

Tuberculosis - *Human Immunodeficiency Virus* Coinfection: *Bidirectional effect*

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Summary

Tuberculosis (TB) remained a major public health problem all over the world with high incidence particularly in developing countries. There has been a global resurgence of TB in the last decades and the majority of these cases occur in the impoverished countries of Africa, Asia and South America. This is largely due to the pandemic of the Human Immunodeficiency Virus (HIV); the direct effect being immunodeficiency caused by HIV, which leads to an increased risk of developing TB in those with latent infection, increased risk of re-infection and a higher probability of new infection, with a rapid progression of active TB. On the other hand, TB shortens the survival of patients affected with HIV infection and accelerates the progression of HIV infection to Acquired Immunodeficiency Syndrome (AIDS). The objective of this manuscript was to review the existing literature on TB/HIV co-infection, compile and avail for the readers. Furthermore, the pathological and immunological mechanisms in TB/HIV co-infection were discussed. Due emphasis was given on the effect of one on the other. Lastly, relevant recommendations were forwarded.

Key words: M. tuberculosis, HIV, AIDS, Active tuberculosis, Latent tuberculosis

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1. Introduction

M. tuberculosis, the agent that cause tuberculosis (TB), is estimated to infect about 1/3 of the world population and although only about 5-10 % develop active disease during the first few years following exposure (Mario *et al.*, 2001); which results in a massive case load with eight million cases each year and 3 million deaths. Moreover, the percentage that progress to disease is increasing. The progress of infection towards disease depends on the cell-mediated immunity. T cells plays a pivotal role in combating mycobacterial infection; antigen presenting cells (APC) process and present mycobacteria both to CD4 and CD8 T cells, which then release cytokines such as the gamma interferon (γ -IFN). The latter leads to activation macrophages and thereby control of the infection (Chan *et al.*, 1994).

Worldwide, TB is the most frequent occurring co infection in subjects with HIV type 1 infection and TB is one of the first secondary infections to be activated in HIV positive individuals. HIV-1 infection remains the most common risk factor for the development of active TB (Dye C *et al.*, 1999). Both reactivation of latent *M. tuberculosis* infection and progressive primary TB are substantially more common in HIV-1 infected subjects (Mario *et al.*, 2001). The resurgence of TB has been attributed, in part, to HIV-1 epidemic in developing and developed countries. In developing countries 60-70% of TB cases occur in HIV-1 infected individuals (Elliott *et al.*, 1993; WHO, 2001). There is a mutual interaction between HIV-1 and *M. tuberculosis* infection i.e. HIV-1 infection predisposes to the development of active TB while the course of HIV-related immunodeficiency is worsened by active TB infection. Indeed, the immunosuppression induced by HIV modifies the clinical presentation of TB and its management, while immune restoration induced by highly active anti-retroviral therapy (HAART) may be associated with paradoxical manifestation related to immune reconstitution. And, of course, TB influences the prognosis of HIV infection, and anti-TB drugs interfere with anti-retroviral drugs, including protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNTRIs) (Rook *et al.*, 2001; Toossi, 2003). The objective of this manuscript is to review, compile and avail for the readers the available information on the TB/HIV co-infection. In addition, the underlying immunological mechanisms, which play key role in promoting the effect of one of the infections on the other, were discussed.

2. Biology of *M. tuberculosis* and HIV

2.1. Biology of *M. tuberculosis*

Mycobacteria belong to the family Mycobacteriaceae, and the pathogenic species belonging to the *M. tuberculosis* complex. *M. tuberculosis* is a rod-shaped, non-spore-forming, thin aerobic bacterium measuring 0-5 μm by 3 μm . It is often neutral in Gram's staining. However, once stained, the bacilli cannot be decolorized by acid alcohol, a characteristic justifying their classification as acid-fast bacilli. Acid fastness is due to mainly to the organisms' high content of mycolic acid, long chain cross-linked fatty acid and other cell walls lipid (Jawetz *et al.*, 2004). The cell wall lipids (e.g. mycolic acids) are linked to underlying arabinogalactan and peptidoglycan. This structure confers very low permeability of the cell wall, thus reducing effectiveness of most antibiotics. Another molecule in the mycobacterial cell wall, lipoarabinomannan, is involved in the pathogen-host interaction and facilitates the survival of *M. tuberculosis* with macrophage. A large proportion of genes are devoted to the production of enzymes involved in cell wall metabolism (Jawetz, 2004; Mario *et al.*, 2001).

2.2. Biology of HIV

HIV is an RNA virus belonging to the lentivirus, subfamily of retroviruses. It has two types named HIV-1 and HIV-2. HIV-1 is the main cause of AIDS all over the world. HIV-2 also causes AIDS but is mainly present in West African countries (Jawetz, 2004). Both HIV-1 and HIV-2 are enveloped viruses with positive-sense; single stranded ribonucleic acid (RNA) genome. The virion contains two copies of genomic RNA and a number of proteins. The viral genes *env* encode for the glycoprotein (gp) 160, gp 120 and gp41, *gag* for p24, p17, p7, p9 and *pol* for p32, p66, p51, p11 (Schupbach *et al.*, 1999). HIV is known for its rapid mutation and genetic recombination. This has resulted in the evolution of different groups and subtypes of HIV. HIV-1 has groups M, O and N. Group M is subdivided into 10 subtypes (A to J). Six subtypes, A to F, have been defined in HIV-2. M group viruses are responsible for the AIDS pandemic. During replication, single stranded RNA of the HIV virion is reverse transcribed to DNA and it is integrated into the host cell genome, which is then called the provirus (Schupbach *et al.*, 1999; William, 2004). HIV measures 100 to 150 nm in diameter. Mature viral particles are characterized by an electron-dense conical core. The HIV genome is approximately 10kb in length and is organized similarly to that of other retroviruses (John, 2004).

The major structural and core proteins of HIV are synthesized from gag and as a large, myristoylated precursor protein (pr 55), which is subsequently cleaved by the viral protease to yield the matrix (MA) (p 17), capsid (CA) (p24), and nucleocapsid (NC) (p7) proteins. The matrix protein is primarily a peripheral membrane protein located along the inner leaflet of the viral lipid envelope, where it directs the incorporation of the envelope glycoproteins (ENV) into the forming virion. Some p 17 is also found in the virion core, where it participates in the transport of the viral pre-integration complex to the nucleus. The capsid protein assembles to form the conical core of the virion. The nucleocapsid protein (p7) is an RNA binding protein required for packaging of the genomic RNA into the virion (John, 2004; Anthony *et al.*, 2001).

3. Pathogenesis and Immunity

3.1. Pathogenesis of *M. tuberculosis*

M. tuberculosis is most commonly transmitted from a patient with infectious pulmonary TB to other persons by droplet nuclei, which are aerosolized by coughing, sneezing or speaking. The probability of contact with a case, intimacy and duration of the contact, degree of infectiousness of the case, and the environment of the contact are all-important determinants of transmission (Mario *et al.*, 2001). TB patients whose sputum contains acid-fast bacilli (AFB) visible by microscopy play the greatest role in the spread of infection. These patients often have cavitary pulmonary TB of the respiratory tract and produce sputa containing as many as 10^5 AFB/ml (WHO, 2003). Patients with sputum smear-negative/culture positive TB are less infectious, and those with culture negative pulmonary disease and extra pulmonary TB are essentially non-infectious (WHO, 2003). Generally, the risk of acquiring *M. tuberculosis* infection is determined by exogenous factors. But, the risk of developing disease after being infected depends largely on endogenous factors, such as the individual's innate susceptibility to disease and level of function of cell-mediated immunity. This risk is, however, greatly increased among HIV-infected individuals (WHO, 2003).

The interaction of *M. tuberculosis* with the human host begins when the droplet nuclei containing microorganisms from infectious patients are inhaled. While the majority of inhaled bacilli are trapped in the upper airways and expelled by ciliated mucosal cells, only a fraction (usually <10%) reaches the alveoli. Activated alveolar macrophages ingest the bacilli. The balance between the bactericidal activity of the macrophage, and the number and virulence of the bacilli determines the events following phagocytosis (Mario *et al.*, 2001).

Several genes thought to confer virulence to *M. tuberculosis* have been identified (Jayasankar *et al.*, 1999): Kat G encodes for catalase -an enzyme protective against oxidative stress, rPOV – is the main sigma factor initiating transcription of several gene and erp gene encoding a protein required for multiplication also contributes to virulence. Defect of the first 2-genes result in loss of virulence.

About 2 to 4 weeks after infection, two additional host responses to *M. tuberculosis* develop: a tissue-damaging response and a macrophage activating response. The tissue damaging response is the result of a delayed type hypersensitivity (DTH) reaction to various bacillary antigens; it destroys non-activated macrophages that contain multiplying bacilli. The macrophage activating response is a cell-mediated phenomenon resulting in the activation of macrophages that are capable of killing and digesting tubercle bacilli. Although both of these responses can inhibit mycobacterial growth, it is the balance between the two that determines the form of TB that will develop subsequently (Schlesinger *et al.*, 1996). With the development of specific immunity and the accumulation of large numbers of activated macrophage at the site of the primary lesion, granulomatous lesion (tubercles) are formed which consist of lymphocyte & activated macrophage, such as epithelioid cell and giant cells (Mario *et al.*, 2001).

3.2. Immunity of *M. tuberculosis*

After the bacilli are processed and presented to T cells, the T cells produce IFN- γ , interleukin -2 (IL-2), tumor necrosis factor alpha (TNF- α) and macrophage colony-stimulating factor, which activate macrophages and cytotoxic cells to inhibit the intracellular growth of the bacilli (Selvaraj *et al.*, 1998). TB appears when the immune response inducing granuloma is insufficient to limit the growth of mycobacteria. IFN- γ plays a pivotal role at this stage and individuals harboring genetic defects that result in reduced production of either IFN- γ or its cellular receptors develop severe and fatal TB (Ottenhoff *et al.*, 1998). Alveolar macrophages secrete a number of cytokines including IL-1 (induces fever), IL-6 (causes hyperglobulinemia), and TNF- α (kills mycobacteria, contribute to the formation of granuloma, and a number of systemic effects such as fever and weight loss) (Selvaraj *et al.*, 1998). Macrophage also process and present antigens to T lymphocyte and result in proliferation of CD4⁺ lymphocyte, which is crucial to the host defense against *M. tuberculosis*.

Reactive CD4⁺ lymphocyte produce cytokines of the TH 1 pattern and participate in MHC class II–restricted killing of cells infected with *M. tuberculosis*. IFN- γ may induce release of nitric oxide and TNF- α also seems to be important (Selvaraj *et al.*, 1998; Vishwanath *et al.*, 1998).

3.3. Pathogenesis of HIV

HIV is transmitted by homosexual and heterosexual contact, blood and blood products, and infected mothers to infants either intrapartum, perinatally, or via breast milk. Nevertheless, there is no evidence that HIV is transmitted by casual contact or that the virus can be spread by insects such as mosquito bite (UNAIDS/WHO, 2003). The hallmark of HIV disease is a profound immunodeficiency resulting primarily from a progressive quantitative and qualitative deficiency of CD4 T cells. CD4 molecule serves the primary cellular receptor for HIV. A number of mechanisms responsible for cytopathicity and immune dysfunction of CD4⁺ T cells have been demonstrated *in vitro*, it remains unclear as to which mechanisms or combination of mechanisms are primarily responsible for the *in vivo* progressive depletion and functional impairment. When the number of CD4⁺ T cells declines below a certain level, the patient is at high risk of developing a variety of opportunistic disease, particularly the infections and neoplasms that are AIDS defining illness (John, 2004; Anthony *et al.*, 2001).

The combination of viral pathogenic and immunogenic events that occur during the course of HIV disease from the moment of initial (primary) infection through the development of advanced-stage disease is complex and varied. So it is important to appreciate that the pathogenic mechanisms of HIV diseases are multifaceted and multiphase and are different at different stages of the disease. Therefore, it is essential to consider the typical course of untreated HIV-infected individuals in order to more fully appreciate these pathogenic events (John, 2004; Anthony *et al.*, 2001; Schlesinger *et al.*, 1996).

3.4. Immunity of HIV

Figure 1 demonstrates schematic presentation of immune responses in HIV infection. In HIV, the immune system is chronologically activated owing to the persistence of virus's replication throughout the course of HIV infection particularly in untreated patients. Aberrant immune activation is the hallmark of HIV infection and is a critical component of the pathogenesis of HIV diseases. It is characterized by activation of both humeral and cellular immune responses.

Activation of B cells leads to hypergammaglobulinemia while lymphocytes proliferate and cause activation of monocytes. In the early phase of the disease, lymph nodes become hyperplastic. Secretions of proinflammatory cytokines is increased, and the levels of neopterin, Beta 2-microglobulin, acid-labile interferon and soluble IL-2 receptors are elevated. On top of these, autoimmune phenomenon develops (John, 2004; Anthony *et al.*, 2001). In addition to endogenous factors such as cytokines, a number of exogenous factors such as other microbes those are associated with lightened cellular activation can enhance HIV replication and thus may have important effects on HIV pathogenesis. Co-infection or simultaneous cotransfection of cells with HIV and other viruses or viral genes can up regulate HIV expression. Cytokines that are important components of this immunoregulatory network have been demonstrated to play a major role in the regulation of HIV expression. *In vitro* cytokines which induce HIV expression include IL-1, IL-2, IL-3, IL-6, IL-12, TNF- α , TNF- β , Macrophage colony stimulating factor (M-CSF), Granulocyte monocyte colony stimulating factor GM-CSF. Among these cytokines, the most consistent and potent inducers of HIV expression are the proinflammatory cytokines, which consists of TNF- α , IL-5 & IL-6. IFN- α and IFN- β suppress HIV replication, whereas IL-4, IL-10 & IFN- γ can either induce or suppress HIV expression, depending on the system involved (John, 2004; Anthony *et al.*, 2001; Feng, 2000). Figure 1 shows the network of cytokines during HIV infections.

4. Interaction between TB and HIV in co-infection

TB is the most common serious opportunistic infection in HIV positive patients and is a manifestation of AIDS in more than 50% of cases in developing countries. TB shorten the survival of patients affected with HIV infection and may accelerate the progression of HIV infection to AIDS and, hence is a cause of death in one third of people with AIDS worldwide (UNAIDS/WHO, 2003). Higher mortality observed in co-infected individuals is due to progression into AIDS rather TB due to the fact that *M. tuberculosis* increases viral replication. On the other hand, the HIV epidemic has the potential to worsen the TB situation as has happened in certain African countries. HIV is the most potent risk factor for the progression of TB infection to active TB. Individuals infected with *M. tuberculosis* have an approximately 10% life time risk of developing active TB, compared to 60% or more in persons dually infected with HIV/TB (Anthony *et al.*, 2001). Most cases of TB in HIV infected patients are due to endogenous reactivation though HIV infection also greatly increases the risk of developing TB following new infection.

Thus, active TB can accelerate the progression of HIV to AIDS and as such HIV infection facilitates the progression of *M. tuberculosis* infection to active TB.

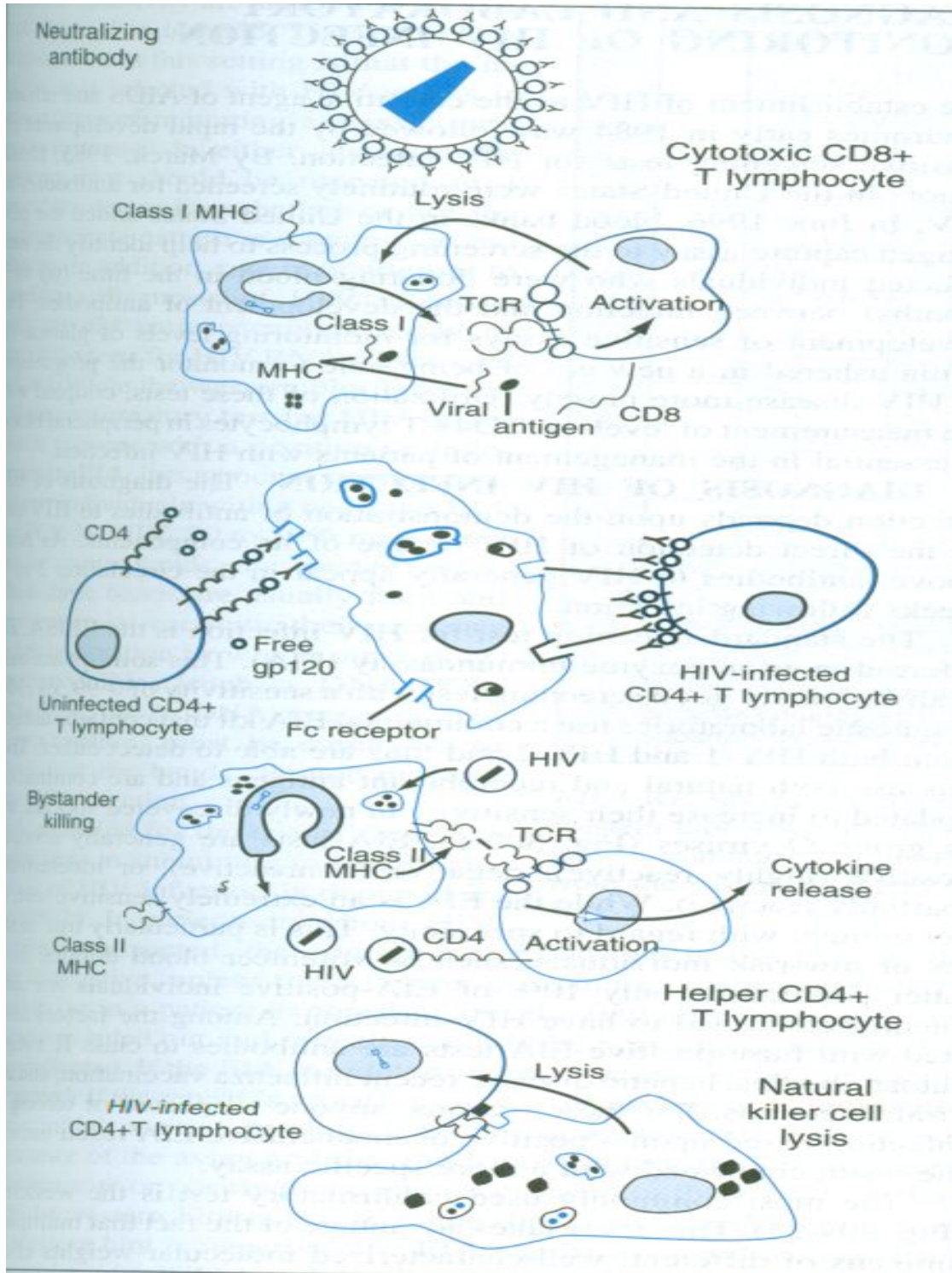


Figure 1. Immunological effectors mechanisms during HIV infection (Anthony *et al.*, 2001)

During the course of HIV infection, IFN- γ production is decreased dramatically in parallel with the reduction of CD4⁺ T-lymphocytes, which in turn leads to increased risk of developing reactivation or reinfection by *M. tuberculosis* (Havlir *et al.*, 1999). Conversely, TB may also influence HIV evolution in that proinflammatory cytokine production by TB granulomas (in particular TNF- α) has been associated with increased HIV viraemia, which may accelerate the course towards severe immunosuppression. The risk of death in HIV infected patients with TB is twice that of patients infected in HIV without TB (Garrait *et al.*, 1997).

A number of studies have indicated that the development of TB is associated with increased HIV-1 replication. Both HIV-1 load and heterogeneity appear to be affected by *M. tuberculosis* infection. For example, Goletti *et al.* (1996) showed increased viral load in serum sample from HIV-1 infected patients at the time of diagnosis of TB, compared to serum samples obtained before diagnosis. Similarly in a survey of purified protein derivatives (PPD) skin test positive HIV-1 infected subjects who were evaluated for preventive chemotherapy, HIV activity was shown to be enhanced at the time of diagnosis of TB (Toossi *et al.*, 2001; Whalen *et al.*, 1996).

Limited studies conducted in developed countries (Dean *et al.*, 2002) have shown significant reductions in HIV-1 plasma viral load in patients after successful treatment of TB. Those conducted in a few sub-Saharan African countries, however, did not find significant decrease in HIV-1 viral load months after anti-TB therapy (Kalou *et al.*, 2005; Wolday *et al.*, 2005). In Ethiopia, a significant decline in the HIV plasma viral load of 5 patients after deworming and anti-TB treatment was observed (unpublished data). Similarly, Wolday *et al.* (2002) demonstrated a significant decline in viral load following de-worming of the patients.

During *M. tuberculosis* infection, excess proinflammatory cytokines, such as TNF- α may be critical to the expansion of virus burden. The interaction of *M. tuberculosis* with mononuclear phagocyte induces the expression of TNF- α before and at the phagocytosis of the bacilli due to exposure to *M. tuberculosis* protein. In patients co-infected with HIV-1/TB, the level of circulating TNF- α activity correlate with HIV activity (Aung *et al.*, 1996). TB/HIV co-infection can also result in severe wasting. The wasting in turn, affects the inflammatory response, suppresses cellular immunity and aggravates the severity and outcome of disease. In these complex interactions among TB/HIV co-infection, trace elements play an important role (Failla, 2003).

Variation in the concentration of essential trace elements was reported among patients co-infected with TB and HIV in Gondar, Ethiopia (Kassu *et al.*, 2006). The result of this study showed that TB patients with HIV co infection had significantly lower serum Z and Se concentration and significantly higher Cu/Zn ratio compared TB patients without HIV co infection.

5. Epidemiology of TB-HIV co-infection

Almost half of the world's population is infected with *M. tuberculosis* with 20 million new infections occurring annually worldwide, 90% of them are from developing countries and hence at risk of developing active disease. About 8.4 million people develop active TB every year, and 3 million die of the disease each year (WHO, 2003). In Africa, the incidence of TB in the year 2000 was 290/100,000 population.

The burden of TB in Ethiopia is one of the highest in the world. The prevalence of TB in Ethiopia is not well known, but it is estimated to range from 0.36%- 0.62% per year in the general population (MOH, 2002). According to the 2002 National TB and Leprosy control Program report, 94,957 cases of TB from the Directly Observed Treatment (DOTs) implementing areas of the country have been registered, among which 33,028 were new smear-positive pulmonary TB cases (36 % of the total new cases)(MOH, 2002).

Figure 2 shows worldwide distribution of HIV infection at the end of 2005. At the end of 2005, WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that over 40.3 million people were infected with HIV (UNAIDS/WHO, 2004). And 20 million people around the world had already lost their lives to AIDS. In Sub-Saharan Africa at the end of 2005, people living with HIV were 25.8 million (23.8-28.9 million) with new HIV infections of 3.2 million (2.8-3.9 million). The number of deaths due to AIDS at the end of 2005 were 2.4 million (2.1 - 2.7 million) and the proportion of adults living with HIV was 7.2% (6.6 – 8.0%) (UNAIDS/WHO, 2004).

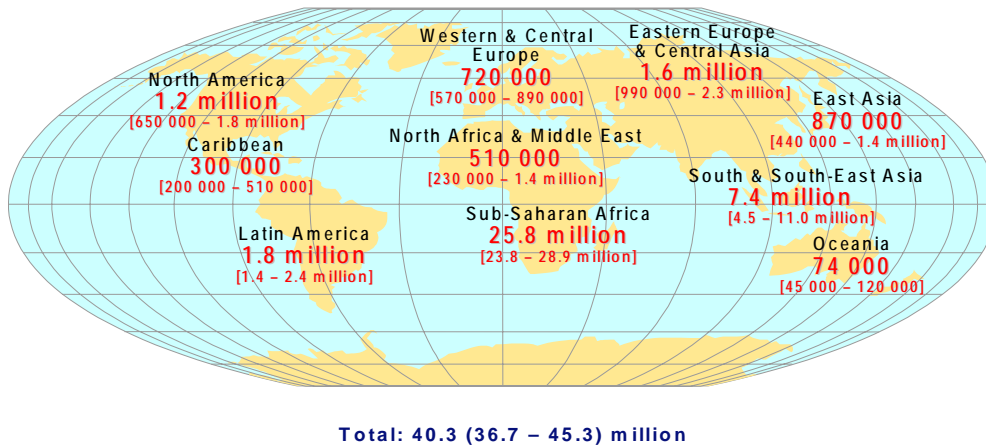


Figure 2: Distribution of HIV in the world as of end 2005 (UNAIDS/WHO, 2004)

The HIV prevalence in Ethiopia among adults at the end of 2004 was 4.4% with 1.5 million people living with HIV/AIDS, new infections of 197,000, new AIDS cases of 98,000 and AIDS deaths of 90,000 (UNAIDS/WHO, 2004). The trends in HIV-1 prevalence at urban antenatal care sites in various parts of Ethiopia are summarized in Table 1.

Table 1: Trend in HIV-1 prevalence (%) at urban antenatal care (ANC) sites in various parts of Ethiopia (MOH, 2004)

Location	Site name	Year				
		2000	2001	2002	2003	2005
North central	Bahir Dar Health Center	20.8	23.4	20.0	20.2	-
West	Gambella Hospital	19.0	14.6	15.4	18.7	-
East	Diredawa Hospital	13.6	15.2	12.1	14.4	-
Northwest	Gondar Health Center	-	15.1	18.3	13.9	-
Central	Addis Ababa (5 health centers)	15.2	15.6	13.2	12.4	-
South	Dilla Hospital	11.7	9.8	11.5	12.1	-
West central	Jimma Hospital	-	8.6	16.9	10.2	-
North	Mekelle Health Center	-	17.2	16.8	9.3	-

There has been a global resurgence of TB in the last decades and the majority of these cases occur in the impoverished countries of Africa, Asia and South America. This is largely due to the pandemic of the HIV, which has worst hit on Sub-Saharan African countries (UNAIDS/WHO, 2004). The occurrence and distribution of TB/HIV co-infection is depicted in Figure 3. In New Delhi, a study of 555 patients with TB demonstrated an HIV seropositivity of 9.4% vs an overall seropositivity of 0.4% during 1994-1999. Prevalence rates among TB patients of 30% in Mumbai¹¹, and 40% in Northern Thailand have been noted (Preetish *et al.*, 2003).

Studies from Uganda and Zambia have recorded HIV rates of 50-70% among TB patients (Jai *et al.*, 2004). In Tanzania, the survey conducted during 1994-1998 on 10,612 new smears positive TB patients revealed 40% HIV prevalence (Range *et al.*, 2001). In general, the proportion of TB infections due to HIV varies between countries and has reached level above 80% in some African countries. In Ethiopia, the prevalence of HIV among TB patients is variable from area to area. Study conducted in 2002 showed 57% prevalence of TB/HIV co-infection (Bruchfeld, 2002). Another study conducted in the southern Ethiopia showed prevalence of 19% and 26% TB/HIV co-infection among smear positive and smear negative PTB cases, respectively (Mohammed *et al.*, 2004). More recently a prevalence of 47% TB/HIV coinfection has been reported from the Northwest part of Ethiopia (Kassu *et al.*, 2006).

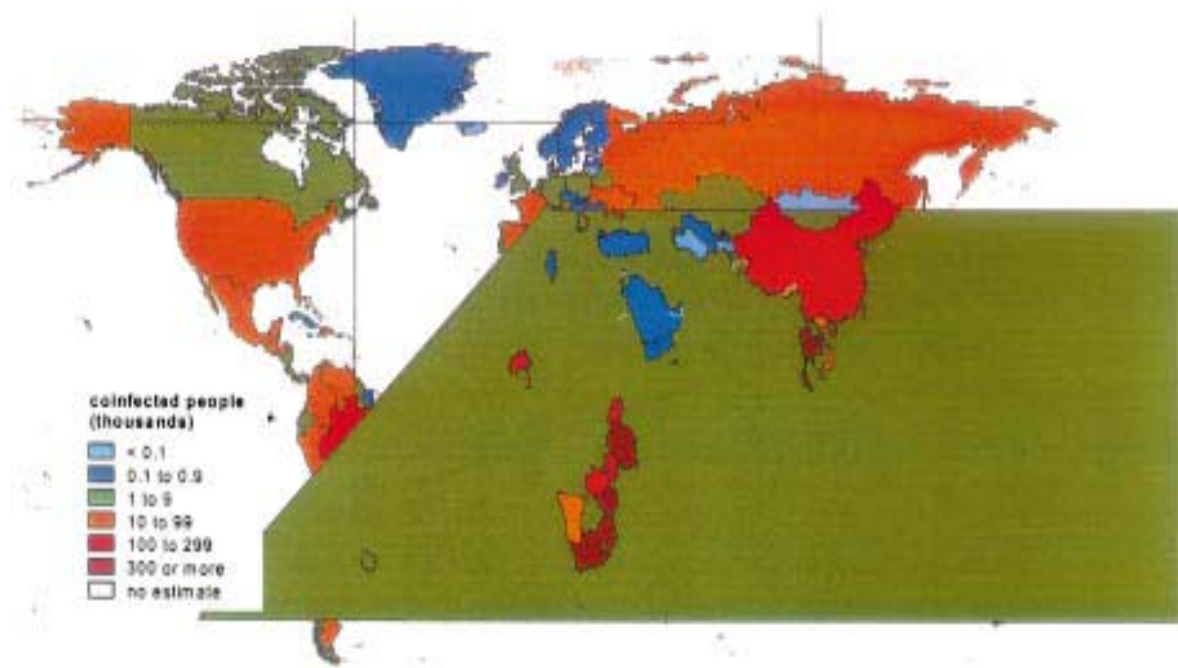


Figure 3: Distribution of TB/HIV in the world (UNAIDS/WHO, 2004)

6. Laboratory diagnosis of TB-HIV infection

6.1. Diagnosis of *M. tuberculosis*

The clinical diagnosis of TB differs with the degree of immunity. The classic picture of pulmonary TB is seen mainly in non-severely immunocompromised patients (CD4 > 200), and is secondary to a recent infection. Pulmonary involvement is associated with cough, sputum, and more rarely haemoptysis, thoracic pain and dyspnoea. A typical feature consist of lower lobe involvement with a trend towards diffuse infection rather than cavitations, are seen frequently. Cavitory lesions are encountered rarely in patients with a CD4 T-lymphocyte count < 200. TB can be diagnosed by AFB microscopy, Mycobacterial culture, nucleic acid amplification, radiographic examinations, PPD skin test and cytokine release assay (Mario C *et al.*, 2001).

6.2. Diagnosis of HIV infection

HIV infection can be detected by serologic assays for detecting antibodies to HIV and by direct detection assays. The latter involves p24 antigen detection, nucleic acid detection and quantification (detection of proviral DNA and HIV-1 RNA) and culture of HIV (Demeter *et al.*, 2000).

6.3. Diagnostic problems in TB/HIV co-infection

The diagnosis of TB in HIV-positive patients is difficult for three main reasons: a) the sensitivity of the direct sputum smear examination is reduced in HIV-positive patients. Compared to HIV-negative patients with pulmonary TB, a lesser proportion of HIV-positive patients with pulmonary TB will have positive sputum smears; b) X-ray abnormalities, which are not specific for TB in HIV-negative patients, are even more non-specific in the HIV-infected, with only minor abnormalities seen on chest X-ray or with abnormalities which do not look like classical TB, and c) Patients infected with HIV have frequent illnesses with pulmonary involvement caused by agents other than *M. tuberculosis* (Jai *et al.*, 2004; Anthony *et al.*, 2001).

6.4. Monitoring of patients with HIV infection

The epidemic of HIV infection and AIDS has provided the health care workers with new challenges for integrating clinical and laboratory data to effect optimal patient's management. The close relation between clinical manifestation of HIV infection and CD4+ T cells count has made measurement of CD4 T cells a routine part of the evaluation of HIV infected individuals.

And, thus determination of CD4 T cells count and, measurement of the levels of HIV RNA in serum or plasma provide a powerful set of tools for determining prognosis and monitoring of response to therapy. CD4 T cells count provides information on the current immunological status of the patients and the HIV RNA level predicts what will happen to the CD4 T cells count in the near future, and hence provides an important piece of prognostic information (John, 2004; Anthony *et al.*, 2001).

7. Combating TB/HIV co-infection

Figure 4 shows the schematic presentation of TB/HIV combating. In most cases, TB infection comes first and HIV is contracted subsequently when the person achieves adolescence or adulthood. Once co-infected, the progression to active TB occurs quite rapidly, which could be prevented through the use of TB prevention therapy. Those who progress to active TB could be managed with DOTS and through provision of care and support, including the use of antiretroviral therapy. Therefore, at each point in the scheme, interventions can be planned and implemented to try and interrupt TB and HIV infection from progressing to active TB and/or AIDS. Management of HIV-associated TB through DOTS can prevent community transmission of TB (Jai *et al.*, 2004).

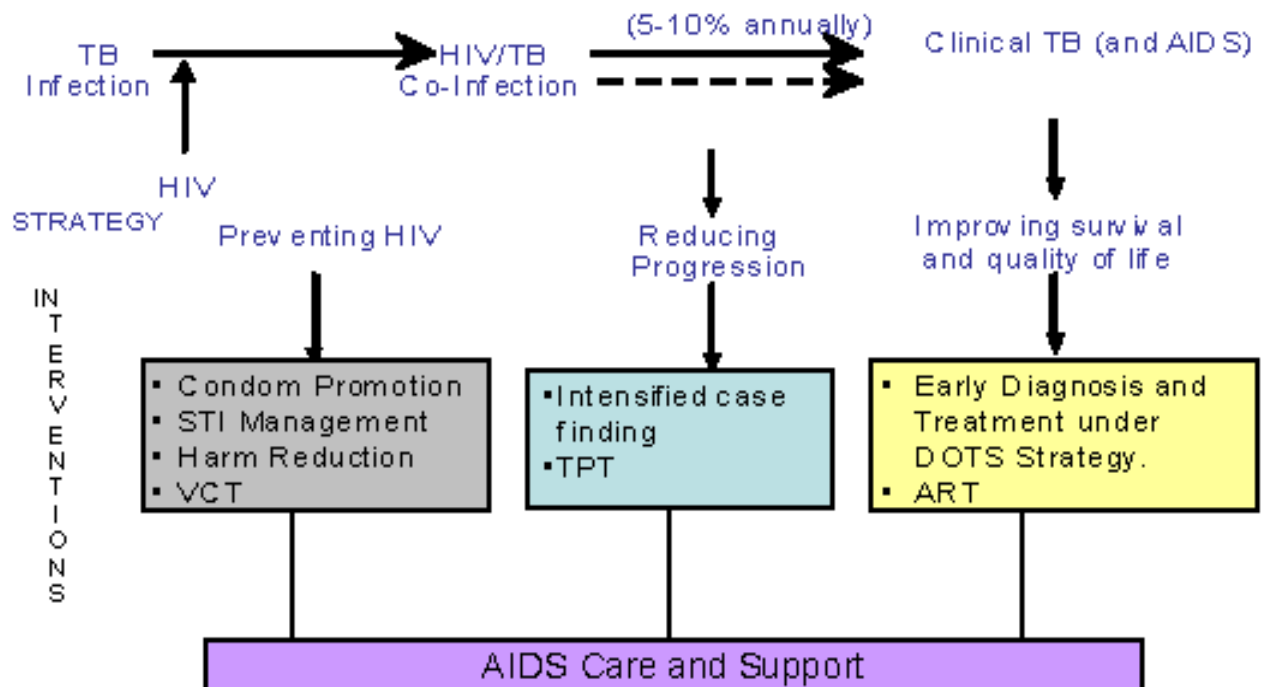


Figure 4: Combating TB/HIV: The conceptual framework and intervention points (Jai *et al.*, 2004).

Keys: ART, antiretroviral therapy; TPT, TB preventive therapy; STI, sexually transmitted infections; VCT, voluntary counseling and testing; DOTS, directly observed treatment short course.

7.1. Preventing HIV infection

Action for prevention of HIV transmission must include: a) information and education aimed at all men and women, particularly those at high risk of infection, including sex workers and injecting drug users; b) health and social services especially for the purpose of providing condoms, clean needles and syringes to reduce harm, and the early diagnosis and treatment of sexually transmitted infections using syndromic approach; and c) creating an enabling environment, in the absence of stigma and discrimination directed against people living with HIV/AIDS or those at risk (Jai *et al.*, 2004).

7.2. Reducing progression to active TB

Preventing the occurrence of clinical TB among co-infected persons requires the people with HIV to be diagnosed in the first place. The primary intervention required is availing the Voluntary Counseling and Testing (VCT) services to those with HIV infection. Those found infected both with TB and HIV can use TB preventive therapy with isoniazid (INH) to prevent progression to TB (Jai *et al.*, 2004 ;). The efficacy of INH in preventing TB in HIV-positive people has been proven. However, it must be administered to the patient for a long period, for at least six months. A two-month course of rifampicin and pyrazinamide daily can also be used instead of INH alone (Jai *et al.*, 2004; Mario *et al.*, 2001).

Short-course chemotherapy under the directly observed treatment (DOTS) strategy is as effective among HIV positive TB patients as in HIV negative patients in curing patients of TB. Thus, besides lowering individual suffering, implementing DOTS through effective TB control programme can reduce the transmission of TB infection, even in the context of increased HIV prevalence (Jai *et al.*, 2004; Mario *et al.*, 2001).

8. Conclusions and recommendations

As evidenced from the reviewed literatures, TB/HIV co-infection is an important emerging crisis all over the world particularly in Africa, including Ethiopia. Both re-activation of latent *M. tuberculosis* infection and primary infection of *M. tuberculosis* are common in HIV infected individuals. A mutual relationship has been observed between HIV and *M. tuberculosis* infections in that HIV infection leads to the progression of *M. tuberculosis* infection to active TB; while on the other hand, TB facilitates the progression of HIV infection to the stage of AIDS.

Thus it can be suggested that the resurgence of TB is attributed to HIV epidemic in developing as 60-70% of TB cases occur in HIV-1 infected individuals in developing countries.

On the basis of these remarks, the following recommendations were forwarded:

- ❖ Establishing functional collaboration between National HIV/AIDS and TB programme,
- ❖ Preventing HIV through behavioral change in the context of sexual practices, injecting drug uses and harmful traditional practice,
- ❖ Preventing the progression of TB infection to clinical TB through TB preventive therapy,
- ❖ Effective case management of patients with HIV associated TB or those with AIDS,
- ❖ Partnership- building for surveillance, advocacy and program management for the control of TB and HIV.

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