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A COMPREHENSIVE REVIEW ON TUBERCULOSIS

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ABSTRACT
Tuberculosis is one of a disease that has afflicted the human race for centuries by *Mycobacterium tuberculosis*. Highly effective drugs for treating TB were introduced over 40 years ago, yet deaths from the disease continue to increase. Agents that reduce the duration and complexity of the current therapy would have a major impact on compliance and overall cure rate. Thus, many potential drug targets have been identified, dozens of vaccine candidates have been tested in animal models in recent years, and several of these are poised to move into clinical trials in the next several years. The overall goals for treatment of tuberculosis are 1) to cure the individual patient, and 2) to minimize the transmission of *M. tuberculosis* to other persons. Thus, successful treatment of tuberculosis has benefits both for the individual patient and the community in which the patient resides, but in all cases the health department is ultimately responsible for ensuring that adequate, appropriate diagnostic and treatment services are available, and for monitoring the results of therapy. This article provides a comprehensive review about the science of tuberculosis, types, diagnosis and its evaluation techniques and treatment procedures.

Key words: *Tuberculosis, Mycobacterium, AIDS, DOTS, MDR-TB,*

INTRODUCTION

Mycobacterium tuberculosis is the organism that is the causative agent for tuberculosis (TB). There are other "atypical" *mycobacteria* such as *M. kansasii* that may produce a similar clinical and pathologic appearance of disease. *M. avium-intracellulare* (MAI) seen in immune-compromised hosts (particularly in persons with AIDS) is not primarily a pulmonary infection in terms of its organ distribution (mostly in organs of the mononuclear phagocyte system).

Tuberculosis is becoming a world-wide problem. War, famine, homelessness, and a lack of medical care and awareness of the disease all contribute to the increasing incidence of tuberculosis among disadvantaged persons. Since TB is easily transmissible between persons, the increase in TB in any segment of the population represents a threat to all segments of the population. This means that it is important to institute and maintain appropriate public health measures, including screening, vaccination (where deemed of value), and treatment. A laxity of public health measures will contribute to an increase in cases. Failure of adequate treatment promotes the development of resistant strains of tuberculosis[1-3].
The management of TB has improved greatly with the expansion of DOTS (directly observed therapy, short-course) programmes. DOTS ensure the best use of today's drugs, in particular avoiding emergence of MDR-TB. However, uptake has been slow in some high-burden countries due to the additional expense and it is unlikely that coverage will ever reach 100% of TB patients. New tools will aid the DOTS programme. In particular, drugs that simplify or shorten the regimen will make it easier to deliver DOTS. At the same time, widespread implementation of DOTS will ensure that any new drug that is brought into the clinic will be used correctly, avoiding, or at least delaying, the emergence of resistance.

Incremental improvements have been made by modifying the rifampicin structure to generate derivatives with improved activity. Rifapentine, registered in the USA in 1998, is more active than rifampicin (although it lacks activity against rifampicin-resistant isolates), but, its major advantage is its long half-life. It can be used in intermittent chemotherapy, twice weekly in the intensive phase, and once weekly in the continuation phase. Other rifamycins like rifabutin have found use against *Mycobacterium avium* infections rifalazil in early trials[4,5].

Science of Tuberculosis

Bacteriology of Tuberculosis

Tuberculosis is an infectious disease caused by multiplication of bacilli belonging to the genus *Mycobacterium*. The principal bacterium responsible for the disease is *Mycobacterium tuberculosis* (the Koch bacillus), which was isolated by Robert Koch in 1882. *Mycobacterium africanum* is a variety that sometimes appears in West Africa and is often resistant to thioacetazone[6].

Characteristics of Tubercle Bacilli

Tubercle bacilli are aerobic, with lipid-rich walls and a

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slow rate of growth (they take 20 hours on average to double in number). The lungs, dark and oxygen rich, at a temperature of 37°C, provide an ideal environment for the bacilli to replicate[7,8]. They are rapidly destroyed in the ambient environment by ultraviolet rays (sunlight). It is difficult to stain the bacilli with stains commonly used for other bacteriological examinations. They require special stains that can penetrate the wax-rich wall of the bacillus.

Sampling for diagnosis

For bacteriological examination, the quality of the samples sent to the laboratory is of fundamental importance.

i) **For pulmonary tuberculosis:** The specimen that should be collected for examination is sputum obtained from the patient after coughing (more rarely the sample is obtained by gastric aspiration or bronchoscopy). As sputum can be contaminated by other bacteria, it must be collected in clean sputum containers (non-sterile) that can be firmly sealed. All sputum samples that are not examined at the centre where they are collected must be stored and transported following strict guidelines[9,10].

ii) **For extrapulmonary tuberculosis:** Fluid from serous effusion, cerebrospinal fluid (CSF) or biopsied fragments can be sent to the laboratory for culture. All sampling must be performed in strictly sterile conditions so that culture can be performed directly without prior decontamination. Samples must never be placed in formalin, which kills the bacilli[11,12].

Modes of Transmission

Tuberculosis is a bacterial disease spread from one person to another principally by airborne transmission. In a small proportion of cases, the bacillus is transmitted to humans from infected cows through drinking non-sterilized milk. This mode of transmission plays only a minor role in the natural history of the disease in humans. Tuberculosis can affect any organ in the body. Pulmonary tuberculosis is the most frequent site of involvement; extrapulmonary tuberculosis is less frequent. Only pulmonary tuberculosis is infectious.

Sources of Infection

The main reservoir of *M. tuberculosis* is the patient with pulmonary tuberculosis. Such patients may have pulmonary "cavities" that are rich in bacilli (100 million bacilli in a cavity of approximately 2cm in diameter). The diagnosis of pulmonary tuberculosis is straightforward in such patients, as they almost always have chronic respiratory symptoms such as cough and sputum production. The definitive diagnosis is simple when the patient has large numbers of bacilli in the sputum (more than 5000 bacilli/ml), as these can be seen on microscopic examination of a sputum smear; these patients are termed "smear-positive".

Patterns of Infection

There are two major patterns of disease with TB:

- **Primary tuberculosis**: seen as an initial infection, usually in children. The initial focus of infection is a small sub-pleural granuloma accompanied by granulomatous hilar lymph node infection. Together, these make up the Ghon complex. In nearly all cases, these granulomas resolve and there is no further spread of the infection.
- **Secondary tuberculosis**: seen mostly in adults as a reactivation of previous infection (or reinfection), particularly when health status declines. The granulomatous inflammation is much more florid and widespread. Typically, the upper lung lobes are most affected, and cavitation can occur[13].

Exposure and Primary Infection

When patients with pulmonary tuberculosis speak, and particularly when they cough or sneeze, they produce an aerosol of droplets from the bronchial tree, each of which contains a number of bacilli, these droplets are infectious. The number of infectious droplets projected into the atmosphere by a patient is very high when coughing (3500) or sneezing (1 million). When they come into contact with the air these droplets rapidly dry and become very light particles, still containing live bacilli that remain suspended in the air. In an enclosed space, the droplets can remain suspended for a long time, and the bacilli remain alive for several hours in the dark, these are "infectious particles".

As direct sunlight rapidly destroys the bacilli, letting air and sunshine into rooms where tuberculosis patients live can reduce the risk of infection for those living in contact with them. When people live or sleep near a patient, they are at risk of inhaling infectious particles. When a person inhales infectious particles, the large particles, are deposited on the mucous of the nasopharynx or the tracheo-bronchial tree and are expelled by mucociliary clearance. The smallest particles, less than a few microns in diameter, can penetrate to the alveoli[14-16].

The closer and the more prolonged the contact with an infectious patient, the greater the risk of infection, as this risk is linked to the density of the bacilli in the air the individual breathes and the amount of the air inhaled. As a result, children living in the same household as a source of infection are at a particular risk of becoming infected.

Types of Tuberculosis

When resistance to infection is particularly poor, a "miliary" pattern of spread can occur in which there are a myriad of small millet seed (1-3 mm) sized granulomas, either in lung or in other organs.

Dissemination of tuberculosis outside of lungs can lead to the appearance of a number of uncommon findings with characteristic patterns:

- **Skeletal Tuberculosis:** *Tuberculous osteomyelitis* involves mainly the thoracic and lumbar vertebrae (known as Pott's disease) followed by knee and hip. There is extensive necrosis and bony destruction with compressed fractures (with kyphosis) and extension to soft tissues, including psoas "cold" abscess.
- **Genital Tract Tuberculosis:** *Tuberculous salpingitis* and *endometritis* result from dissemination of tuberculosis to the fallopian tube that leads to granulomatous salpingitis, which can drain into the endometrial cavity and cause a granulomatous endometritis with irregular menstrual bleeding and infertility. In the male, tuberculosis involves prostate and epididymis most often with non-tender induration and infertility.
- **Urinary Tract Tuberculosis:** A "sterile pyuria" with WBC's present in urine but a negative routine bacterial culture may suggest the diagnosis of renal tuberculosis. Progressive destruction of renal parenchyma occurs if not treated. Drainage to the ureters can lead to inflammation with urethral stricture.
- **CNS Tuberculosis:** A meningeal pattern of spread can occur, and the cerebrospinal fluid typically shows a high protein, low glucose, and lymphocytosis. The base of the brain is often involved, so that various cranial nerve signs may be present. Rarely, a solitary granuloma, or "tuberculoma", may form and manifest with seizures.
- **Gastrointestinal Tuberculosis:** This is uncommon today because routine pasteurization of milk has eliminated *Mycobacterium bovis* infections. However, *M. tuberculosis* organisms coughed up in sputum may be swallowed into the GI tract. The classic lesions are circumferential ulcerations with stricture of the small intestine. There is a predilection for ileocecal involvement because of the abundant lymphoid tissue and slower rate of passage of lumenal contents.
- **Adrenal Tuberculosis:** Spread of tuberculosis to adrenals is usually bilateral, so that both adrenals are markedly enlarged. Destruction of cortex leads to Addison's disease.
- **Scrofula:** *Tuberculous lymphadenitis* of the cervical nodes may produce a mass of firm, matted nodes just under the mandible. There can be chronic draining fistulous tracts to overlying skin. This complication may appear in children, and *Mycobacterium scrofulaceum* may be cultured.
- **Cardiac Tuberculosis:** The pericardium is the usual site for tuberculous infection of heart. The result is a granulomatous pericarditis that can be hemorrhagic. If extensive and chronic, there can be fibrosis with calcification, leading to a constrictive pericarditis[17].

Evaluation Techniques

The most common specimen screened is sputum, but the histological stains can also be performed on tissues or other body fluids. Culture of sputum or tissues or other body fluids can be done to determine drug sensitivities[18]. The presence, intensity of infection, and anti-bactericidal activity of the new form of old drug can be evaluated by using the following methods (Figure 1).

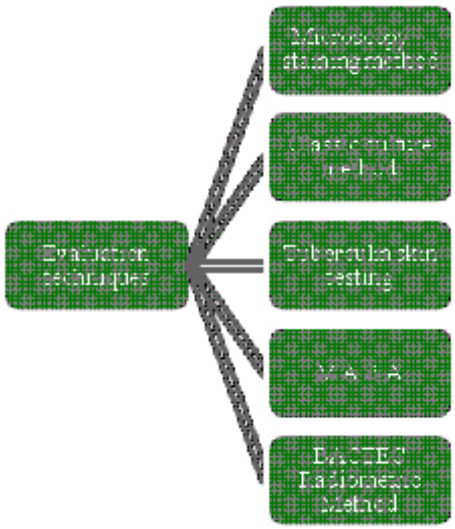

Fig. 1: *Evaluation technique chart*

Staining Methods

a) Ziehl-Neelsen (ZN) staining

The smear is covered with carbol fuchsin and the bacilli are stained red by the fuchsin and are resistant to the acid and alcohol, hence the name is called as **acid-fast bacilli** (AFB/Ziehl-Neelsen or Kinyoun's acid fast stains)[19,20]**.** The smear examinations of Ziehl-Neelsen staining details are given in Table 1.

Table 1. *Reading method for smears stained by Ziehl-Neelsen (immersion lens / 100)*

Number of AFB	Code
No AFB per 100 immersion fields	0
1–9 AFB per 100 immersion fields	exact number of AFB
10–99 AFB per 100 immersion fields	+
1–10 AFB per field	++
More than 10 AFB per field	+++

b) Fluorescent auramine staining

Here, the fuchsin is replaced by auramine and the stained smear is examined by fluorescence microscopy with a dry lens of low magnification (25 or 40). On

fluorescence staining, the smaller the lens the larger the surface examined. All forms of extrapulmonary tuberculosis (except sometimes renal tuberculosis) are usually poor in bacilli, as the conditions in these sites do not encourage the replication of bacilli[21,22] for this reason they are rarely detected on smear examination. Smear examination details are given in Table 2.

Table 2: *Reading method for smears stained by auramine (dry lens / 25)*

Number of AFB	Code
No AFB on the slide	0
1–10 AFB on the slide	doubtful (use Ziehl-Neelsen)
Fewer than 1 AFB per field but more than 10 on the slide	+
1–9 AFB per field	++
10–99 AFB per field	+++
More than 100 AFB per field	++++

Classic Culture Methods

Culture of a pathological specimen suspected of containing bacilli is the most rigorous method of diagnosing tuberculosis. The specificity of this test is much higher, as each live bacillus forms colonies on culture. In order to avoid contamination of the culture media, it is important to decontaminate the samples with basic antiseptics, which kill the contaminants much more rapidly than the *mycobacteria*[23].

Tuberculin Skin Testing

In countries where BCG vaccination has been widely used, the TB skin test is not useful, because persons vaccinated with BCG will have a positive skin test. Microscopically, the inflammation produced with TB infection is granulomatous, with epithelioid macrophages and Langhans giant cells along with lymphocytes, plasma cells, may be a few PMN's, fibroblasts with collagen, and characteristic caseous necrosis in the center. The inflammatory response is mediated by a type IV hypersensitivity reaction. This can be utilized as a basis for diagnosis by a TB skin test.

For the TB skin test, a measured amount of tuberculin purified protein derivative (PPD) is injected intracutaneously to form a small wheal, typically on the forearm. In 48 to 72 hours, a positive reaction is marked by an area of red induration that can be measured by gentle palpation (redness from itching and scratching doesn't count). Reactions over 10 mm in size are considered positive in non-immunocompromised persons.

BACTEC Method

The BACTEC system is a liquid medium with radiometric/nonradiometric growth detection of Mycobacterium which has the advantage of more rapid detection as compared to traditional cultures. Antibiotic susceptibility testing can also be done. Susceptibility can be determined more rapidly with the radiometric BACTEC 460 system, the clinical drug susceptibility system of choice for most of the last decade, but the high cost, high volume, lack of high-throughput format, and requirement for radioisotope disposal all limit its usefulness for mass screening.

Microplate Alamar Blue Assay (MABA)

Commercially available systems such as the BACTEC system, Mycobacteria Growth Indicator Tubes, E-test, Agar Proportion Susceptibility Method and Oxidation-Reduction Dyes are simple and rapid but each of them having their own drawbacks. The clinical isolates have shown a good correlation between the proportion technique and a broth method with Alamar Blue, a novel proprietary, resazurin-based oxidation-reduction indicator which delivered colorimetric MICs for *M.tuberculosis* isolates in 14 days[24-27]. The Alamar blue oxidation-reduction dye is a general indicator of cellular growth and/or viability; the blue, non-fluorescent, oxidized form becomes pink and fluorescent upon reduction. Growth can therefore be measured with a fluorometer or spectrophotometer or determined by a visual color change.

Yajko found agreement in MICs of four first-line anti-TB drugs for 50 clinical isolates of *M. tuberculosis* when comparing the agar proportion method and a microbroth tube dilution technique which employed visual determinations of Alamar blue reduction for growth determination. This study assesses the antimycobacterial mass drug screening potential of visual and fluorometric microplate-based Alamar blue assays (MABAs) by comparing MICs of 30 established antimicrobial agents with those obtained with the BACTEC 460 system against *M. tuberculosis* H37Ra (H37Ra), *M. tuberculosis* H37Rv (H37Rv), and *M. avium*[28-31].

Definitions

a) Tuberculosis Cases

- **Case of Tuberculosis:** A known tuberculosis case is once which has been bacteriologically confirmed, or has been diagnosed by a clinician.
- **Definite Case:** Patient with positive culture for the *Mycobacterium tuberculosis* complex. In countries where culture is not routinely available a patient with 2 sputum smears positive for acid-fast bacilli (AFB+) is also considered a definite case.
- **Smear-Positive Pulmonary Case :** At least two initial sputum smear examinations (direct smear microscopy) AFB+; or one sputum examination AFB+ and radiographic abnormalities consistent

with active pulmonary tuberculosis as determined by the treating medical officer; or one sputum specimen AFB+ and culture positive for M. tuberculosis.

- **Smear-Negative Pulmonary Case**: Pulmonary tuberculosis not meeting the above criteria for smear-positive disease. Diagnostic criteria should include: at least 3 sputum smear examinations negative for AFB; and radiographic abnormalities consistent with active pulmonary TB; and no response to a course of broad-spectrum antibiotics; and decision by a clinician to treat the patient with a full course of anti-tuberculosis therapy; or positive culture but negative AFB sputum examinations.
- **Extrapulmonary Case**: Patient with tuberculosis of organs other than the lungs e.g. pleura, lymph nodes, abdomen, genito-urinary tract, skin, joints and bones, meninges. Diagnosis should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active extrapulmonary disease, followed by a decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy.

Note: A patient diagnosed with both pulmonary and extrapulmonary tuberculosis should be classified as a case of pulmonary tuberculosis.

- **New Case**: Patient who has never had treatment for tuberculosis, or who has taken anti-tuberculosis drugs for less than 1 month.
- **Relapse Case**: Patient previously declared cured but with a new episode of bacteriological positive (sputum smear or culture) tuberculosis.
- **Retreatment Case**: Patient previously treated for tuberculosis whose treatment failed, who defaulted, or who relapsed.

b) Treatment Outcomes

- **Cured:** Initially smear-positive patient who is smear-negative in the last month of treatment, and on at least one previous occasion.
- **Completed Treatment:** Patient who has completed treatment but does not meet the criteria for cure or failure.
- **Died:** Patient who dies for any reason during treatment.
- **Failed:** Smear-positive patient who remained smear-positive, or became smear-positive again, at least 5 months after the start of treatment.
- **Defaulted:** Patient whose treatment was interrupted for two consecutive months or more.
- **Transferred Out:** Patient who has been transferred to another reporting unit and for whom the treatment outcome is not known.
- **Successfully Treated:** The sum of cases that were cured and that completed treatment (expressed as a percentage of the number registered in the cohort).

Chemotherapy for Tuberculosis

Chemotherapy for Tuberculosis (TB) was established after the discovery of streptomycin in the 1940s. Before this, bed rest, good food, fresh air and sunshine in sanatoriums built on hill sides, with or without surgery (e.g. thoracoplasty) were the only way to treat TB[32-34]. Now it is treated in two phase – an initial phase at least three drugs and a continuation using two drugs. The concurrent use of at least three drugs during the initial phase is designed to reduce the bacterial population as rapidly as possible and to prevent the emergence of drug resistance. The classification of drugs is given in Table 3.

Table 3: *Classification of drugs*

Group 1	Oral first line agents	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
Group 2	Injectables	Streptomycin, Kanamycin, Amikacin, Capreomycin
Group 3	Fluoroquinolones	Ciprofloxacin, Ofloxacin, Levofloxacin, Moxifloxacin, Gatifloxacin, Sparfloxacin
Group 4	Bacteriostatic Second- Line drugs	Ethionamide, Cycloserine, P-aminosalicylic acid
Group 5	Other drugs	Amoxicillin, Clarithromycin, Rifabutin, Thiacetazone

Factors that modify the natural history of tuberculosis

The natural history of the disease can be modified by a number of factors and explains how it perpetuates itself. A smear-positive patient can infect 20 people during his/her lifetime and create two new cases of tuberculosis, at least one of which will be infectious. As long as at least one new case of tuberculosis is created by each existing case and thus the disease is maintained in the community. For an individual, the likelihood of getting the disease is directly related to the likelihood of becoming infected and the efficiency of the body's immune defense[35-37].

Factors that accelerate progression from infection to disease

These are factors that are likely to reduce the efficiency of the body's means of defense, malnutrition, conditions leading to immune deficiency such as HIV infection, diabetes, or long-term treatment with corticosteroids or immunosuppressive medications. Among these risk factors, HIV infection plays a major role; it increases the probability of progression from infection to disease and also increases the risk of reactivation of old tuberculosis. The risk of an HIV-positive subject developing tuberculosis disease is 5–8% per year[38,39].

Recommended Treatment Regimens

There are four recommended regimens for treating patients with tuberculosis caused by drug-susceptible organisms. Although these regimens are broadly applicable, there are modifications that should be made under specified circumstances, described subsequently. Each regimen has an initial phase of 2 months followed by a choice of several options for the continuation phase of either 4 or 7 months[40-42]. The recommended regimens together with the number of doses specified by the regimen are described in Table 4. The initial phases are denoted by a number (1, 2, 3, or 4) and the continuation phases that relate to the initial phase are denoted by the number plus a letter designation (a, b, or c).

Table 4: *Drug Regimens for Culture-positive Pulmonary Tuberculosis Caused by Drug-susceptible Organisms*

Regimen	Phase	Drugs Used	Interval and Doses	Range of Total Doses	Rating
1	Initial Phase	INH/RIF/PZA/EMB	[@] 7 d/wk for 56 doses or 5 d/wk for 40 doses[&]		
1a	Continuation Phase	INH/RIF	[@] 7 d/wk for 126 doses or 5 d/wk for 90 doses[&]	182-130 (26 wk)	HIV-:A (I) HIV+:A (I)
1b	Continuation Phase	INH/RIF	[@] Twice weekly for 36 doses	92-76 (26 wk)	HIV-:A (I) HIV+:A (I)
1c[**]	Continuation Phase	INH/RPT	[@] Once weekly for 18 doses	74-58 (26 wk)	HIV-:B (I) HIV+: E(I)
2	Initial Phase	INH, RIF, PZA, EMB	[@] 7 d/wk for 14 doses, then twice weekly for 12 doses or 5 d/wk for 10 doses, [@] then twice weekly for 12 doses		
2a	Continuation Phase	INH/RIF	[@] Twice weekly for 36 doses	62-58 (26 wk)	HIV-:A (I) HIV+:B (I)[$]
2b[**]	Continuation Phase	INH/RPT	[@] Once weekly for 18 doses	44-40 (26 wk)	HIV-:B (I) HIV+: E(I)
3	Initial Phase	INH, RIF, PZA, EMB	[@] Three times weekly for 24 doses		
3a	Continuation Phase	INH/RIF	[@] Three times weekly for 54 doses	78 (26 wk)	HIV-:B (I) HIV+:B (I)
4	Initial Phase	INH, RIF, EMB	[@] 7 d/wk for 56 doses or 5 d/wk for 40 doses[&]		
4a	Continuation Phase	INH/RIF	[@] 7 d/wk for 217 doses or 5d/wk for 155 doses[$]	273-195 (39 wk)	HIV-:C (I) HIV+:C (I)
4b	Continuation Phase	INH/RIF	[@] Twice weekly for 62 doses	118-102 (39 wk)	HIV-:C (I) HIV+:C (I)

'@' When direct observation of therapy (DOT) is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.

'$' Patients with cavitations on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

'&' Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimen is AIII.

'#' Not recommended for HIV-infected patients with CD4+ cell counts <100 cells/microliter

'**' Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph.

Tuberculosis & HIV

The link between HIV and TB remains a substantial worldwide health problem. TB is the most common lung complication of HIV in developing countries. One-third of the new cases of TB in the last 5 years are attributable to HIV. One-third (1/3) of the 34.3 million HIV cases worldwide are co-infected with Tuberculosis (12.7 million or 0.19% of the world population - 2007). 70% of these persons are in Sub-Saharan Africa. TB is the leading killer of HIV-infected persons worldwide (1/3 of AIDS deaths worldwide). In most of the developing world, TB is the most common opportunistic infection in persons living with HIV. Compared to the general population, HIV infected persons have higher rates of active TB and higher rates of reactivating inactive TB due to being immunocompromised by the infection[43-46].

CONCLUSION

The establishment of The Global Alliance for TB Drug Development (GATB) changed the landscape in TB drug development. Launched in 2000, the Alliance overcame the natural barriers to TB drug development. By working in partnership with organizations as diverse as academic institutions, government research laboratories, non-governmental organizations, the pharmaceutical industry and contract research houses, the GATB will plug gaps in the R&D pipeline. It will also stimulate TB drug development by providing a framework in which the various elements of the process may be brought together.

Any new drug for TB must offer some advantage over the current therapy. The GATB has identified a number of objectives for TB drug development. These include shortening the total duration of effective treatment and/or significantly reducing the total number of doses needed to be taken under DOTS supervision; improving the treatment of MDR-TB; and providing a more effective treatment of latent TB. Our knowledge and understanding of persistence is poor, few targets have been identified, and even fewer compounds conclusively shown to kill *M. tuberculosis* in anything other than a rapidly growing state.

Despite the overwhelming need in the public health sector for new TB drugs, there is relatively little drug discovery activity in the pharmaceutical industry. This reflects a number of serious disincentives to drug development such as the relatively modest size of the global market, its complexity, the cost of TB drug development, and pressures on pricing and access.

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