of HIV, at least tolerate the associated treatment. It is discouraged when after diagnosis of HIV, or vice versa (53% abandonment).
Familiar	Death and other diseases in the family, motivation, recommendation to stop (by others); Living away from family; Overpopulation in a single family home (sleeping more than two in same bed); Absence of familiar support.
Social behavior and sex	An anthropological phenomenon is observed with male younger, unmarried and/or separated which seek to preserve their particular way of life believing that they are not susceptible to TB disease. This group has not a tendency to modify some habits to contribute for the TB treatment during the 6 months of treatment (Gonçalves et al., 1999).
Risk groups	A community in contact with contagious TB or focus intra-household is recommended prophylaxis with isoniazid, however, is not accepted by individuals. Typically, these individuals end up contaminating and seek treatment lately; Alcoholic: 24% abandonment; Smokers: 40% (Mendes & Fensterseifer, 2004) 48.8% (Christmas 1997) abandoned; Drinker and smoker: 86.6% abandonment (Lima et al., 2001); Drug addict: 12% abandonment;
Others	Patient does not trust in the treatment, doctors or the health system itself. Wait for the health service; Distance from health service; System health bureaucracy.

Table 1. Main reasons related to treatment abandonment.

- Isoniazid: Peripheral neuritis (prevent with the use of pyridoxine); may occur again, optic neuritis, ataxia, mental disturbances and incoordination. Hypersensitivity to isoniazid can cause fever, various skin rashes, hepatitis and skin rashes, hematologic reactions may occur (agranulocytosis, eosinophilia, thrombocytopenia, anemia); neuritis and optic atrophy. Twitches, dizziness, ataxia, paresthesias, numbness, toxic encephalopathy are other manifestations of neurotoxicity of isoniazid. It may also appear several mental abnormalities. May precipitate seizures in patients with previous history of seizures.
- Rifampicin: Facial flushing, generalized itching and skin rash, purpura, epistaxis, menorrhagia, gingival bleeding and hemolytic anemia. Pseudogripal syndrome with fever, malaise, headache, chills and myalgia, which may progress to interstitial nephritis, acute tubular necrosis, thrombocytopenia and shock. In the digestive tract: Malaise, loss of appetite, nausea, vomiting, jaundice, liver failure and diarrhea.
- Pirazinamide: Liver damage with elevation of plasmatic AST and ALT is the main adverse effect. Furthermore it is observed arthralgia, anorexia, nausea and vomiting, dysuria, malaise and fever.
- Ethambutol: The observed adverse reactions include itching, joint pain, gastrointestinal disorders, abdominal pain, malaise, headache, dizziness, mental confusion, disorientation and possible hallucinations, acute gout or hyperuricemia. Although rare the peripheral neuritis and retrobulbar optic neuritis (blurred vision, eye pain, red-gray images, decreased vision) are reported. The retrobulbar optic neuritis is dose-dependent, occurring more frequently with daily doses of 25 mg / kg and after two months of therapy, in many cases is reversible after several weeks or several months.

In general, the adverse effects related to first line antitubercular drugs include skin rash, itch, nausea and vomiting, thrombocytopenia, symptoms influenza-símile, arthralgias and neuropsychiatric manifestations (Yee et al., 2003; Fekih et al., 2011; Fountain et al., 2005).

It has been reported that the rate of adverse effects during the treatment could reach 30% of the patients or 7,3 per 100 patients/month. Therapy with four drugs increase the incidence to 23,3 events by 100-patients/month. In addition, the adverse effects are used to appear during the first 100 days of treatment and the most common effects observed were hepatitis (28%), gastrointestinal disorders (19%), skin rash (15%), weakness or tiredness (7%) and joint pain (6%) (Yee et al., 2003).

The hepatotoxicity is a deleterious adverse effect responsible to determine changes in therapy. TB first line drugs such as rifampicin, rifabutin, isoniazid and pyrazinamide can cause hepatotoxicity, alone isoniazid is responsible to 20% of reported cases. The combination of drugs increases the probability to develop hepatotoxicity. Risk factors such as HIV co-infection, hepatitis B and/or C, alcohol abuse or the use of some medicines (i.e. anticonvulsant) should be taken in consideration due the due to the increased likelihood of causing liver toxicity.

In situation which patients present previous diagnosis of advance liver disease, when the doctor wants to keep only one hepatotoxic drug, rifampicin is usually selected. However, other agents should be added the therapy such as fluorquinolone, cycloserine and aminoglycoside. The treatment time of these schemes can vary from 12-18 months (American Thoracic Society, 2003).

It is important to note that the assessment of adverse effects should be performed throughout therapy, and compared with pre-treatment parameters. The patient should be prepared to identify adverse effects related to the use of anti-TB drugs.

Environment factors are determinants for TB treatment. The family has a crucial role to the treatment. The knowledge of the disease by all familiar members is an important factor to control TB. After the first phase of the treatment, when some symptoms decrease, is common identify problems with adherence by patients. So, educational interventions by health professionals are important to improve the TB treatment management. Some studies demonstrated that previous cases in the family increase the knowledge and the adherence by patients (Costa et al., 2011). However, some factors such live away from family, absence of familiar support and overpopulation in a single family home (with more than two people sleeping in the same bed) is a risk factor to abandon TB treatment.

Gender is another factor relate to TB. Worldwide, more men than women are diagnosed with TB. This higher TB notification in men is relate to epidemiological differences such as risk of exposure, infection and progression to disease. However, it has been reported that women have higher case of fatalities in the early reproductive ages and higher rates of progression from infection to disease (Holmes et al., 1998).

The association of TB with co-morbidities is a complicated factors related to increase of adverse effects and high rate of abandonment treatment by patients. It has been reported that treatment fail is increased 8.5 times in diabetic patients with TB, general relate to abandonment. In diabetic group infection with TB seems to be more severe that in people no-diabetic (Gupta et al., 2011).

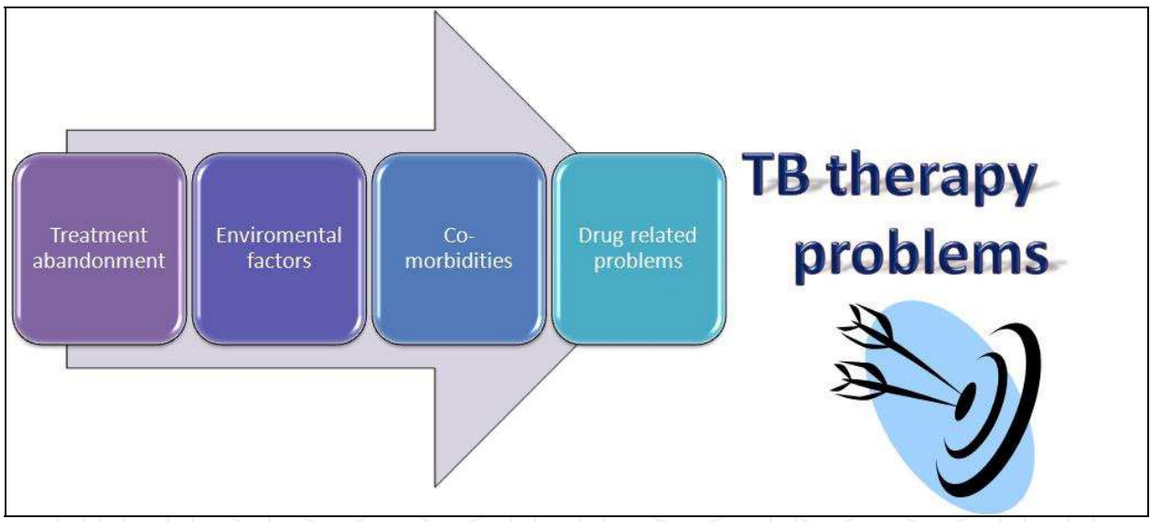

Fig. 2. Some TB therapy problems.

The abandonment of HIV co-infection patients could reach 53% (Table 1). The recommended TB treatment of HIV-negative people is the same of HIV-positive people but sometimes the therapy is extended to 9 months or more in patients with extra-pulmonar TB. However, some management of the therapy is complicated due to paradoxical reaction, drug interactions and the difficulty to ingest a large number of tablets (Yew, 2002). The paradoxical reactions, is an exacerbation of TB symptoms, due to due to immune recovery, called immune reconstitution syndrome. Although the mechanism is not totally clear it is presumed to represent an interaction between the host responses and effects produced by mycobacterial products leading to inflammatory lesions (Orlovic & Smego, 2001). Some

symptoms include restart or worsening of fever, lymphadenopathy, dyspnea, worsening of brain injury (Navas et al., 2002).

3. Anti-TB drug interactions

Concurrent treatment of TB and HIV is associated with a higher risk of adverse reactions compared to treatment of either infection alone. The first-line anti-TB drugs isoniazid, rifampin, and pyrazinamide may each cause hepatotoxicity, which may be compounded by concomitant use of protease inhibitors (PI) and nonnucleoside reverse transcriptase inhibitors (NRTI). Pharmacokinetic interactions between HIV and TB regimens can have a significant impact on the therapeutic efficacy of each regimen.

Rifamycin antibiotics, the main drug in TB therapy induce the synthesis of drug metabolizing enzymes (cytochrome P450 emzyme system, particulary the CYP 3A4, CYP 2C8/9 isoenzymes and to a lesser extent CYP2C19 and CYPD6 isozymes; the rifamycins vary in their potential as CYP450 inducers. Potency of induction: Rifampin > rifapentine > rifabutin. Rifampin also upregulates the synthesis of cytosolic drug-metabolizing enzymes, including glucuronosyl transferase, an enzyme involved in the metabolism of zidovudine and raltegravir. Potent induction of the cytochrome p450 system by rifampin can lead to subtherapeutic levels of the protease inhibitors accompanied by virological failure

Antiretroviral treatment (ART) improves survival in co-infected TB patients and vice-versa, however, these concomitant drug therapy in the early stage can increase risk of paradoxal TB- immune reconstitution inflammatory syndrome, risk of overlapping drug toxicities with possibility in drug treatment interruption, high pill burden that can impact in adherence and increased potential drug-drug interactions. The delayed treatment can promote the advancing immunosuppression and the development of others opportunist conditions that may increase mortality.

The estimated cumulative probability to develop an adverse event was significantly higher in HIV/TB co-infected in Ruanda patients: 20.9% within the first month of antituberculous treatment (vs. 3.0% in HIV-uninfected) and up to 29.9% at two months of treatment (vs. 6.9% in HIV-uninfected) (Gordin et al., 1996)

Rifamycin is related to interact with four classes of anti-HIV drugs (protease inhibitors, non-nucleoside reverse-transcriptase inhibitors [NNRTI], CCR5-receptor antagonistis and integrase inhibitors. Zidovudine, the nucleoside analogues and enfuvirtide do not have significant interactions with rifamycins.

The initial ATR regimens in areas with high rates of TB use efavirenz (in combination with nucleoside analogues), because of its potency and durability on randomized clinical trials.

The co-adminstration rifampin decrease plasma concentration of efavirenz but not in a significant way. Some expertise suggested an increase of efavirenz to 800 mg in TB/HIV concomitant treatment to patients weighing more than 60 kg (WHO guidelines). However, Cohen and Meinttjes (2010), do not recommend these proceedings based on the fact that the CYP 450 2B6 516 G>T polymorphism, which impairs the function of the primary pathway of efavirenz metabolism (2B6) is present in African populations. So, the consequence of even

		Cmax	AUC	Cmin	
nevirapine + **RIFAMPIN**	Decrease plasma Concentration Caution: Sub-therapeutic dosage found	↓50%	↓58%	↓68%	The standard dose of neveriapine should be used among patients taking rifampin (200 mg daily for 2 weeks, followed by 200 mg twice daily *Increasing nevirapine dose by 50% to 300 mg twice/daily would achieve therapeutic concentration but safety has not been adequately explored as a routine clinical practice and my result in hypersensivity reactions.
nevirapine + **RIFABUTIN**	Not significant changes in plasma concentration				300 mg rifabutin daily or thrice weekly **no changes recommended**
Efavirenz + **RIFAMPIN**	not significant decrease plasma concentration	↓24%	↓25%	↓22%	Rifampin 600 mg once/day 200 mg efanvirenz twice/day No changes recommended
	Increase clinical toxicity : anxiety, depression, hepatitis (mainly in African descendent) * efavirenz has been associated with hepatotoxicity during postmarketing use. **-co-administration of drugs with caution**: drugs that induces liver damages such as acetaminophen, kava-kava, statins, metformin				(600 mg once daily) in combination with an anti-TB regimen containing rifampin (480 to 720 mg/day based on body weight) for 7 days

Efavirenz + RIFABUTIN	↓rifabutin plasma concentration		↓ 38%		**Recommendation:** ↑ to 450-600 mg of rifabutin (daily or intermittent)
Delavirdine + RIFAMPIN	Strongly ↓ delavirdine plasma concentration **NOT RECOMMEND CONCOMITANT USE**	↓90%,	↓97%	↓100%	rifampin (600 mg once daily for 15 days) ↓ plasma concentration of delavirdine (400 mg 3x/ day for 30 days)
Delavirdine + RIFABUTIN	Strongly ↓ delavirdine plasma concentration and ↑rifabutin concentration by 100% (AUC) **NOT RECOMMEND CONCOMITANT USE**	↓72%	↓82%	↓94%	300 mg once daily for 15 days
Etravirine + RIFAMPIN	Strongly ↓ etravirine plasma concentration **NOT RECOMMEND CONCOMITANT USE**				Predicted (etravirine is a substrate of CYP450 2C19, 2C9, and 3A4).
	The risk of peripheral neuropathy may be increased during concurrent use of two or more agents that are associated with this adverse effect. In some cases, the neuropathy may progress or become irreversible despite discontinuation of the medications				**+ ETHABUTOL + ISONIAZIDE (same effect can be observed when use ethambutol + isoniazide only)**

Etravirine + RIFAMPIN	**+ food**		↓50%		Food increase bioavailabitily of etravirine (unknown mechanism, but ranging from 345 kilocalories containing 17 grams fat to 1160 kilocalories containing 70 grams fat did not impact on etravirine bioavailability
Etravirine + RIFABUTIN	Decrease etravirine Cmin			↓ 45%	No clinical experience. (300 mg rifabutin daily or 3 x weekly) **No changes recommended**
Atazanavir * + RIFAMPIN	Strongly ↓ atazanavir plasma concentration **NOT RECOMMEND CONCOMITANT USE**		↓95%		* with etravirine may ↓ atazanavir, with or without low-dose ritonavir as a pharmacokinetic booster. The mechanism is etravirine induction of CYP450 3A4, the isoenzyme responsible for the metabolic clearance of atazanavir and other protease inhibitors
Atazanavir + RIFABUTIN	Increase rifabutin plasma concentration		↑250%		Recommendation: ↓ribatutin dose to 150 mg/day or 3 x week
	+ food **Recommendation:** To ensure maximal oral absorption of atazanavir, it should be administered with or immediately after a meal	↑57%	↑70%		administration with a light meal ↑increased AUC of a single 400 mg dose of atazanavir relative to the fasting state.
Fos-amprenavir + RIFAMPIN	Strongly decrease fosamprenavir plasma concentration – NOT RECOMMEND CONCOMITANT USE		↓75-95%		the mechanism is rifampin induction of CYP450 3A4, the isoenzyme responsible for the metabolic clearance of PIs.

Fos-amprenavir + RIFABUTIN	Increase significantly rifabutin plasma and 25-) desacetylrifabutin in 7.39 fold(Cmax) 13.35 fold (AUC) 32.9 fold (Cmin) **Use with caution**	↑119%	↑193%	↑271%	The mechanism is amprenavir inhibition of CYP450 3A4, the isoenzyme responsible for the metabolic clearance of rifabutin and 25-O-desacetylrifabutin **Recommendation:** ↓ribatutin dose to 150 mg/day or 3 x week
saquinavir /indinavir or nelfinavir + RIFAMPIN	Strongly decrease of protease inhibitors (PIs) plasma concentration **NOT RECOMMEND CONCOMITANT USE**		↓75% to 95%		The mechanism is rifampin induction of CYP450 3A4, the isoenzyme responsible for the metabolic clearance of PIs.
Indinavir + RIFABUTIN	↑ RIFABUTIN concentration and ↓ indinavir by 34%		↑170%		**Recommendation:** ↓ribatutin dose to 150 mg/day or 3 x week
nelfinavir + RIFABUTIN	↑ RIFABUTIN concentration		↑207%		Not significant change in nelfinavir concentration. **Recommendation:** ↓ribatutin dose to 150 mg/day or 3 x week.
Ritonavir + RIFAMPIN	**Use with caution**		↓35%		no change in rifampin concentration (600 mg/day) rifampin will decrease the level or effect of ritonavir by P-glycoprotein (MDR1) efflux transporter **Recommedantion:** Monitor for antiretroviral activity of ritonavir
Ritonavir + saquinavir + RIFAMPIN	Hepatotoxicity. Transaminase elevations up to or even exceeding 20 times the upper limit of normal.(38 %) **Use with caution**				Drug-induced hepatitis with marked ↑ transaminase has been observed in healthy volunteers receiving rifampin 600 mg once daily with ritonavir 100 mg and saquinavir 1000 mg twice daily (i.e., ritonavir-boosted saquinavir). The mechanism has not been described.

Ritonavir + lopinavir + rifampin	Hepatotoxicity. **Use with caution**				Lopinavir / ritonavir– 2 tablets (200 mg of lopinavir with 50 mg of ritonavir) + 300 mg of ritonavir twice-daily + 600 mg rifampin/day Have favorable pharmacokinetic and clinical data among young children
Ritonavir + lopinavir + rifampin	Rifampin decrease plasma concentration of lopinavir **Use with caution:**				Increase the dose of lopinavir / ritonavir to 4 tablets (200 mg of lopinavir with 50 mg of ritonavir) twice-daily. This combination resulted in hepatitis in all adult healthy volunteers in an initial study.
Ritonavir + lopinavir Rifabutin	↑ RIFABUTIN and 25-o-desacetil rifabutin (47,5 fold) concentration		303%		**Recommendation**: ↓ribatutin dose to 150 mg/day or 3 x week
atazanavir/ tipranavir or darunavir + ritonavir + rifampin	Rifampin strongly decrease of protease inhibitors (PIs) plasma concentration – **NOT RECOMMEND CONCOMITANT USE**				The mechanism is rifampin induction of CYP450 3A4, the isoenzyme responsible for the metabolic clearance of PIs.
Ritonavir + saquinavir/indinavir/amprenavir/fos-amprenavir/ atazanavir/tipranavir or darunavir + RIFABUTIN	↑ RIFABUTIN and 25-o-desacetil rifabutin concentration (varyng degreee)				**Recommendation:** ↓ribatutin dose to 150 mg/day or 3 x week

Maraviroc + rifampin	↓ maraviroc plasma concentration	↓66%	↓63%	↓ 78%	No clinical experience with increased dose of maraviroc + rifampin Recommendation: no changes in rifampin dose (600 mg/day)
Maraviroc + rifampin	Patients with severe renal impairment or end-stage renal disease (CrCl <30 mL/min) given maraviroc may have an increased risk of postural hypotension due to increased maraviroc exposure. Moreover, these patients often have cardiovascular comorbidities that could predispose them to adverse cardiovascular events triggered by postural hypotension.				No studies have been performed in subjects with severe renal impairment or ESRD co-treated with maraviroc and potent CYP450 3A4 inducers. Hence, no dosage recommendation for maraviroc is available for these patients.
Maraviroc + rifabutin	Not studied				
Raltegravir + rifampin	↓ **Raltegravir** plasma concentration		↓ 40-61%		No clinical experience with increased dose of raltegravir + rifampin Recommendation: no changes in rifampin dose (600 mg/day)
Raltegravir + rifabutin	No studied				
Isoniazid + indinavir	↑		↑13%		The mechanism probably is competitive inhibition of isoniazid metabolism **Recommendation:** monitor isoniazide-related toxicity

Isoniazid + lopinavir	The magnitude and clinical significance of this interaction are unknown				Coadministration with inhibitors of CYP450 3A4 may increase the plasma concentrations of lopinavir, which is metabolized by the isoenzyme
Streptomycin + tenofovir	Coadministration of tenofovir with other nephrotoxic agents may increase the risk and severity of renal impairment due to additive effects on the kidney. Additionally, renal impairment secondary to the use of these agents may reduce the clearance of tenofovir, which is primarily eliminated by renal excretion.				the risk is low in patients with adequate renal function receiving the normally recommended dosage but may increase in patients with underlying renal impairment
Zidovudine + rifampin	↓ zidovudine plasma concentration not significantly rifabutin also reportedly decreased zidovudine AUC by 32% and increased its clearance by 43%				rifampin (600 mg orally once a day for 14 days) recomemmendation Monitor for antiretroviral activity of zidovudine

Table 2. Antitubercular Drug Interactions.

No changes were observed when use nevirapine and rifabutin. Others some important considerations area presented below:

TB/HIV treatment need to avoid co-administration: with potent inducers of CYP450 isoenzymes such as carbamazepine, phenobarbital, phenytoin, rifampin and rifapentine due the risk of reduced viral susceptibility and resistance development associated with sub-therapeutic antiretroviral drug levels.

The use of tenofovir in HIV/TB need avoid the co-administration: with other potentially nephrotoxic agents (e.g., aminoglycosides; polypeptide, glycopeptide, and polymyxin antibiotics; amphotericin B; adefovir; cidofovir; foscarnet; cisplatin; deferasirox; gallium nitrate; lithium; mesalazine; certain immunosuppressants; intravenous bisphosphonates; intravenous pentamidine; high intravenous dosages of methotrexate; high dosages and/or chronic use of nonsteroidal anti-inflammatory agents. Renal function should be evaluated prior to and during therapy with tenofovir. Patients with renal insufficiency at baseline or during treatment may require dosage adjustment in accordance with the manufacturer's product labeling.

The use of efavirenz in HIV/TB need avoid the co-administration: with potentially hepatotoxicity agents: pyrazinamide, isoniazid, acetaminophen; alcohol; androgens and anabolic steroids; azole antifungal agents; ACE inhibitors; endothelin receptor antagonists; interferons; other nucleoside reverse transcriptase inhibitors; retinoids; thiazolidinediones; anticonvulsants such as carbamazepine, hydantoins, felbamate, and valproic acid; lipid-lowering medications such as fenofibrate, HMG-CoA reductase inhibitors, and niacin; herbals and nutritional supplements such as chaparral, comfrey, DHEA, kava, pennyroyal oil, and red yeast rice. Patients should be advised to seek medical attention if they experience potential signs and symptoms of hepatotoxicity such as fever, rash, itching, anorexia, nausea, vomiting, fatigue, right upper quadrant pain, dark urine, light-colored stools, and jaundice. Monitoring of liver function should occur before and during treatment, especially in patients with other hepatic disease (including hepatitis B or C co-infection) or marked transaminase elevations. The benefit of continued therapy with efavirenz should be considered against the unknown risks of significant liver toxicity in patients who develop persistent elevations of serum transaminases greater than five times the upper limit of normal.

The use of tenofovir in HIV/TB treatment with streptomycin: Caution for renal function impairment due to additive effects on the kidney. The deleterious effect on the kindney can occur with concomitant use of others nephrotoxic drugs such as aminoglycosides; polypeptide, glycopeptide, and polymyxin antibiotics; amphotericin B; adefovir; cidofovir; foscarnet; cisplatin; deferasirox; gallium nitrate; lithium; mesalamine; certain immunosuppressants; intravenous bisphosphonates; intravenous pentamidine; high intravenous dosages of methotrexate; high dosages and/or chronic use of nonsteroidal anti-inflammatory agents. Renal function should be evaluated prior to and during therapy. Patients with renal insufficiency at baseline or during treatment may require dosage adjustment in accordance with the manufacturer's product labeling.

The use of maraviroc in HIV/TB treatment with rifampin and others CYP 450 3A4 inhibitors: maraviroc should be administered at a dosage of 600 mg twice daily during coadministration with potent CYP450 3A4 inducers such as efavirenz, rifampin, carbamazepine, phenobarbital, and phenytoin. However, if a potent CYP450 3A4 inhibitor such as itraconazole, ketoconazole, delavirdine, clarithromycin, telithromycin, nefazodone, or any protease inhibitor (except tipranavir + ritonavir) is also used in combination with the inducer, then maraviroc dosage should be reduced to 150 mg twice daily. Maraviroc is contraindicated for use in combination with potent CYP450 3A4 inducers in patients with severe renal impairment or end-stage renal disease (CrCl <30 mL/min).

The use of Isoniazid in HIV/TB treatment with ritonavir/lopinavir and others PIs: The isoniazid will increase the level or effect of PIs by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Avoid co-administration with others inhibitors of the hepatic/intestinal enzyme CYP3A4 metabolism such as macrolide antibiotics, itraconazole, ketoconazole, nefazodone, fluconazole, verapamil, diltiazen, grapefruit juice.

Isoniazid + ethambutol: increase the risk of peripheral neuropathy: burning, tingling, pain, or numbness in the hands and feet

Isoniazid + rifampin/rifabutin: The risk of hepatotoxicity is greater when rifampin and isoniazid are given concomitantly than when either drug is given alone. Rifampin alters the metabolism of isoniazid and increase the amount of toxic metabolites. Similar reaction may occur with rifabutin and isoniazid. Patients who are elderly, have hepatic impairment, are slow acetylators of isoniazid, drink alcohol daily, are female, or are taking other CYP450-inducing agents may be at greater risk of hepatotoxicity. Recommend the monitoring for clinical or laboratory evidence of hepatic function during the treatment. Discontinuation of either or both drugs may be necessary when simptoms of hepatite such as fatigue, weakness, malaise, anorexia, nausea, or vomiting appears.

Isoniazid + food: Food significantly reduces isoniazid absorption, increasing the risk of therapeutic failure or resistance. The mechanism is unknown. In addition, the ingestion of certain histamine-rich fish (e.g., tuna) and cheeses during isoniazid therapy may cause a flushing reaction in some patients. The proposed mechanism is inhibition of monoamine oxidase and histaminase by isoniazid, resulting in histamine intoxication. The associated symptoms is: flushing, tachycardia, chills, headache, nausea, vomiting, diarrhea, burning sensation, sweating, or shortness of breath after eating certain foods. Isoniazid cause depletion of B6 vitamin during the treatment. Since HIV-infected persons are at increased risk for isoniazid-induced peripheral neuropathy, these patients should take vitamin B6 and avoid antiretroviral drugs with potential peripheral neurotoxicity (e.g., stavudine and didanosine).

4. Adherence to therapy – Process to improve medication efficacy

It has been reported that treatment abandonment rate reaches until 25% of all patients during the treatment (Veronesi & Focaccia, 1996). In developing countries such as Brazil, this rates decreased in the last years to 4,5%, but it is possible to find out in some regions values until 20,3% (Costa, Gonçalves & Menezes, 1998; Lima et al., 2001). The WHO's recommendation is that abandonment rates must be until 5%, however, it is possible to find in some countries such as Colombia abandonment rates of 65,6% (Mateus-Solarte & Carvajal-Barona, 2008).

In order to reduce the abandonment of therapy and ensure the correct treatment of patients some strategies have been adopted to improve adherence to therapy. According to WHO "Adherence corresponds to the behavior of one person - in terms of taking a drug, a diet or executing lifestyle changes - that is in accordance with recommendations arising from health professionals" (WHO, 2003).

Adherence to therapy is a serious problem responsible for the evolution of diseases and complications, loss of quality of life and even death. In the United States it is estimated that

the cost of low compliance reach over $ 147 billion (Council on Patient Information and Education, 2007). WHO estimate that rate of adherence of patients which treat chronic diseases is only 50% (WHO, 2003). These same values were found in a study with TB patients (Cuneo, 1989).

Literature reports show that interventions to promote adherence are effective in short treatments, but these same interventions are less effective in prolonged treatments. In the latter situation it requires a combination of strategies, becoming more complex the interventions performed by health professionals (Haynes et al., 2009).

Several methods are available in the literature to assess adherence to treatment. These methods can be divided into direct and indirect. In direct methods is possible to quantify the drug in the body. These methods are expensive, invasive and not available for all drugs, however are suitable methods to say whether or not adherence to therapy allowing include adjust the dose. The indirect methods allow assessing the use of medicines by health professionals. These methods are usually overestimated and with low sensitivity. Among the indirect methods can include: patient's self-report; prescriber's report; pill count; measurement of prescription replacement (allowing indirect evaluation of non-compliance by the lack of access to medication). Strategies using devices of separation and counting of medicines may be useful for patients who do not understand the regimen. These devices can be purchased at pharmacies and separate properly in accordance with the therapy the patient by the pharmacist.

However, in the therapy of tuberculosis, one of the strategies most used and recommended by the World Health Organization (WHO) treatment involves supervised therapy (DOTS - Directly Observed Therapy). DOTS strategy includes the delivery of a short course of standard drugs, lasting 6 months for new Patients (and 8 months for retreatment Patients). The delivery includes the direct observation of therapy (DOT), either by a health worker or by caregiver (WHO, 2002).

During the promotion of strategies to increase adherence is important to consider some factors related to therapy adherence that may be related to: patient, health professional, the disease condition, treatment and health care system (and the policies government).

With regard to the patient an important strategy to be adopted is empowerment. This strategy is an educational intervention that aims to transfer responsibilities to patients which is tone of the most important person responsible to conduct the therapy, based in the principle that the decision to follow or not the treatment is only taken by the patient. The patient must know about the disease and treatment to participate in the process of using the medicine. Factors such as social stigma are common in patients with tuberculosis, however, this factor must be worked in the intervention. Economic factors and access to health services are factors that also interfere with the patient's decision to adhere to therapy or not.

With regard to health professionals, active participation is required in treating patients, because is often the situation that them cannot understand the proper way to use the anti-tubercular drugs. The treatment cannot be seen as the sole responsibility of the patient. Health professionals have a large portion of the contribution of adherence to treatment. With regard to health status, disease severity and the observation of improvement with the medicines use is important for maintenance adherence. In situations where the goal of

therapy is not immediately improve the main symptoms, should be established an accord with the patients which should be aware of the goals of therapy. Treatment should be simplified to suit the patient's situation. Complex dosing regimens tend have higher dropout rates. The health system has an important role in the adherence. Access to professional and medicines is a determining factor for treatment. There is no possibility to discuss adherence even if the patients do not have access to health care. In this case, it is essential to adopt policies to control diseases such as tuberculosis ensuring access to the entire population.

Several strategies have been described in the literature to promote adherence to therapy. Educational interventions may involve pedagogical strategies (oral or written) aiming increase the knowledge. This strategy can be used individually or collectively. The uses of written or audiovisual materials help the patient to understand the strategy.

Behavioral interventions aimed changing certain habits. They are guided by theories about behavior change. In these strategies the role of health professionals is essential in promoting adherence. This one can work with combinations of rewards and communication strategies, such as reminders to join the proposed therapy. Praise for the efforts is the reward commonly used. The possibility of monitoring the condition at home is also very useful and enables patient involvement in the action plan proposed.

Interventions with affective character take into account social relationships and may be done with the patient or the family. Family visits provide a good opportunity for this type of intervention. The professional can intervene, in educational way, with all the family doing them to understand the situation and help the patient. In TB intervention the combination of strategies seems to be more appropriate to increase therapy adherence.

5. Pharmacotherapeutic monitoring

Some care should be taken into account in monitoring patients for tuberculosis to detect adverse effects or ineffective therapy since the beginning of treatment. After 3 months of treatment, most patients (90-95%) will have negative smears (American Thoracic Society, 2003). Thus, situations of therapeutical inefficacy will be characterized with smear-positive after this period. Among factors responsible for ineffective treatment can be mentioned: bacterial resistance, poor absorption of drugs, inadequate adherence to treatment and drug interactions (Figure 3).

Some adverse effects such as peripheral neuritis induced by isoniazid can be prevented by supplementation with vitamin B6 (pyridoxine). This approach should be considered in special situations such as malnutrition, pregnancy, HIV co-infection and alcohol abuse.

Monitoring liver function is especially important for patients with any risk factor. About 20% of patients will have elevated levels of liver transaminases without symptoms. In such cases, after treatment the enzymes return to levels considered normal. Hepatitis should be suspected only when the elevation of transaminases is three to five times higher than considered normal associated with symptoms such as nausea, vomiting and abdominal pain. Some risk factors for hepatotoxicity are: chronic liver disease or hepatitis, alcohol abuse, use of isoniazid, female, HIV infection, low body mass index and age over 60 years

Fig. 3. Some factors responsible to inefficacy.

The action plan for monitoring patients with hepatotoxicity during the treatment includes withdrawal of all medicines. After the reduction of transaminases levels, reintroduction of individual drug must be re-thinking. It is recommended to start treatment with rifampicin (less hepatotoxic), and between 3-7 days to introduce a new drug. Treatment regimens without isoniazid are possible. In this last case, one possibility is treating the patient with rifampicin, ethambutol and pyrazinamide for six months.

Drug interactions should be identified and prevented. Beyond the hepatotoxic effect already discussed, some antituberculosis drugs like rifampicin are metabolic enzymatic inducers and may interfere with the metabolism of many drugs. One example is the oral contraceptive whose effectiveness can be compromised with concomitant use of rifampicin. In these situations alternative reproductive control methods should be used. Isoniazid may increase serum levels of drugs of narrow therapeutic index such as theophylline used by asthma patients.

Regimen that includes rifabutin is generally preferred, as rifabutin appears to be as effective as rifampin but is a much less potent inducer of CYP450 3A4. Non rifamycin-containing regimens is related to higher rates of treatment relapse and failure; longer treatment duration with increased adverse effects and higher mortality rates. This regimen is only recommended to patients who are intolerant of rifamycins or are infected with rifamycin-resistant strains.

Usual dosages of rifampin may be used in patients receiving ritonavir 600 mg twice/day or ritonavir 400 mg twice/day in combination with another PI at reduced dosage (e.g., saquinavir 400 mg twice/ day). If the patients have not begun antiretroviral therapy at the time TB treatment is initiated, clinicians may also consider using rifampin and postponing ATR therapy, because in the early HIV stage of the disease, there is low risk of HIV disease progression or death. During this period the physician may monitor CD4 cell count and

postpone antiretroviral therapy until TB treatment is complete. However, the optimal time for starting ATR therapy should be individualized based on initial response to TB treatment and occurrence of adverse effects such as IRIS.

A patient who cannot take efavirenz, and when rifabutin is not available, the alternative is nevirapine - with rifampin. The pharmacokinetic effect of the rifamycin is moderate in this regimen. When used with isoniazid, rifampin, and pyrazinamide, there is some concern about hepatotoxicity. However, given the risk of reduced viral susceptibility and resistance development associated with subtherapeutic antiretroviral drug levels of nevirapine, some experts recommend that alternative antimycobacterial agents be considered in patients already receiving effective nevirapine-containing antiretroviral therapy.

Other alternatives for patients who cannot take efavirenz, and when rifabutin is not available, are as follows: rifampin with a) zidovudine/lamivudine/abacavir/tenofovir treatment; b) zidovudine/lamivudine/tenofovir or c) zidovudine/lamivudine/abacavir. The toxicity of these alternative regimens is primarily anemia. Pharmacokinetic concerns are a 50% decrease in zidovudine and the effect on abacavir is not yet evaluated. For the treatment of latent TB infection, a nine-month regimen of isoniazid may be considered.

In general, treatment of TB /HIV in the context of ATR therapy is complex and requires an individualized approach. Experts in the treatment of HIV-related tuberculosis should be consulted, and TB and HIV care providers should work in close coordination throughout the best treatment considering patient quality of life.

Additional care should be conducted with patients who have resistant infection. To decrease the resistance some principles should be adopted: a) the scheme more effective should be adopted, b) the therapeutic regimen should include at least three antimycobacterial drugs, c) the treatment should be daily and preferably monitorate by health professional and d) medicines should not be left for possible "future use".

In situations of resistance to isoniazid, one possibility is the use of rifampicin, pyrazinamide, ethambutol (and some fluoroquinolone) for a period of 6 months. For resistance to rifampicin and isoniazid regimen can be use fluoroquinolone, pyrazinamide and ethambutol associated with some other drug for a period of 18-24 months. In situations of resistance to rifampin, isoniazid, pyrazinamide (or ethambutol) the scheme would be to use a fluoquinolone (ethambutol or pyrazinamide depending on the susceptibility) and two alternative agents for a period of 24 months.

In cases of latent infection, correctly detected, should be assessed the risk and benefit of treatment. People living with HIV, immunocompromised, malnourished, drug users and from endemic regions with positive test to TB are considered at risk of developing tuberculosis. A study by Wilkinson and colleagues (1998) demonstrated that treatment for latent infection in HIV people decreased by 43% the risk of developing tuberculosis (Wilkinson et al., 1998). Among the schemes that have been proposed that it should be noted: a) isoniazid for 6-9 months in the absence of active infection b) rifampicin and isoniazid for 3 months and others (Balcells et al. 2006; Ena et al., 2005).

All these factors must be taken into account during the pharmacotherapeutic monitoring of tuberculosis patients to adequate the therapy and improve quality of life of patients with tuberculosis.

6. Conclusion

The current TB treatment presents several challenges. The absence of development new drugs is the cruelest face of this disease. This fact associated with inadequate treatment and TB-drug resistance contributes to survival of the disease today. Anti-TB therapy has several problems relate to noncompliance, lack of adherence to therapy, patients with co-morbidity, socio-economic factors, environmental factors and problems related to drugs such as adverse effects and drug interactions. Health interventions can improve the medication efficacy, reduce the resistance and improve patients quality of life. Pharmacotherapeutic follow-up and adequate strategies to increase therapy adherence are important factors to be monitored during TB therapy. It is important to keep in mind that interventions that guarantee the adequate use of the medication are the first step to improve TB treatment.

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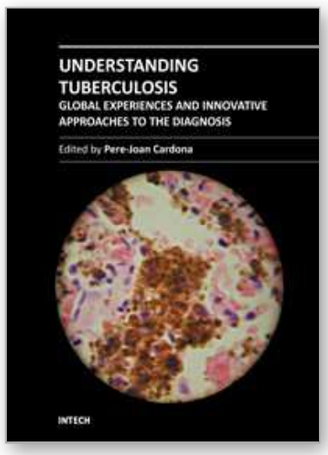

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Mycobacterium tuberculosis is a disease that is transmitted through aerosol. This is the reason why it is estimated that a third of humankind is already infected by Mycobacterium tuberculosis. The vast majority of the infected do not know about their status. Mycobacterium tuberculosis is a silent pathogen, causing no symptomatology at all during the infection. In addition, infected people cannot cause further infections. Unfortunately, an estimated 10 per cent of the infected population has the probability to develop the disease, making it very difficult to eradicate. Once in this stage, the bacilli can be transmitted to other persons and the development of clinical symptoms is very progressive. Therefore the diagnosis, especially the discrimination between infection and disease, is a real challenge. In this book, we present the experience of worldwide specialists on the diagnosis, along with its lights and shadows.

How to reference

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