

TB: An Overview and Co-infection with HIV

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ABSTRACT

Tuberculosis commonly abbreviated as TB is a clinical manifestation of serious concern which has indeed challenged the medical and scientific community. It is a primary manifestation of the respiratory tracts which includes the upper and lower respiratory compartments and is caused by *Mycobacterium tuberculosis* which is an obligatory aerobe. The organism requires oxygen for its metabolism and survives at a temperature of 37°C. The pathogen is capable of transmitting the disease for an infected individual to a healthy person through air in the form of tiny droplets that is released when the infected person coughs or sneezes. Since they are aerobes, they are capable of manifesting the lungs of mammals that have higher oxygen volume in lungs. The current review focuses on the clinical impact of the disease on infected individuals and also attempts to emphasize on the synergistic impact of the TB in synchronization with HIV infection. The prime objective of the article is to have a basic level understanding of tuberculosis and the role of the organism in causing the disease and the article simultaneously attempts to disclose the vulnerability HIV patients to TB.

Keywords: TB, HIV, AIDS, *Mycobacterium tuberculosis*

INTRODUCTION

One of the dreadful diseases capable of compromising an individual's health and wellbeing is tuberculosis (TB). TB has got its own prominence in terms of having a detrimental impact on the affected individual and the most interesting feature is its synchronization with other ailments that are closely affiliated with a compromised immune system. The disease is common in individuals with compromised immunity and can also be transmitted from an infected individual when he discharges microscopic particles in to the air through sneezing, coughing, talking, etc. The transmission of the disease from an infected person to a healthy person is common among people with close proximity than from a stranger. This validates that people with close relation are at higher risk of getting TB. In simple terms, the disease can be acquired from those people who are known to us rather than strangers [1]. It is globally regarded as serious infection and targets the lungs of the affected individual. It is an air borne disease and rapidly spreads from one person to the other through tiny particles in air. Though it was a rare condition, the onset of HIV has in turn enhanced the increase in the prevalence of TB [1]. It is a widely accepted fact HIV negatively influences an individual's immune system, which would in turn lessen the person's defense mechanism against other pathogens and scientific studies have disclosed this factor as one of the crucial facet for the prevalence of TB [1,2].

Though developed nations have succeeded in reducing the extent of TB prevalence, it still remains an issue of serious concern. Another aspect of TB that has challenged the scientific community is the ability of TB causing microbe to tolerate the antimicrobial agent which is a consequence of antimicrobial resistance. Another requirement for the affected person is to go through a stringent course of medication which in simple terms means that the infected person has to be on a strict medical regime. The disease is caused by a bacterium which uses air as its medium for transmission. The bacterium responsible for outbreak of the infection is *Mycobacterium tuberculosis* which is an acid fast Gram positive bacterium. Due to its nature, it requires specialized staining techniques rather than the conventional Gram staining. An interesting feature associated with the bacterium is the presence of extra fat component in the cell wall comprising of mycolic acid. This fat layer indeed acts

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as armor which offers protection against antimicrobial agents [3]. As the mycolic acid layer serves as the first line of defense against several antimicrobial drugs, the efficacy of the drugs against the organisms reduces which in turn will not have an inhibitory response. In addition to the complex nature of the organism, the disease also comprises of different stages which decide the level of damage caused on the individual. The disease comprises of stages like latent and active phase depending on its ability to cause a mild effect or a long lasting consequence that can spread to leading to other parts. Though several studies have highlighted the significance of TB in pulmonary diseases, it can also have an impact on the other organs like kidneys and spine. The symptoms vary according to the part that has been compromised like severe back pain in case of spine and blood during urination as a consequence of kidney invasion. Though there are many species of mycobacterium genus, the most commonly known perpetrator responsible for this disease is *M. tuberculosis* [4].

ABOUT THE ORGANISM

Mycobacterium tuberculosis is regarded as one of the most pathogenic bacteria and is responsible for causing a range of health ailments which under certain circumstances can lead to death. The organism requires oxygen for its metabolism and has been labeled as obligatory aerobe. Since it requires high concentration of oxygen for its survival, it is commonly found in the lungs of the mammals resulting in pulmonary manifestations. The convenient conditions required for the growth of the organisms includes a temperature of 37°C and pH close to neutral condition [5]. Oxygen levels greater than 95% enhances the microbial activity which can lead to

clinical manifestations. Several scientific studies have confined the organism to the mammalian respiratory system because of their invasion of the lungs and can be diagnosed through tuberculin test, acid fast staining and polymerase chain reaction [6,7]. The bacterium is a very slow grower when compared to its counter parts and takes about 20 h for division. It is a rod shaped bacterium capable of withstanding extreme conditions such as dry and desiccated conditions. Scientific evidences have been provided to illustrate the ability of the organism to overcome extreme conditions and a very unusual feature of the microorganism has been connected with this ability. The microorganism is composed of more amount of lipid content known as mycolic acid which allows the organism to survive these conditions for days and sometimes weeks. The prominence of mycolic acid in enhancing the virulence in the microorganism has also been validated by demonstrative studies [8]. The only known host for *M. tuberculosis* is human beings and the only means of transmission occurs through air droplets originating from an infected person [9]. In simple terms *Mycobacterium tuberculosis* is a human pathogen which has a global impact from the context of an individual's health and wellbeing. The association of *M. tuberculosis* with humans is not clearly understood and it is believed that domestication of cattle has resulted in the proximity of *M. bovis* with humans. This in turn has enhanced the transmission of bovine tuberculosis among humans and this is considered as the onset of bovine tuberculosis strain. However till the dawn of the seventeenth century, tuberculosis was not a threatening condition until the beginning of urbanization (Figure 1).



Figure 1. The above image depicts the microscopic structure of Mycobacterium [4].

The growth and development of Western Europe as a consequence of urbanization has led to the increased scope of air borne infection as the disease is very common in crowded and thickly populated places. This was the start of the air borne infection from person to person resulting in the emergence of an epidemic often referred to as the great white plague. Interesting feature of *M. tuberculosis* is its ability to overcome the efficacy of phagocytosis. In lungs when the bacterium is engulfed by the alveolar macrophages, the cell wall of the engulfed organism prevents the union of the phagosome with lysosome which in turn prevents the intracellular digestion of the engulfed bacterial cell [10].

TB OVERVIEW

During the early eighties, TB was not in the lime light till the emergence of HIV and the prevalence of HIV infection was gaining its pace in the middle eighties and it was in 1985 that witnessed the rapid spread of the disease. Many studies have also reported the connection between TB and AIDS; since individuals with HIV infections were high prone to TB. Studies have revealed the role of the compromised immune system in individuals which has favored the occurrence of the disease. However, stringent measures and healthy practices have had an impact on TB control and by 1993, there was a downfall in the prevalence of TB; however, the condition still remains a concern on a global scale. Patients diagnosed with TB have to be under strict medical supervision and should go through a medical regime comprising of several types of medication in order to come out of the ailment. Another factor that has challenged the scientific community is the growing resistance which has geared the scientific investigators to put across novel treatment methods and measures [1].

Symptoms

Symptoms in case of TB are highly varied and it depends upon the stage of the disease and the extent of infestation in the patient. The initial medical signs include coughing which later proceeds to severe and serious manifestations. Based on the severity and communicability, TB is classified as latent and active TB. It is estimated that 2 billion people on a global scale have latent stage of TB where the patient harbors the bacteria in an inactive state. Since, the bacteria stays in an inactive form, symptoms will not be caused at this stage. As the bacterium is in its inactive form this stage is also called as inactive TB and it is not contagious. However, this stage should not be ignored because at any point the inactive stage can transform in to active stage. Appropriate treatment is needed to curb the disease at an early stage to ensure its control. In contrast, the active stage is much more severe than the earlier stage and can lead to serious manifestation. The onset of the active stage occurs after the first few weeks of bacterial invasion and in some cases it might take years for the transformation of latent stage in to an active stage [1].

The following signs and symptoms confirm the traces of TB in an individual:

- Cough lasting for over three weeks or more
- Hemoptysis (coughing up blood)
- Chest pain
- Tiredness and fever
- Sweating during nights
- Loss of appetite
- Chills
- Breathing constraints

Despite the fact that majority of the symptoms cited above are synchronized with the lungs and corresponds to clinical conditions associated with the pulmonary area, TB can also affect kidneys and spine leading to severe clinical signs. Several studies have substantiated the role of TB in morbidity and mortality and have labeled it as a global threat from the context of health and wellbeing [11,12]. It is indeed a fact that one in every three individuals across the globe is infected with TB which is a consequence of *M. tuberculosis* infestation and the scope of developing active form of TB accounts to 5 to 15% [13]. In recent times the prevalence of the disease has reached its pinnacle resulting in 9.6 million positive cases all over the world and the studies claim that 1.5 million people across the globe lost their lives due to TB. This included HIV negative and positive subjects accounting to 1.1 million and 400000 subjects, respectively [13]. Though TB is global issue, the occurrence is found to be endemic because of higher incidence in areas with low income including sub Saharan and South East Asian countries. Due to its severity, TB has gained the most attention over the last decade and stringent measures have resulted in a significant control on the condition and the mortality rate has gone down by 47% during the nineties because there has been great success in developing effective techniques for preventive care, treatment and infection control.

It is estimated that over 40 million lives were saved since 2000 due to the measures that were implemented to eradicate TB through sustainable goals [13,14]. It is estimated that by 2030, the death rates due to TB will reduce to 90% if appropriate measures are directed against the disease. However, an emerging issue over the last few decades has been the extent of drug resistant TB which can lead to dire consequences. Existence of multi drug resistant TB has been an issue to be dealt with and has in turn challenged the scientific community. Studies illustrate that the outcomes of drug resistant TB from the context of treatment is yet to gain pace in terms of productive output and studies also claim that the number of cases of drug resistant TB is far beyond the number of cases identified. In 2014, out of a staggering

480,000 MDR-TB cases (multi drug resistant-Tuberculosis) only 25% were detected and disclosed. Furthermore, details provided by certain studies also substantiate that 7000 TB patients with multi drug resistance in 13 countries across the globe have been successfully treated in 2007 [13]. Hence, it would be appropriate to say that the TB management has played a vital role in the regulation of the disease and its aim to reduce the incidence in decades to come.

Pathogenesis of TB infection

It is a well-known fact that TB is a consequence of air borne factors caused by *M. tuberculosis* and is capable of influencing any body part with prime impact on lungs. Activities like sneezing, coughing, release the organism in to the atmosphere through tiny droplets. Ingestion or inhalation of these droplets by a normal individual can lead to severe clinical manifestation [15]. Several studies have indeed claimed the spread of the disease through the inhalation of infected droplets released from the diseased individual. The ingested droplets will make its way in to the mouth and will reach the upper respiratory and will then reach the alveoli of lungs [16]. In the alveoli the ingested droplets attract the alveolar macrophages which leads to the destruction of the ingested particles due to phagocytosis [17].

However, studies also illustrate the prominence of microbial composition in counteracting the efficacy of phagocytosis. The mycolic acid content in the cell wall of the organism makes the microbe very stringent and this very fact allows the microorganism to overcome the impact of macrophages. Following the death of macrophages, these unaffected portions within the macrophages are released which can have access to body tissues and organs through the bloodstream and lymphatic channels [18]. In response to the infection, the immune system retaliates by producing white blood cells to destroy the foreign particle and it would take 2-8 weeks for the immune system to react. The white blood cells produced in response will encapsulate the tubercle bacilli resulting in the formation of granuloma [17]. This encapsulated structure within the white blood cells is believed to be under control and the tubercle bacilli is said to have entered a stage called as latent phase and the condition is commonly referred to as latent tuberculosis infection (LTBI). Patients diagnosed with this stage of TB will not reveal any clinical symptoms and will not be able to transmit the condition to others [19]. However, many studies have synchronized TB with the conduct of an individual's immune system. It has been proved that TB is highly prevalent in people with compromised immune system. If the immunity

of an individual misfires and fails to keep the tubercle bacilli, it could lead to dire consequences. There is every possibility of the transformation of latent TB into active TB which could take few days to few years for reactivated infection. Under these circumstances, the infection is highly detrimental and is highly communicable [20].

Evaluation and analysis of TB

Deep-seated analysis of TB encompasses the following vital components:

- Undertaking the patient's medical history
- Physical examination of the patient
- Confirmatory tests to reveal *Mycobacterium tuberculosis* infestation
- Chest radiograph
- Bacteriological evaluation of the clinical specimen.

The analysis of patient's medical history can be considered as the onset of overall clinical diagnosis without which the medical investigation cannot be carried out. Coughing over 3 weeks with or without the sputum formation can be taken as a sign of TB onset among individuals that could lead to lung manifestation leading to pulmonary conditions. In addition, other clinical signs like weight loss, lack of appetite, sweating during nights, chest pain and tiredness are affiliated to TB [21]. TB is classified in to extra pulmonary and pulmonary depending upon its impact inside or outside the lungs. Clinical manifestations like lack of appetite, night sweats and fever are common in case of extra pulmonary TB [22]. Inflammation of the meninges (meningitis) due to TB can result in conditions like headache and confusion and if the infection reached the spine of the individual, it will lead to severe back pain [23,24]. It is a widely accepted fact that areas with higher prevalence of HIV have experienced drug resistant tuberculosis [25]. Tuberculosis is indeed considered as an epidemic and has been an issue from the context of public health priority [26]. Several studies and scientific demonstrations have urged on the need of improved diagnostic procedures to counteract the negative impact of the disease due to its prominence as one of the critical facets compromising the well-being of humans.

There is a need for improvised diagnostic tools not only for counteracting the pathogen but also to comprehend the extent of drug resistance exhibited by the pathogen [27] (Figure 2).

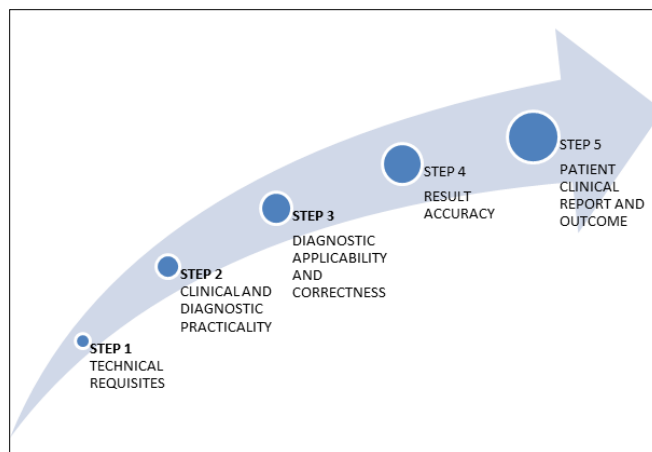


Figure 2. Hierarchical strides involved in the evaluation of TB.

TB and HIV

Since the dawn of clinical and diagnostic microbiology, several demonstrative studies and scientific hypothesis have attempted to disclose various allied and distinct facets of diseases that are detrimental to humans and TB is one among those diseases that has been extensively studied and has been an issue of serious concern leading to severe consequence. Tuberculosis has also been deeply studied in accordance to another life threatening manifestation called HIV infection which leads to AIDS. Studies have reported the severity of tuberculosis among HIV positive people [28]. Studies have revealed a staggering estimate of about 14 million people globally with HIV and TB infection which remains one of the leading reasons for increased death rate among the infected individuals [29]. According to the World Health organization (WHO), estimates of an increase in HIV up to 20 folds have been disclosed in HIV affected areas [30]. Global estimates of TB patients co infected with HIV have been demonstrated by several researchers and it has been substantiated that 1.1 million were positive for HIV out of 8.7 million with TB which accounts to 13% of occurrence in people already diagnosed with TB [30]. The increased prevalence of vigorous TB among HIV positive individuals has been attributed to enhanced reactivation of dormant TB and elevated levels of susceptibility to the diseases among people due to the fact that TB and HIV will impede the immune levels in the infected individuals [31]. On a global scale, the scientific community has validated Tuberculosis (TB) and human immunodeficiency virus (HIV) as the 2 leading causes of infectious disease-associated mortality worldwide through their scientific demonstrations.

It is indeed a fact that TB and HIV are inseparably bound since the global declaration of HIV as an epidemic. The collaborative impact as a consequence of TB and HIV in an individual ranging from pathogenesis to epidemiological profile leads to a variety of clinical manifestations. The extent of disease profile and degree of pathogenesis reflects upon the intensity of treatment and measures for prevention.

According to certain research studies, eight million new cases of active TB have been registered on a global scale which is quite high when compared to the scenario that was existing in the past [32]. Joint United Nations Program on HIV/AIDS (UNAIDS) has revealed a staggering estimate of 2-3 million positive cases for TB leading to death. However, in comparison to HIV which is a more recent pathogen, it is estimated that about 40 million people have been diagnosed with HIV and AIDS infection [32]. Over the last few decades, TB and HIV/AIDS have been labeled as global pandemics and they are gaining pace from the context of their prevalence. However, the prevalence of these diseases among people in a geographical location strictly depends on the dominance of perpetrators responsible for causing these conditions. Several studies and demonstrative experiments have related the preponderance of *Mycobacterium* and the prevalence of the disease. In developed and industrialized countries, the rate of TB and HIV was less when compared to other developing or under developed nations and the number of individuals with confirmed HIV increased in back trodden areas due to lack of proper awareness and appropriate preventive requisites. Some researchers have focused on the available resources and its prominence as a facet in the onset of the disease. Countries with limited resources and lack of sufficient supply of essential relevant have been the most affected as a consequence of TB and HIV. Those countries with high prevalence of *Mycobacterium* have revealed an increase in the incidence of TB and HIV [33]. The positive cases for TB in countries with lack of appropriate resources has increased to about 5 to 10 folds and the prevalence of HIV in individuals with TB has exceeded to 80% [34].

In addition to enhanced prevalence of HIV among TB patients, another issue of serious concern is the extent of multi drug resistance exhibited by *Mycobacterium*. The growing altitude of multi-level drug resistance has been demonstrated through scientific procedures which in turn provided the hidden insights of the disease [35]. Though sub

Saharan African countries are highly prone to these diseases, the rate at which these diseases are spreading globally cannot be denied. Despite the advancements in medical field, that has led to the discovery of novel methods and approaches to counteract the efficacy of clinical manifestations and diseases, the treatment for TB and HIV still remains a challenge due to major diagnostic and therapeutic deficiencies which could be due to decreased sensitivity of sputum smear analysis or examination as these examinations are quite vital in the diagnosis, prevention and treatment. Several positive cases of TB have been diagnosed in various parts of Asia and studies have revealed its impact on infected individuals. India has registered the highest number of TB in the world which accounts to about 14 million cases. Studies in the past have revealed an estimate of about 1.8 million cases annually in India of which 0.82 million have been diagnosed with active TB [36]. TB was declared as an emergency by WHO in accordance with AIDS and these diseases have shown to exhibit a synergistic relation which was predominant among the individuals between 15-49 years of age [37,38]. The probability of developing the TB over the years depends on the quality of an individual's immune system and the persons infected by tubercle bacilli constitute to about 10% of causing TB during the course of their lives. Hence the chances of developing TB are less in normal individuals when compared to those with HIV infection. The elevation rate of dormant TB to an active form is quite vigorous among individuals with HIV infection due to compromised immune system leading to progression of the disease to elevated levels causing death [39]. Several research studies have substantiated TB as an opportunistic infection among people diagnosed with HIV infection in developing countries.

Reports also claim that the active tuberculosis has resulted in an increased transformation of morbidity to mortality among HIV infected patients accounting to one-third of deaths [40].

CONCLUSION

Mycobacterium tuberculosis is an opportunistic pathogen that belongs to the family Mycobacteriaceae and is known for causing severe respiratory manifestations. It is an obligatory aerobic bacterium that requires oxygen for its metabolism and is capable of causing manifestations in the lungs of mammals with high volume of oxygen. The bacterium requires a temperature of 37°C with pH of 6.4-7.0 and oxygen levels of >95% for its metabolism. It is a tiny rod shaped straight or curved tubercle bacilli consisting of mycolic acid in its cell wall. Studies have validated the prominence of mycolic acid in conferring the organism with extreme tolerance to antimicrobial drugs. The mycolic acid present in the cell wall in association with arabinogalactan and peptidoglycan results in the formation of a rigid structure that reduces the permeability of antibiotics. In addition, the pathogen is bestowed with features that allow

them to survive in macrophages and protects them from the process of phagocytosis.

Mycobacterium tuberculosis (MTB) and human immunodeficiency virus (HIV) co-infection is an issue of severe concern and is regarded as a global threat towards the public health. It is indeed undeniable fact that *Mycobacterium tuberculosis* (MTB) and human immunodeficiency virus (HIV) co-infection is one of the major public health issues. According to world Health Organization (WHO), individuals with MTB were highly prone to HIV infections which accounted to 15% causing over 300,000 deaths among individuals co-infected with MTB-HIV. In recent years, several scientific investigators and researchers have emphasized on the synergistic impact of TB and HIV. It is a well-known fact that TB and HIV are known for targeting the immune system of an individual and people with compromised immune system are vulnerable to these clinical manifestations. On the contrary, several other factors including therapeutic, clinical and socio economic factors have increased the probability of these diseases. Surveys conducted by several registered and reputed organizations have validated higher prevalence of TB among HIV infected patients in developing and under developed nations due to the lack of appropriate therapeutic measures and clinical facets. However, further research is required to comprehend the insights of these clinical conditions.

REFERENCES

1. <https://www.mayoclinic.org/diseases-conditions/tuberculosis/symptoms-causes/syc-20351250>
2. <https://www.medicalnewstoday.com/articles/17131.php>
3. https://en.wikipedia.org/wiki/Mycolic_acid
4. <https://www.flickr.com/photos/niaid/5149398656/in/phostream/>
5. Jabir RA, Rukmana A, Saleh I, Kurniawati T (2003) The existence of *Mycobacterium tuberculosis* in microenvironment of bone. *Mycobacterium Res Dev* 16: 463-496.
6. Ryan KJ, Ray CG (2004) *Mycobacteria*. Sherris Medical Microbiology: An Introduction to Infectious Diseases. ISBN 978-0-83-858529-0. McGraw-Hill: New York, p: 439.
7. Cudahy P, Shenoi SV (2016) Diagnostics for pulmonary tuberculosis. *Postgrad Med J* 92: 187-193.
8. Murray PR, Rosenthal KS, Pfaller MA (2005) *Medical Microbiology*. Elsevier Mosby.
9. (2018) How TB spreads? Center for Disease Control. Retrieved 14 March 2018.
10. Keane J, Balcewicz-Sablinska MK, Remold HG, Chupp GL, Meek BB, et al. (1997) Infection by

- Mycobacterium tuberculosis* promotes human alveolar macrophage apoptosis. *Infect Immunity* 65: 298-304.
11. Raviglione M, Sulis G (2016) Tuberculosis 2015: Burden, challenges and strategy for control and elimination. *Infect Dis Rep* 8: 6570.
 12. Maartens G, Wilkinson RJ (2007) Tuberculosis. *Lancet* 370: 2030-2043.
 13. World Health Organization (2015) Global Tuberculosis Report. Geneva, Switzerland: WHO.
 14. World Health Organization (2015) Implementing the end TB strategy: The essentials. Geneva, Switzerland, WHO.
 15. Dye C, Floyd K. Tuberculosis. In: Jamison DT, Breman JG, Measham AR, et al. (2006) Disease control priorities in developing countries. 2nd Edn.
 16. CDC (2016) How TB spreads? Available online: <https://www.cdc.gov/tb/topic/basics/howtbspreads.htm>
 17. Schluger NW (2005) The pathogenesis of tuberculosis. The first one hundred (and twenty-three) years. *Am J Respir Cell Mol Biol* 32: 251-256.
 18. Smith I (2003) *Mycobacterium tuberculosis* pathogenesis and molecular determinants of virulence. *Clin Microbiol Rev* 16: 463-496.
 19. World Health Organization (2016) What is TB? How is it treated? Available online: <http://www.who.int/features/qa/08/en/>
 20. CDC (2016) Chapter 2: Transmission and Pathogenesis of Tuberculosis. Available online: <https://www.cdc.gov/tb/education/corecurr/pdf/chapter2.pdf>
 21. Campbell IA, Bah-Sow O (2006) Pulmonary tuberculosis: Diagnosis and treatment. *BMJ* 332: 1194-1197.
 22. Lee JY (2015) Diagnosis and treatment of extra pulmonary tuberculosis. *Tuberc Respir Dis (Seoul)* 78: 47-55.
 23. Cormican L, Hammal R, Messenger J (2006) Current difficulties in the diagnosis and management of spinal tuberculosis. *Postgrad Med J* 82: 46-51.
 24. Rasouli MR, Mirkoohi M, Vaccaro AR (2012) Spinal tuberculosis: diagnosis and management. *Asian Spine J* 6: 294-308.
 25. Lessells RJ, Cooke GS, Newell ML, Godfrey-Faussett P (2011) Evaluation of tuberculosis diagnostics: Establishing an evidence base around the public health impact. *J Infect Dis* 204: 1187-1195.
 26. World Health Organization (2009) Global tuberculosis control: Epidemiology, strategy, financing. WHO report. Geneva, Switzerland.
 27. Abdool Karim SS, Churchyard GJ, Karim QA, Lawn SD (2009) HIV infection and tuberculosis in South Africa: An urgent need to escalate the public health response. *Lancet* 374: 921-933.
 28. Bruchfeld J, Correia-Neves M, Källenius G (2015) Tuberculosis and HIV co-infection. *Cold Spring Harb Perspect Med* 5: a017871.
 29. Getahun H, Gunneberg C, Granich R, Nunn P (2010) HIV infection-associated tuberculosis: The epidemiology and the response. *Clin Infect Dis* 50: 201-207.
 30. WHO (2013) Global tuberculosis report. WHO Geneva.
 31. Girardi E, Raviglione MC, Antonucci G, Godfrey-Faussett P, Ippolito G (2000) Impact of the HIV epidemic on the spread of other diseases: The case of tuberculosis. *AIDS* 14: 47-56.
 32. World Health Organization (WHO) (2006) Global tuberculosis control surveillance, planning, financing. WHO report 2006: Geneva.
 33. Joint United Nations Programme on HIV/AIDS (UNAIDS) (2006) Report on the global AIDS epidemic. UNAIDS/05.19E.
 34. Corbett EL, Marston B, Churchyard GJ, De Cock KM (2006) Tuberculosis in sub-Saharan Africa: Opportunities, challenges and change in the era of antiretroviral treatment. *Lancet* 367: 926-937.
 35. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, et al. (2006) Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 368: 1575-1580.
 36. Vidyanathan PS, Singh S (2003) TB-HIV co-infection in India. *NTI Bull* 39: 11-18.
 37. Jain SK, Aggarwal JK, Rajpal S, Baveja U (2000) Prevalence of HIV infection among tuberculosis patients in Delhi - A sentinel surveillance study. *Indian J Tuberc* 47: 21-26.
 38. Styblo K (1990) The global aspects of tuberculosis and HIV infection. *Bull Int Union Tuberc Lung Dis* 65: 28-32.
 39. Escott S, Nsuteby E, Walley J, Khan A (2001) Management of TB in countries with high HIV prevalence. *Afr Health* 23: 12-15.
 40. DeCock KM, Sero B, Coulibaly IM, Lucas SB (1992) Tuberculosis and HIV infection in Sub-Saharan Africa. *JAMA* 278: 1581-1587.