Tuberculosis chemotherapy in the 21st century: Back to the basics

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ABSTRACT

The key to successful elimination of tuberculosis (TB) is treatment of cases with optimum chemotherapy. Poor chemotherapy over time has led to drug-resistant disease. Drug resistance of Mycobacterium tuberculosis develops by the selective growth of resistant mutants. The incidence of drug-resistant cases depends on the number of bacilli and the drug-resistant mutants in the lesion. The latter is low for individual drugs and even lower for two and three drugs. Therefore, use of combination chemotherapy with three or more drugs results in cure. However, irregular treatment, inadequate drugs, inadequate drug doses or addition of a single drug to a failing regimen allows selective growth of resistant mutants and acquired drug-resistant TB. Contacts of these resistant cases develop primary drug-resistant TB. Thus, drug resistance in tuberculosis is a "man-made problem". Anti-TB chemotherapy must be given optimally by (i) ensuring adequate absorption of drugs, (ii) timely diagnosis and management of drug toxicities and (iii) treatment adherence. New classes of anti-TB drugs are needed; but are unlikely to become available soon. It is vital that the 21st century physicians understand the basic principles of TB chemotherapy to ensure efficient use of available drugs to postpone or even reverse epidemics drug-resistant TB.

KEY WORDS: Extremely drug-resistant (XXDR) TB, extensive drug (XDR) resistant, first-line drugs, multidrug-resistant (MDR) TB, second-line drugs, total drug-resistant (TDR) TB

INTRODUCTION

Failure to eliminate tuberculosis (TB) that is 100% preventable and 100% curable is mankind's worst ongoing blunder.[1] The key to successful elimination of TB is optimum treatment of cases. We have always known that erratic drug supplies and failure of patients to complete treatment lead to even more dangerous forms of TB i.e. drug-resistant disease. Equally important are prescription practices and failure to ensure treatment adherence by the treating physicians. Standard diagnostic and treatment protocols are available using highly effective drugs[2-9] based on sound scientific principles and years of research. However, neglect of these basic principles by large sections of the medical community has contributed to emergence of drug-resistance.

Drug resistance of Mycobacterium tuberculosis develops by the selective growth of resistant mutants.[10] The incidence of drug-resistant cases depends on the number of bacilli and the probability of drug-resistant mutants in the lesion. The latter is as low as $10^{-3}$–$10^{-8}$ for individual drugs, $10^{-12}$–$10^{-14}$ for two drugs and $10^{-18}$–$10^{-20}$ for three drugs.[11,12] When three or more drugs are utilized together for treatment of TB, the chances of acquiring drug resistance is negligible.[11,13] Poor chemotherapy however, in the form of inadequate drugs, inadequate drug doses or addition of a single drug to a failing regimen (addition syndrome) results in selective growth of the drug-resistant mutants and consequently acquired drug-resistant TB. Contacts of these resistant cases develop primary drug-resistant TB.[14] Thus, drug resistance in tuberculosis is a “man-made problem”, acquired resistance, a mark of a poor treatment practices in the current time and primary resistance an indicator of treatment practices in the past.[15]

Good treatment is a pre-requisite to the prevention of
Table 1: Newer anti-TB drugs in clinical development

| Drug/Group, phase of development | Activity | Likely use |
|----------------------------------|----------|------------|
| TMC207 (Diarylquinolines) Phase Ib | Bactericidal activity against drug-sensitive similar to that of isoniazid or rifampin and good activity against drug-resistant strains M. tuberculosis | As an additional second-line drug in patients with newly diagnosed MDR-TB |
| Linezolid (Oxazolidinones) Phase Ia | Broad spectrum of activity against anaerobic and Gram-positive aerobic bacteria, modest *in vitro* activity against drug-susceptible and drug-resistant strains of M. tuberculosis | It is being evaluated for treatment of i) XDR-TB-600 mg dose and ii) MDR-TB-300 mg dose |
| PNU-100480 (Oxazolidinones) Phase I | Better activity than linezolid against both drug-susceptible and drug-resistant strains of M. tuberculosis | Mouse model studies showed improvement of bactericidal activity when added to current first-line TB drugs |
| OPC-67683 (Nitroimidazoles-Nitroimidazo-oxazole subclass) Phase II | Activity against both drug-susceptible and drug-resistant strains of M. tuberculosis | Being evaluated for the treatment of MDR-TB |
| PA-824 (Nitroimidazoles-Nitroimidazo-oxazine subclass) Phase I | Activity against both drug-susceptible and drug-resistant strains of M. tuberculosis | Has shown good safety and tolerability in adult pulmonary TB patients when given once daily for 7 days |
| SQ 109 (Ethylenediamine compound) Phase I | Activity against both drug-sensitive and drug-resistant M. Tuberculosis | Substitution for ethambutol in the standard regimen demonstrated increased efficacy in the mouse model |

MDR TB: Multidrug-resistant tuberculosis, XDR TB: Extensive drug resistant tuberculosis

emergence of resistance. The outcome of “careless care”[14] over time has resulted in emergence of progressive resistance to the anti-TB drugs. Resistance to the main first-line drugs isoniazid and rifampin multidrug-resistant tuberculosis (MDR TB)[17] was followed by recognition of additional resistance to injectable second-line drugs (kanamycin, amikacin, capreomycin) plus a fluoroquinolone-extensive drug-resistant tuberculosis (XDR TB).[18] “Extremely” drug-resistant (XXDR TB) or total drug-resistant TB (TDR) have now been proposed for cases resistant to all available first- and second-line drugs.[19-21] Although several new agents that may be used as “third-line drugs” are in the preclinical stage of development; presently there are only six drugs with potential activity against TB in the clinical pipeline [Table 1].[22] It is vital that the 21st century physicians understand the basic principles of TB chemotherapy to ensure efficient use of available drugs to postpone or even reverse epidemics of drug-resistant TB.[22]

**MANAGEMENT OF TB**

The American Thoracic Society (ATS) and Centers for Disease Control (CDC) have classified persons, exposed to and/or infected with *M. tuberculosis*. The classification[4] is based on the broad host–parasite relationship as described by exposure history, infection and disease. The suggested intervention required in each of the categories is shown in Table 2. This classification helps us to understand the natural history of TB infection in man and the rationale for intervention required at each stage.

**THE ANTI-TUBERCULOSIS DRUGS**

Isoniazid (H), rifampin (R), ethambutol (E), pyrazinamide(Z) and streptomycin (S) are the essential first-line anti-tuberculosis drugs.[6] Aminoglycosides (kanamycin, amikacin), quinolones (ciprofloxacin, ofloxacin,
**Table 4: Adverse effects of the anti-tuberculosis drugs**

| Drugs            | Adverse effects                                                                 |
|------------------|---------------------------------------------------------------------------------|
| Isoniazid        | Mild: rash, urticaria, arthralgias, shoulder-hand syndrome, drowsiness, mood changes, acne, gynecomazia. Severe: Hepatitis, hypersensitivity, peripheral neuritis, optic neuritis, anemia, pellagra, SLE syndrome, rarely pancreatitis, seizures, psychosis. Metabolic acidosis, coma due to over dosage Drug interactions: increased blood levels of phenytoin, psychotic episodes with disulfiram. |
| Rifampin         | Mild: abdominal distress, red discoloration of body fluids, contact lenses may be irreversibly stained Severe: Hepatitis hypersensitivity, anemia, thrombocytopenia, flu-like syndrome, acute renal failure, exfoliative dermatitis in HIV-positive cases Drug interactions: prednisolone, digoxin, quinidine, ketoconazole, propranolol, sulfonlureas, oral contraceptives, oral anticoagulants and anti-retroviral drugs (most PIs and NNRTIs). |
| Ethambutol       | Mild: abdominal distress, arthralgia.                                             |
| Pyrazinamide     | Optic neuritis (early changes reversible), arthralgia, hyperuricemia, peripheral neuritis. |
| Streptomycin, kanamycin, amikacin | Hearing loss, ataxia, hypersensitivity, nystagmus, proteinuria, neuromuscular blockade. |
| Ethionamide      | Abdominal distress, nausea, anorexia, dysgeusia, diarrhea, arthralgia.           |
| Cycloserine      | Mood and cognitive deterioration, psychosis, tremors, seizures.                  |
| Para amino salicylic acid | Abdominal distress, diarrhea, hypothyroidism.                                    |
| Ciprofloxacin, ofloxacin, moxifloxacin | Abdominal distress, headache, anxiety, tremors, insomnia, diarrhea, hepatitis, arthralgia. |

Levofoxacin, ethionamide or prothionamide, cycloserine, para-aminosalicylic acid (PAS) and polypeptide (capreomycin) are the second-line anti-tuberculosis drugs. The recommended doses of the anti-tuberculosis drugs and their adverse effects are shown in Tables 3a, 3b and 4. Table 5 shows the other drugs which may be used as salvage therapy for XDR TB.

**PRINCIPLES OF ANTI-TUBERCULOSIS CHEMOTHERAPY**

The anti-tuberculosis therapy is a unique, two-phased chemotherapy consisting of initial intensive phase with multiple drugs (three or more) and continuation phase with two or three drugs. The multidrug initial intensive phase is given to take care of the drug-resistant organisms and to achieve a ‘quick kill’ to reduce the bacillary load, which in turn reduces the number of ‘persisters’ in the lesions. ‘Persisters’ are drug-sensitive organisms, which become dormant and are later responsible for relapses. The continuation phase of chemotherapy, consisting of two drugs is therefore given to kill the “persisters,” which show intermittent activity.

The role of individual drugs in first-line chemotherapy of TB is unique. Isoniazid is responsible for the initial kill of about 95% organisms during the first two days of treatment. Its bactericidal role is then replaced by rifampicin and pyrazinamide during the intensive phase. In the continuation phase, rifampin is the most effective drug against dormant bacilli (persisters), as shown by the similarity of response by patients with initially isoniazid-resistant or sensitive strains. When either rifampin or isoniazid is not used, the duration of chemotherapy is 12 to 18 months. When both isoniazid and rifampin are used in treatment, the optimum duration of chemotherapy is 9 months. Addition of pyrazinamide, but not neither streptomycin nor ethambutol reduces the duration to six months. Prolongation of chemotherapy beyond these periods increases the risk of toxicity while providing no additional benefit. Second-line therapy duration ranges from 18 to 24 months.

**TREATMENT GUIDELINES: PAST, PRESENT AND FUTURE**

Public health programs in many countries follow guidelines for treatment of TB developed by the World Health Organization (WHO). These guidelines were practiced till 2009 in which the treatment regimes were categorized into four categories [Table 6a]. Categories 1–3 used a combination of first-line drugs for the shortest acceptable period. Category 1 is for treatment of new cases (an initial intensive phase (IIP) of four drugs ethambutol, isoniazid, rifampicin, pyrazinamide for 2 months and 4 months of continuation phase (CP) of two drugs). Category 2 is “retreatment” regimen (8 months of isoniazid, rifampin, ethambutol, with pyrazinamide, and streptomycin added for the first 2 months—2SHRZE/4HR). Category 2 is recommended omission of ethambutol for children, patients, with smear-negative pulmonary or extra-pulmonary TB that is fully drug-susceptible and patients negative for Human immunodeficiency virus (HIV). Category 4 was for treatment of drug-resistant TB using a standard treatment regimen (STR) using combination of second-line drugs: the initial phase five drugs, pyrazinamide (Z), kanamycin (Km), ofloxacin (Ofx), ethionamide (Eto) and cycloserine (CS) for 6–8 months and the continuation phase of three drugs, ofloxacin (Ofx), ethionamide (Eto) and cycloserine.
Treatment regimen

**Table 6a: Previous World Health Organization (WHO) treatment categories**

| Category | Treatment regimen |
|----------|-------------------|
| New sputum smear positive, | 2EHRZ+4HR |
| Severe sputum smear negative | |
|Seriously ill extra pulmonary | |
|Relapse | 2SHERZ+HERZ+5HRE |
|Retreatment | |
| Default | |
| New sputum smear negative | 2(E)HRZ+/-4HR |
|Not seriously ill extra pulmonary | |
|Treatment failure | 8Km-Ofx-Eto-Cs-E-Z+12Ofx-Eto-Cs-E |

**Table 6b: World health organization (WHO) treatment categories**

| Category | Treatment regimen |
|----------|-------------------|
| Treatment of new cases | 2EHRZ+4HR |
| Treatment of previously treated cases | |
| a) low to medium likelihood of MDR | 2SHERZ+HERZ+5HRE |
| b) high likelihood of MDR | Treat as MDR |

**Table 6c: Proposed treatment categories**

| Category | Treatment regimen |
|----------|-------------------|
| Treatment of new cases | 2EHRZ+4HR |
| Treatment of relapse cases | 2HERZ+7HRE |
| i) Previous cure with supervised standard first line therapy | |
| ii) HR sensitive on DST | |
| Treatment of MDR cases | 6/8Km-Ofx-Eto-Cs+/-12/18Ofx-Eto-Cs |
| i) Failure of supervised standard first-line therapy | |
| ii) MDR on DST | |
| Treatment of XDR cases | CM-Mfx-PAS-2 or |
| i) Failure of standard second-line therapy | 3 Group 5 agents +/- Cs |
| ii) XDR on DST | |

in 2–3 months or DST shows drug-sensitive disease, CP may be commenced and given for 7 months.\[^{39}\] Cases that show failure of fully supervised first-line therapy or show MDR-TB on DST should be treated with second-line drugs. Cases failed on MDR treatment or showing XDR on DST may be treated with salvage regimens.

**CHEMOTHERAPY OF TB IN SPECIAL SITUATIONS**\[^{37,39-43}\]

**Pregnancy**

Rifampin, isoniazid, ethambutol, and pyrazinamide can be used safely during pregnancy. Streptomycin is not given as it can cause ototoxicity to the fetus. Addition of pyridoxine in the dose of 10 mg/day is recommended to prevent isoniazid peripheral neuropathy.

**Diabetes mellitus**

Standard recommended chemotherapy must be used. Tight glycemic control is desirable. Doses of oral hypoglycemic agents may have to be increased due to drug interaction with rifampin. Prophylactic pyridoxine...
in the dose of 10 mg/day is recommended to prevent isoniazid peripheral neuropathy.

Renal failure
Dosages may have to be adjusted according to the creatinine clearance especially for streptomycin, ethambutol and isoniazid. In acute renal failure, ethambutol should be given 8 hours before hemodialysis. Creatinine clearance should be estimated for adjustment of some of the antituberculosis drugs. The formula, creatinine clearance = (140 - Age) Weight / 72 × serum creatinine, gives a rough estimate of the glomerular filtration rate. According to the creatinine clearance, either the dosage interval is changed or the dose is reduced as a percentage of the normal daily dose [Table 7].

Post transplant patients and other special situations
Rifampin-containing regimens are avoided as rifampin causes increased clearance of cyclosporin.

Pre-existing liver disease
In stable disease with normal liver enzymes, all antituberculous drugs may be used but frequent monitoring of liver function tests is required.

Treatment in unconscious patient/patients unable to swallow
If patients are fed by nasogastric tube or gastrostomy tube, usual doses and drugs may be powdered and administered avoiding feeds 2–3 hours before and after the dose. In cases where enterostomy has been performed or parenteral nutrition is being used, intramuscular streptomycin and intravenous quinolones may be used and switch to oral therapy once oral feed resume.

TB with HIV co-infection
In early stages, the presentations of TB in TB-HIV co-infection is the same as HIV negative but in late stages extra-pulmonary and dissemination are common. Diagnostic problems arise as other respiratory diseases occur frequently and tuberculin test may be negative. The usual short course chemotherapy as per treatment categories is indicated in HIV-positive patients. The response is usually good but relapse is more frequent.

Seriously Ill Patients with Suspected TB
Use of specific empiric anti-tuberculosis therapy (SEATT) with isoniazid, ethambutol, pyrazinamide can be used as a method for rapid presumptive diagnosis and treatment of febrile patients with clinical and radiological suspicion of TB, who are seriously ill and where no bacteriological or histological proof is available. Fever is used as guide for response to therapy. Rifampicin and aminoglycosides or quinolones are not used, to ensure that defervescence of fever is due to action of specific anti-TB drugs i.e. isoniazid, ethambutol and pyrazinamide. Rifampicin may be added as soon as the patient is afebrile.

| Drugs   | Glomerular filtration rate
|---------|-----------------------------|
| >50 ml/min | 10–50 ml/min | <10 ml/min |
| Kanamycin | 60–90% | 30–70% | 20–30% |
| Streptomycin | 24 h | 24–24 h | 72–96 h |
| Ethambutol | 24 h | 24–36 h | 48 h |
| Isoniazid | 100% | 100% | 66–75% |

FOLLOW-UP AND EXPECTED RESPONSE TO ANTI-TB THERAPY

The role of chemotherapy is limited to sterilizing the lesion by killing maximum number of TB bacilli. Evaluation of anti-TB therapy should ideally be bacteriological for example, by appropriate smear and culture in pulmonary and extra-pulmonary TB. Standard prescribed regimens should be used if follow-up bacteriological evaluation cannot be performed in extra-pulmonary TB. Fever, accurately documented may be used as a guide for response to chemotherapy initially. However, it must be remembered that occasionally fever may take up to several weeks to subside after starting ATT. There may also be secondary rise of fever after initial defervescence particularly in cases of military TB and requires treatment with corticosteroids. Tuberculosis, like leprosy has a spectrum of disease from reactive type to unreactive type, Lenzini described the spectral concept based on immunology, RR (Reactive) with nodular opacities, RI (reactive intermediate) with nodular opacities and cavitation, UI (unreactive intermediate) with diffuse fibrocavitary lesion and UU (unreactive) with disseminated disease. These stages occur with progressive fall in cell mediated immunity. The differences in immune response result in differences in tissue damage and repair and residual lesions. Hence success of chemotherapy must not be judged by radiology. In fact paradoxical worsening of lesions may occur during successful TB treatment. This phenomenon is called “paradoxical response (PR)” or “immune reconstitution inflammatory syndrome (IRIS)” and is well known with or without HIV co-infection. In TB lymphadenopathy, appearance of new nodes, enlargement of existing nodes, cold abscess formation and sinus formation can occur while on effective chemotherapy. Ten percent of cases may be left with residual nodes at the end of chemotherapy. Similarly, TB meningitis may be complicated by hydrocephalus, tuberculosis and abscess formation that cause clinical deterioration despite effective ATT. Tuberculomas may enlarge during chemotherapy probably due to an immunological mechanism. Further, several complications like bronchopleural fistula, empyema and hemothysis may occur during or after therapy and cause apparent clinical or radiological worsening. Anti-TB chemotherapy cannot prevent or cure persistent residual lesions, paradoxical worsening and complications, which are either immunologically mediated or due to mechanical complications of the disease. Steroids or surgery may be required as appropriate and ATT should not be modified or prolonged.
OPTIMIZING TO ANTI-TB THERAPY

Once prescribed, anti-TB chemotherapy must be given optimally by (i) ensuring adequate absorption of drugs, (ii) timely diagnosis and management of drug toxicities and (iii) treatment adherence.

ENSURING ADEQUATE ABSORPTION OF ANTI-TB THERAPY

Administration of drugs in divided doses, rifampicin after meals and concomitant administration of antacids and prokinetic drugs affect the outcome of therapy. All anti-tuberculosis drugs should be administered preferably in single daily doses to achieve peak serum levels.[55] The greater the ratio between peak serum levels and the minimum inhibitory concentration (MIC) of the drug, the greater is the drug’s bactericidal action. The pharmacokinetics of rifampin and isoniazid are influenced by meals,[56] and 50% of the patients are at risk of having sub-optimal concentration if rifampin is taken with food.[57] Carbohydrates and proteins seem to have virtually no influence, but a fatty meal reduces serum concentrations considerably.[58] Prokinetic drugs and antacids containing aluminum and magnesium reduce the absorption of rifampicin.[59] As anti-TB drugs are preferably administered in fixed dose combinations, ATT must be given on empty stomach followed by meals 1–2 hours after drug intake to ensure absorption.

MANAGING DRUG TOXICITY TO ANTI-TB THERAPY[43]

Gastrointestinal intolerance
Nausea due to gastrointestinal intolerance is usually self-limiting. However if symptoms persist or are intolerable, the patient may be advised to take drugs 2 hours after breakfast or at bedtime, 2–3 hours after dinner, which may help the patient to “sleep off” the side effects. Treatment with H2 antagonists or proton pump inhibitors may be prescribed in severe cases as they do not affect absorption of ATT unlike prokinetics.

Itching and skin rash
Itching or rash with ATT is a minor side effect provided it is not accompanied with fever or symptoms of hepatitis. In these cases, reassurance, treatment with antihistamines and application of calamine lotion allows ATT to be continued uninterrupted.

Drug hypersensitivity
Hypersensitivity reactions can occur with practically all anti-tuberculous drugs. It may present with fever, joint pains, skin reactions, hepatitis, lymphadenopathy and splenomegaly. A new fever or increase in fever after starting ATT indicates hypersensitivity. All ATT must be discontinued immediately and if fever subsides within 24 hours, drug hypersensitivity is confirmed. Re-introduction can be attempted with one drug at a time with careful clinical monitoring after initial symptoms subside. If one drug is identified as the causative agent, it may be omitted and a modified regimen should be given.

Hepatotoxicity
Hepatotoxicity with ATT is of three distinct types (i) an asymptomatic increase (up to four-fold elevation) of liver enzymes occur frequently but the enzyme levels revert back to normal despite continuation of chemotherapy; (ii) dose-related derangement in liver function tests may occur frequently if therapy is not given in the recommended doses adjusted for body weight; (iii) idiosyncratic hepatitis secondary to isoniazid and rifampicin; although rare may lead to fatal hepatic failure. Drug-induced hepatitis has a clinical syndrome similar to viral hepatitis and usually occurs within 2 months but may occur even later during therapy. If viral etiology is excluded or tests for viral studies are not available, it is wise to presume an idiosyncratic reaction to isoniazid or rifampicin. When there is greater than four-fold rise in liver enzymes of elevated bilirubin, all hepatotoxic drugs must be discontinued immediately. Chemotherapy regimens containing non-hepatotoxic drugs like ethambutol, aminoglycosides and quinolones may be considered until liver functions return to normal; particularly in severe forms of TB. Reintroduction of all drugs in corrected doses is well tolerated once liver functions are normal in cases of dose-related hepatotoxicity or viral hepatitis occurring during anti-TB therapy. However, in case of idiosyncratic hepatitis, re-introduction of these drugs must not be attempted.

Thrombocytopenia
Thrombocytopenia has been reported most commonly with rifampicin. However, a few cases of thrombocytopenia with ethambutol have also been reported. It may present with petechiae or frank bleeding from various sites. Drop in platelet count can be documented when done within 24 hours of the drug intake. Previously it was recommended that after occurrence of thrombocytopenia, rifampicin must not be used again. However, recent reports suggest that re-administration can be attempted under clinical supervision and rifampicin may be tolerated well.

ENSURING ADHERENCE TO ANTI-TB THERAPY

Annik Rouillon, Former Executive Director of International Union Against TB and Lung Diseases (IUATLD) had observed “the person who swallows drugs regularly in the absence of encouragement and help is an abnormal one.”[59] Self-administered therapy (SAT) or directly observed treatment (DOT) are two options for giving anti-TB chemotherapy. SAT must always be prescribed using fixed dose combinations (FDC) as they make monotherapy impossible. However, SAT requires time and effort of healthcare workers involved in the treatment to ensure compliance, which is often lacking. Hence, since 1993,
World Health Organization (WHO) recommends DOT as an important component of their five-point program; directly observed treatment, short-course (DOTS) to tackle the TB “global emergency”. Every effort is being made to optimize DOT. “Enhanced DOT” uses incentives tailored to the target population within the context of DOT, for example incentive of food, housing, clothes and medical care. “Expanded DOT” addresses TB/HIV and MDR and collaborates health programs and general health service such as alcohol de-addiction.[60] DOTS-Plus for treatment of MDR TB using a standardized treatment regimen (STR) is currently being implemented.[62] Direct observation of SLDs will be crucial for compliance of MDR TB therapy under DOTS-Plus. An 18–24-month therapy cannot be supervised using hard-pressed health workers at the DOTS centers and hence it was proposed to use DOT providers. Studies have now shown that family members supervising therapy is as effective[61] and may be a convenient and cost-effective alternative.

Reinforcing adherence to therapy through treatment literacy is important for the successful completion of therapy and cannot be substituted by any other intervention. The final option is to use legal action in the form of compulsory detention when an individual refuses treatment.[62] In practice this is seldom used, though some countries have employed compulsory detention in as many as 1% of cases.[63] However, “it is unethical, illegal, and bad public health policy to detain 'noncompliant' persons before making concerted efforts to address the numerous systemic deficiencies that make adherence to treatment virtually impossible.”[64]

**CONCLUSION**

Dubois and Dubois (1952), in their book “The White Plague-Tuberculosis, Man and Society”[61] cited Machiavelli: “Consumption (TB) in the commencement is easy to cure, and difficult to understand; but when it has neither been discovered in due time, nor treated upon a proper principle, it becomes easy to understand, and difficult to cure”. They also predicted that “drugs, vaccines or other options cannot solve the problem of TB as it is through gross errors in organization and individual life that the problem ofTB has reached catastrophic levels”. New classes of anti-TB drugs are needed, but are unlikely to become available soon. Even if new drugs are available they may be rapidly “burnt” as a result of clinical and public health malpractices similar to some of the key old drugs.[19] The only option therefore is to use the existing drugs efficiently based on the knowledge of principles of TB chemotherapy.[60] As Mario Raviglione, director of WHO’s Stop TB Department aptly puts it: “...if we don’t have the basics in place, then the result is drug resistance”.[67]

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