
HIV and tuberculosis in India

SOUMYA SWAMINATHAN* and G NARENDRAN

Department of Clinical Research, Tuberculosis Research Centre, Mayor VR Ramanathan Road, Chetput,
Chennai 600 031, India

*Corresponding author (Fax 91-44-2836 2528 ; Email, doctorsoumya@yahoo.com)

The global impact of the converging dual epidemics of tuberculosis (TB) and human immunodeficiency virus (HIV) is one of the major public health challenges of our time. The World Health Organization (WHO) reports 9.2 million new cases of TB in 2006 of whom 7.7% were HIV-infected. Tuberculosis is the most common opportunistic infection in HIV-infected patients as well as the leading cause of death. Further, there has been an increase in rates of drug resistant tuberculosis, including multi-drug (MDRTB) and extensively drug resistant TB (XDRTB), which are difficult to treat and contribute to increased mortality. The diagnosis of TB is based on sputum smear microscopy, a 100-year old technique and chest radiography, which has problems of specificity. Extra-pulmonary, disseminated and sputum smear negative manifestations are more common in patients with advanced immunosuppression. Newer diagnostic tests are urgently required that are not only sensitive and specific but easy to use in remote and resource-poor settings. Treatment of HIV-TB co-infection is complex and associated with high pill burden, overlapping drug toxicities, risk of immune reconstitution inflammatory syndrome (IRIS) and challenges related to adherence. From a programmatic point of view, screening of all HIV-infected persons for tuberculosis and vice-versa will help identify co-infected patients who require treatment for both infections. This requires good coordination and communication between the TB and AIDS control programs, in India.

[Swaminathan S and Narendran G 2008 HIV and tuberculosis in India; *J. Biosci.* **33** 527–537]

1. Introduction

The increasing rate of human immunodeficiency virus (HIV) infection in many countries has had an impact on tuberculosis (TB) epidemiology. While TB prevalence has remained stable, TB incidence continues to rise, especially in countries most severely affected by the HIV epidemic as well as those facing political turmoil, migration, poverty and unemployment and where intravenous drug abuse is rampant. HIV is the most important known risk factor that promotes progression to active TB in people with *Mycobacterium tuberculosis* infection (TB/HIV A Clinical Manual 2004). The lifetime risk of tuberculosis in immunocompetent

persons is 5% to 10%, but in HIV positive individuals, there is a 5% to 15% annual risk of developing active TB disease (Swaminathan *et al* 2000). WHO estimated 9.2 million new cases of TB globally in 2006 (139 per 100,000); of whom 7,09,000 (7.7%) were HIV positive (World Health Organization 2008). India, China, Indonesia, South Africa and Nigeria rank first to fifth in terms of incident TB cases.

In India, there were 2.5 million people living with HIV and AIDS (PLWHA) at the end of 2007 while the incidence of TB was approximately 1.8 million cases per year (WHO Release 2007, RNTCP 2008). In a survey carried out among new tuberculosis patients by the Revised National TB control Program (RNTCP) in 2007, HIV sero-prevalence

Keywords. Clinical features; control program; HIV; India; tuberculosis

Abbreviations used: DMC, designated microscopy centre; HIV, human immunodeficiency virus; ICTC, integrated counseling and testing centre; IRIS, immune reconstitution inflammatory syndrome; NRTIs, nucleoside reverse transcriptase inhibitors; NSAID, non-steroidal anti-inflammatory drug; PCP, Pneumocystis Jiroveci pneumonia; PGL, persistent generalized lymphadenopathy; PI, protease inhibitor; RNTCP, Revised National TB Control Program; TB, tuberculosis

varied widely and ranged from 1% to 13.8% across the 15 districts (Central TB Division, unpublished observations). Currently, it is not clear what role the HIV epidemic has played in the TB situation in India. If HIV prevalence in the community continues to increase, however, it could affect the TB control program, by decreasing cure rates and increasing mortality and recurrent TB. Further, appropriate management of patients with TB/HIV requires not only treating the tuberculosis but referring them for CD4 count testing and anti-retroviral treatment, if indicated.

2. Impact of HIV on TB manifestations

HIV infection is associated not only with an increased incidence of TB, but with altered clinical manifestations especially in the advanced stages. As HIV progresses, there is cutaneous anergy as well as impaired tissue containment of mycobacteria leading to widespread dissemination of mycobacteria. Figure 1 shows the increasing risk of tuberculosis as CD4 declines. In patients with latent TB infection, the risk of developing active disease is higher among recently infected persons compared to those with chronic infection but is several hundred-fold higher among persons who acquire HIV (figure 2). Further, among persons with HIV infection, newly acquired TB infection can rapidly progress to active disease.

It is clear that HIV infection acquired after TB infection is a significant risk factor for development of active TB - mainly due to its effects on the immune system. HIV is associated with decreased chemotaxis, defective granuloma formation and maintenance, impaired antigen processing

and presentation as well as generalized loss of CD4+ T cells and selective clonal depletion of *M-TB* specific CD4+ T lymphocytes (Lawn *et al* 2002). While TB can develop at any CD4 count, extrapulmonary and disseminated forms of the disease are more common as immunodeficiency increases.

Recently, Miranda *et al* (2007) demonstrated an 80% reduction in incident TB in HAART treated compared to ART-naïve HIV-infected persons in Brazil. It is likely that as access to ART improves world-wide, there will be a reduction in new TB cases, though rates would still be higher than in the general population.

3. Pulmonary TB

Pulmonary involvement occurs in about 75% of all HIV-infected patients with TB. (Deivanayagam *et al* 2001; Ahmad and Shameem 2005; TB/HIV: A Clinical Manual 2004). Unlike other opportunistic infections which have a selective range of CD4 in which the disease occurs, TB occurs throughout the course of HIV. The interaction between HIV and TB in persons coinfecting with HIV and TB is bidirectional and synergistic. Clinical presentation however depends on the level of immunosuppression. Typical manifestations are frequent in early HIV and atypical features begin to occur as the immunity declines with more frequent extra pulmonary manifestations ranging from 46 to 79% (Kumarasamy *et al* 2005; Sharma *et al* 2005). An HIV positive individual with any of the following symptoms should be suspected of having TB and investigated further: cough of more than 2 weeks duration, fever lasting more than

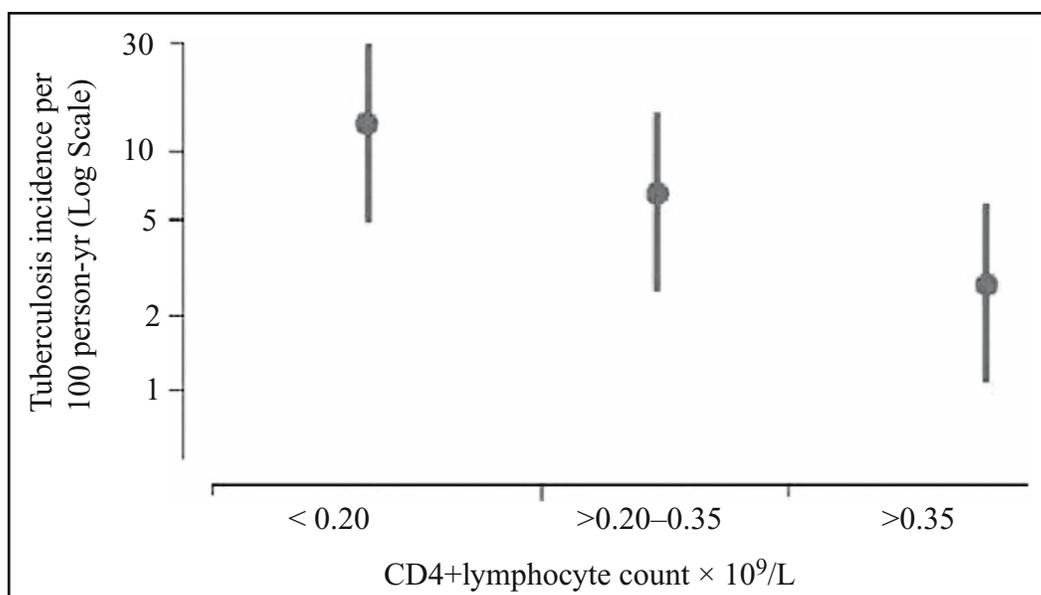


Figure 1. Risk of tuberculosis among HIV infected persons by CD4 + lymphocyte count (Antonucci *et al* 1995).

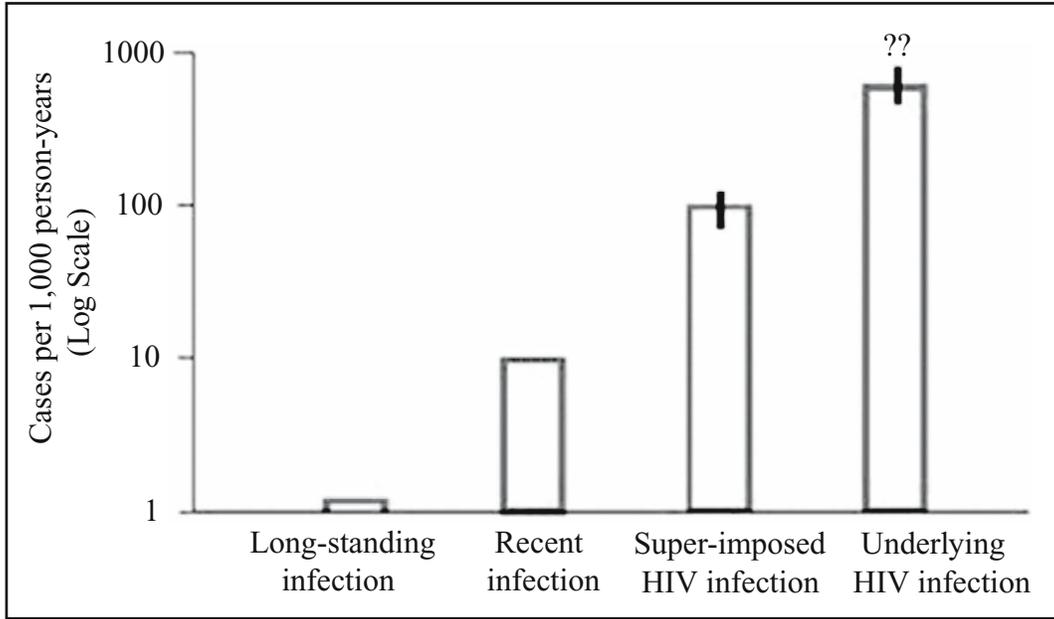


Figure 2. Risk of tuberculosis following tuberculous infection in individuals with chronic infection, recent infection and in those who acquire HIV infection (Rieder 1999).

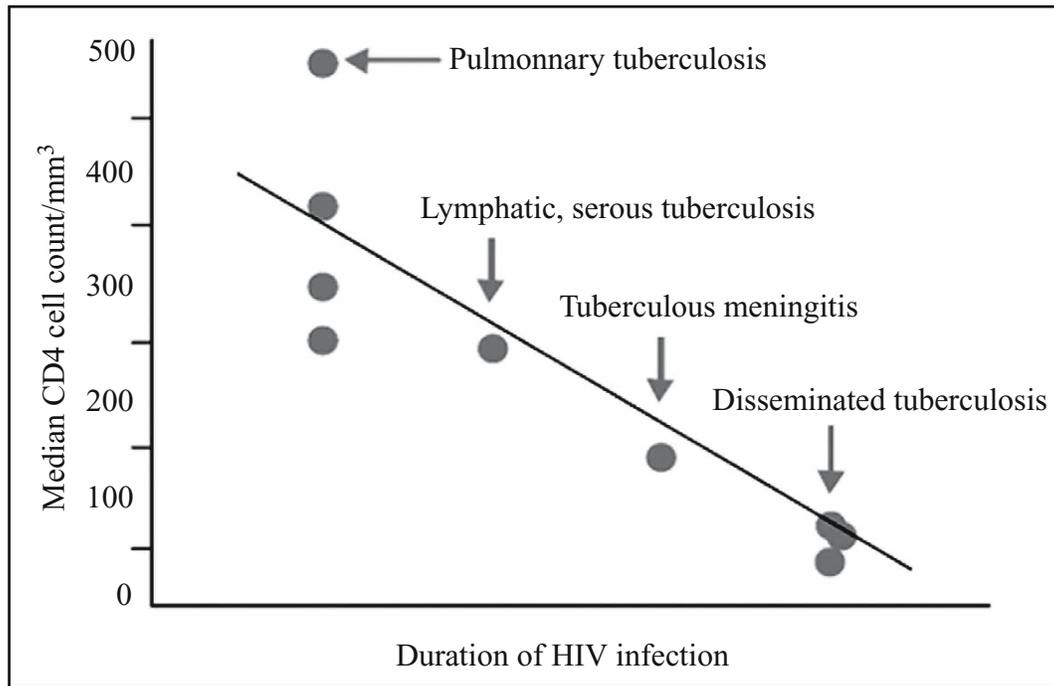


Figure 3. Clinical and immuno pathological course of HIV associated tuberculosis (De Cock *et al* 1992).

2–3 weeks, weight loss, fatigue, listlessness, unexplained dyspnoea, chest pain, or haemoptysis. Accelerated weight loss defined as greater than 10% weight loss in a month in HIV has earned the name “slimming disease”. Differential

diagnoses include bacterial or fungal pneumonias, *Pneumocystis Jiroveci* pneumonia (PCP), lymphoma and wasting syndrome. Cough with productive mucopurulent sputum is in favour of bacterial pneumonias including

TB whereas nonproductive cough with dyspnoea out of proportion to signs is in favour of PCP (TB/HIV A Clinical Manual 2004).

4. Extra pulmonary TB

Extra pulmonary TB is the commonest cause of pyrexia of unknown origin (PUO) among HIV+ individuals in developing countries (Rupali *et al* 2003; Kejarawal *et al* 2001). The most frequent extra pulmonary form of TB is involvement of the lymph nodes with cervical region being the commonest (Arora and Kumar 1999). Persistent generalized lymphadenopathy (PGL) simulates TB of the nodes. In PGL, nodes are symmetrical, asymptomatic and non-tender whereas in TB, lymph nodes are usually larger, asymmetric, painless and matted and maybe associated with constitutional symptoms or mediastinal/hilar adenopathy in the chest x-ray. Intrathoracic lymphadenopathy is not a feature of primary HIV syndrome and should always raise the suspicion of TB or lymphoma. Lymph node involvement in HIV is characterized by poor granuloma formation with abundant AFB picked up by Ziehl Neelsen stain (Havlir and Barnes 1999). Diagnosis can be easily made by FNAC (done as an out-patient procedure) or by lymph node biopsy. While *Mycobacterium tuberculosis* accounts for most mycobacterial infections in India, a small proportion are due to non-tuberculous mycobacteria like *M. avium intracellulare*, *M. fortuitum* etc. – molecular or high performance liquid chromatography (HPLC) assays are required to differentiate between species (Singh *et al* 2007). The other forms of extrapulmonary TB include pleural effusion, pericardial effusion, abdominal TB, TB meningitis and abdominal TB. Pleural effusion is usually unilateral and asymmetric, may be associated with parenchymal opacities.

Intra cranial space occupying lesions are common in HIV-infected individuals: the differential diagnosis includes cerebral toxoplasmosis, tuberculoma, neurocysticercosis, cryptococcoma and lymphoma. In India, cryptococcal meningitis is the commonest form of meningitis followed by TB meningitis. A finding that is strongly suggestive of disseminated TB is the detection of choroidal tubercles associated with miliary TB (Sahn and Neff 1974). Features of abdominal TB include hepatosplenomegaly with focal intra abdominal lymphadenopathy. Ascitis and omental thickening are less common in HIV (Fee *et al* 1995).

Mycobacteremia has been observed to be an important cause of PUO, particularly among patients with severe immunosuppression, but is difficult to diagnose as it requires facilities to perform blood culture using rapid culture techniques like BACTEC (Ramachandran *et al* 2002). In a study done in Africa, in patients with severe wasting at necropsy, nearly half had evidence of disseminated TB (Lucas *et al* 1994).

5. Investigations for diagnosis of TB

5.1 Sputum examination

Three sputum specimens should be collected for patients suspected to have TB, including at least one overnight collection. Smear should be stained by Ziehl–Neelsen (conventional microscopy) or Auramine rhodamine (fluorescent microscopy). The advantages of fluorescence over light microscopy for the detection of pulmonary TB have been confirmed in a systematic review of 45 studies comparing the 2 methods, which found that fluorescence microscopy yielded an average increase in sensitivity of 10% with no loss of specificity (Steingart *et al* 2006). In situations where all 3 smears are negative, the RNTCP recommends a course of broad-spectrum antibiotics (avoiding quinolones) and repeating sputum smear examinations and performing a chest x-ray if the patient is still symptomatic for chest disease (Agarwal and Chauhan 2005). WHO recently proposed a modified algorithm for severely ill patients suggesting that anti-TB treatment can be started based on non-response to antibiotics and a chest x-ray, within 3-5 days (WHO smear negative algorithm 2006). However, this approach needs to be validated in a low HIV-prevalence country like India.

Culture (on Lowenstein-Jensen medium) is much more sensitive but takes 6-8 weeks and requires specialized laboratory facilities and trained staff. Automated liquid culture systems that detect bacterial CO₂ production or O₂ consumption with radiometric (BACTEC), fluorescent (MGIT), colorimetric (MB/BacT system) or pressure sensors (ESP culture system II) roughly halve the time to detection and are being evaluated for use in resource-poor settings (Williams-Bouyer *et al* 2000; Lee *et al* 2003; Gil-Setas *et al* 2004). Molecular assays have been developed for rapid detection of growth as well as species identification and drug susceptibility testing. The 3 most widely used assays, polymerase chain reaction (PCR) (Roche Diagnostics), transcription mediated amplification (Genprobe) and strand-displacement amplification (Becton Dickinson) have shown excellent sensitivity, specificity and speed. Despite the clear advantages of these nucleic acid amplification tests over existing tests, especially for the rapid detection of smear negative disease, they have only limited use in TB endemic settings, primarily because of their cost and complexity.

6. Chest radiography

While radiography is a commonly performed investigation, it must be remembered that patients with HIV co-infection may not have typical radiographic features of pulmonary tuberculosis. While patients with higher CD4 cells (>350 cells/mm³) have radiographic abnormalities similar to their

HIV negative counterparts, patients with immunosuppression often have minimal or atypical findings (Long *et al* 1991). Diffuse pulmonary infiltrates/opacities are the dominant radiological presentation and cavitation is uncommon. Miliary pattern, mediastinal adenopathy and pleural effusion are more common and x-rays may be normal in 5-10% of HIV+ individuals (Swaminathan *et al* 2007). Differential diagnoses include PCP, non-tuberculous mycobacteria, nocardiosis, fungal infections and non-infective complications like lymphocytic interstitial pneumonitis. In the presence of a radiographic lesion suggestive of TB with negative sputum smears in an ambulatory patient, the best approach is to give a course of broad spectrum antibiotics (including co-trimoxazole) and repeat x-ray after 10-15 days. Lack of improvement or deterioration would indicate TB (TB/HIV A Clinical Manual 2004).

7. Tuberculin skin (Mantoux) test

Tuberculin skin reactivity is dependant on cytokine mediated cellular immunity. It has been used as a diagnostic test for tuberculosis infection: an induration of 5 mm or more, in response to 1 TU of PPD-RT 23 tuberculin is usually taken as a positive response, in HIV-infected individuals. In TB high prevalence countries like India, tuberculin skin testing has no value in TB diagnosis, as a positive test indicates prior infection only and false negativity (due to anergy or other unknown factors) is common. In a recent analysis, we found that even with the cut off of 5 mm universally practiced for TB in HIV, in India the positive predictive value of a TST for TB was 48.8% for patients with CD4 < 200 cells / mm³ and only 18.8 for patients with CD4 > 200 cells /mm³ (Swaminathan *et al* 2008). Anergy testing using polyvalent antigens like candida, tetanus toxoid, or mumps has been given up now because it is highly unreliable. Overall, tuberculin testing is not useful in routine practice either for diagnosis of TB or latent TB infection. An initially negative PPD may become positive when IRS occurs and this has been suggested as a marker for IRS (Lawn *et al* 2005).

8. Treatment of TB in HIV positive patients

Current guidelines recommend that irrespective of HIV status, tuberculosis requires a minimum of 6 months of treatment with 4 drugs (including rifampin) in the intensive phase and 2 drugs in the continuation phase. Treatment consists of INH (H), Rifampin (RIF), Ethambutol (EMB) and Pyrazinamide (PYZ) for 2 months followed by INH and RIF for 4 months, given either daily or intermittently. In India, under the RNTCP, patients with newly diagnosed TB receive a 6-month thrice-weekly regimen (Cat I – 2EHRZ₃/

4RH₃) while those with relapse, default or failure receive an 8-month regimen (Cat II – 2SEHRZ₃/1EHRZ₃/5EHR₃). Patients with smear negative pulmonary TB and localized extrapulmonary forms are treated with Cat III - 2HRZ₃/4RH₃, however this regimen should be avoided in persons with HIV infection.

While there have been no randomized clinical trials comparing daily and thrice-weekly treatment, observational studies have documented a higher risk of acquired rifampicin resistance when highly intermittent regimens are used in patients with advanced HIV disease (Nahid *et al* 2007). Factors that have been associated with higher failure and relapse rates along with increased mortality during treatment and follow-up are severe immunosuppression (CD4 < 100 cells/mm³), highly intermittent rifampicin administration, lack of rifampicin in the regimen used and duration of treatment of < 6 months. (Ackah *et al* 1995; Driver *et al* 2001; Jindani *et al* 2004; Lawn *et al* 2007a, b; Nahid *et al* 2007). The Tuberculosis Research Centre (TRC) found, in a pilot study of patients with advanced HIV and TB, a favourable response of 72% and an unfavourable response of 28% (including treatment failure and deaths) when treated with RNTCP Cat I regimen. Further, 37% of patients had died within 24 months of completing ATT. In general, HIV-infected patients with TB have higher mortality during and after treatment compared to HIV uninfected patients (Harries *et al* 2001; Nahid *et al* 2007; Swaminathan *et al* 2008). An ongoing randomized clinical trial at TRC is examining the benefits of a longer (9-month) regimen in reducing recurrences. Wider access to anti-retroviral treatment will help reduce mortality due to HIVTB.

9. Anti-retroviral treatment

Currently available antiretroviral agents fall in the following groups of drugs: Nucleoside reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitor (NNRTI's), Protease inhibitors (PI), Integrase inhibitors, Chemokine receptor antagonists and Entry (fusion) inhibitors. HAART refers to the use of a combination of at least 3 antiretroviral (ART) drugs to form a maximally suppressive regimen. Regimens recommended for use in India for patients with concomitant TB are a combination of 2 NRTI's with Efavirenz or less commonly Nevirapine. The NRTI combinations used commonly are Zidovudine with Lamivudine, Stavudine with Lamivudine, Tenofovir with Lamivudine, and rarely Abacavir with Lamivudine or Didanosine with Lamivudine (only the first two combinations are available in the national program) (National AIDS Control Organization 2007) There is some preliminary data to suggest that nevirapine can be safely given with rifampicin, but results of ongoing clinical trials are awaited

(Manosuthi *et al* 2006, 2008; Cohen *et al* 2008). Among the PI's, nelfinavir, saquinavir, lopinavir and ritonavir can be used but additive hepatotoxicity may occur with anti-TB drugs requiring close monitoring of liver function. (de Jong *et al* 2004).

Table 1 summarizes the WHO recommendations for timing of antiretroviral treatment initiation in HIV/TB patients. In our experience, about 2/3rd of HIV infected individuals have a CD4 < 200 cells/mm³ when they present with TB. Hence, the earlier use of ART is likely to reduce mortality and morbidity in this group of patients. Table 2 compares the advantages of early versus deferred ART in patients with TB. While the risks of IRIS and overlapping drug toxicities are present, the major advantage of early ART is the significant reduction in deaths.

10. Rifampicin –ART interactions and cytochrome P450 – 3A (CYP-3A) system

Rifamycins are unique in their ability to destroy both intracellular and intermittently and slowly growing TB bacilli and therefore form an indispensable component of anti-TB regimens. Non-Rifampicin containing regimens used to treat HIV-TB are associated with greater failure and relapse rates. (Jindani *et al* 2004; de Jong *et al* 2004). However, Rifamycins induce the CYP-3A enzyme system in the liver and intestinal wall, thereby increasing the metabolism of PI and non-nucleoside reverse transcriptase inhibitors (table 3). The effect is weaker with rifabutin than rifampin. Rifampin is metabolized through deacetylation and is not itself affected by the CYP-3A system. When rifampicin and antiretroviral drugs are given together, decreased trough levels may result, leading to therapeutic failure. Nevirapine levels are reduced by about 40–55%, efavirenz by 25% and delavirdine by 96% (McIlleron *et*

al 2007). It has been suggested that the dose of Efavirenz be increased to 800 mg when administered along with Rifampicin, but this may not be necessary in subjects weighing < 50 kg. In India, Efavirenz is the preferred drug for use in HIV-TB co infected individuals at the standard 600 mg dose. However, Nevirapine may be used in HIV-TB patients on concomitant ATT, when Efavirenz is contraindicated as in pregnancy, persons with psychiatric problems or due to toxicity. Alternatively, ATT may be modified with Rifabutin replacing rifampicin with the former given at a dose of 300 mg OD twice/thrice-weekly with nevirapine-based ART.

11. Toxicity

The overlapping toxicities due to the drugs commonly used for HIV associated TB are shown in table 4. Peripheral neuropathy which can be due to HIV *per se* can be further aggravated by Isoniazid, Stavudine and ddI. Almost all the

Table 2. Advantages of early vs deferred ART

Early ART	Deferred ART
Early mortality due to TB is reduced.	Decrease in toxicity
Improvement in cure rate, reduction in relapses	Drug interaction reduced.
Drug resistance caused by malabsorption can be minimized.	Decrease in IRS
Prevents other OI's simultaneously	ATT period can be used to lay a foundation for better adherence to ART
Period of Hospitalization reduced	Management of ATT toxicity is crucial for subsequent ART adherence

Table 1. WHO recommendations for starting ART in HIV-TB patients on ATT (World Health Organization 2006)

CD4 cell count	ART recommendations	Timing of ART in relation to start of TB treatment
CD4 <200 cells/mm ³	Recommend ART ^a	Between two and eight weeks ^b
CD4 between 200 and 350 cells/mm ³	Recommend ART	After eight weeks
CD4 >350 cells/mm ³	Defer ART ^c	Re-evaluate patient at eight weeks and at the end of TB treatment
Not available	Recommend ART ^d	Between two and eight weeks

^aAn EFV-containing regimen is the preferred first-line regimen. Alternative first-line treatment regimens include NVP or triple NRTI (based on TDF or ABC) regimens. For NVP-containing regimens, ALT should be checked at 4, 8 and 12 weeks; treatment should be decided on the basis of symptoms thereafter.

^bART should start as soon as TB treatment is tolerated, particularly in patients with severe immunosuppression.

^cART should be started if other non-TB stage 3 or 4 events are present.

^dFor some TB diagnoses that generally respond well to anti-TB therapy (ie, lymph node TB, uncomplicated pleural effusion), deferral of ART should be considered.

Table 3. Drug interactions of antiretroviral drugs with Rifampicin and Rifabutin

	Rifampicin (normal daily dose 600 mg)	Rifabutin (daily, unless mentioned; normal daily dose 300 mg)
NRTIs	Normal rifampicin dose	Normal rifabutin dose
NNRTIs		
Efavirenz	Efavirenz dose at 600mg	Increase rifabutin dose to 450-600 mg
Normal efavirenz dose		
Nevirapine	Probably can be used at normal nevirapine dose (more data required)	Normal dose each
Delavirdine	NR (not recommended)	NR
Protease inhibitors		
Amprenavir / Nelfinavir	NR	Lower rifabutin dose to 150 mg
Atazanavir	No data	Lower rifabutin dose to 150 mg three times weekly
Saquinavir	Can use with low-dose ritonavir "boost"	Normal rifabutin dose
Ritonavir	Use only with full-dose ritonavir	Lower rifabutin dose to 150 mg two times weekly
Lopinavir / ritonavir	Probably can be used with lopinavir / rotonavir dose increase to 400 / 400 mg or 800 / 200 mg	Lower rifabutin dose to 150 mg three times weekly

Modified from de Jong *et al* (2004).

Table 4. Overlapping toxicities between ATT and ART

	ATT	ART
Hepatotoxicity	H, R, Z,	NVP, NRTI's
Neuropathy	H	ddI, d4T,
Hyperuricemia	Z, E	ddI
Neuropsychiatric disturbances	H	EFZ
GI symptoms	All	All, especially PI's
Skin rashes	R, Z	NVP, EFZ, nelfinavir, Abacavir
Hematological	R	ZDV, PI's
Perioral numbness	Sm	Amprenavir
Nephrotoxic	R, E, Sm	ddI

drugs used are potentially hepatotoxic but the combination of Nevirapine and Rifampicin needs to be monitored closely. Thiacetazone should not be used in HIV+ individuals because of the risk of Stevens-Johnson syndrome. Co-trimoxazole can also produce cutaneous toxicity and has to be considered in the differential diagnosis of a skin rash. While Efavirenz can produce giddiness and sleep disturbances in the first few days/weeks of administration, rarely life-threatening psychiatric manifestations (depression, suicidal tendencies) can occur which require immediate termination of the drug. Most adverse effects of drugs are mild and can be managed symptomatically.

12. Anti-TB drug resistance

While overall patterns of drug resistance to first line anti-TB drugs are similar in HIV positive and negative patients, MDRTB is marginally higher (3-4%) in HIV positive patients with newly diagnosed TB (Swaminathan 2005). Rifampicin mono- resistance is more common in HIV infected patients and arises independently from mutations in drug susceptible strains. The mechanism is unclear but may be due to malabsorption of anti-TB drugs. Treatment for MDR-TB should ideally be based on drug susceptibility patterns and should employ at least 3-4 new drugs. The regimen should include an aminoglycoside and be given under direct observation. A typical regimen would consist of Inj Streptomycin or Kanamycin (three times a week) along with a combination of Ofloxacin, Ethambutol, Ethionamide, Pyrazinamide with or without Cycloserine or PAS given daily. The treatment should be continued for 18-24 months (for at least 12 to 18 months after the cultures have become negative). Outcome of MDR -TB in HIV is poor. A study from South Africa in 2003 has revealed 41% mortality among HIV-infected MDR-TB cases. In the New York study in 1996, the situation was no less different with 72% of MDR -TB cases with HIV dying during treatment. (Finlay *et al* 2004; Park *et al* 1996).

Recently, strains of *M. tuberculosis* labelled as extensively drug resistant (XDR) TB have emerged and spread rapidly through HIV-infected populations leading to high mortality (Andrews *et al* 2007). XDRTB has been reported from India

also (Singh *et al* 2007; Thomas *et al* 2007), and basically is a result of mismanagement of TB. XDRTB is practically untreatable and the best approach, therefore, is to prevent its emergence, by strengthening and supporting the TB control program.

13. TB-IRIS

Immune reconstitution inflammatory syndrome (IRIS) is defined as transient worsening or appearance of new symptoms, signs or radiographic manifestations after initiation of HAART. Tuberculosis is the most frequent pathogen associated with IRIS, of which, lymph node enlargement is the commonest manifestation. In one study, the incidence of IRIS in TB alone was 2%, with HIV co-infection it was 7%, and in those started on HAART it was 36% (Narita *et al* 1998). The median period of IRIS presentation is approximately 4–6 weeks after starting ART, however IRIS has been observed as early as one week after starting ART. Risk factors include high viral load, very low CD4 and initiation of ART soon after TB diagnosis. In TB IRIS, fever is the most frequent symptom, along with worsening infiltrates on chest x-ray. Other manifestations include enlargement and liquefaction of lymph nodes, appearance of fresh crops of nodes, pleural effusion, pericardial effusion, ascites, subcutaneous abscesses, expanding CNS lesions and visceral lesions (Burman and Jones 2001).

Two types of IRIS are observed

- (i) An unmasking of a previously latent or sub-clinical infection precipitated by HAART – induced immunologic changes occurring within 1–4 weeks of initiation of HAART (e.g.) MAC lymphadenitis, TB lymphadenitis and cryptococcal meningitis.
- (ii) Augmented host response to antigens present in low amounts in tissues (paradoxical response).

Risk factors for TB –IRIS include early initiation of ART within two months of starting ATT, low CD4, presence of extrapulmonary TB especially of the central nervous system, disseminated TB and high viral load (Lawn *et al* 2007a, b). The pathogenesis of IRIS includes a sharp amplification of Interferon-gamma producing mycobacteria-specific T cells along with an acute outpouring of Th1 cytokines (Borgarit 2006). It is likely that CD4 + T cells are not the only mediators of IRIS; therefore an increase in CD4 cell count with HAART does not necessarily correlate with the development of IRIS (Manabe *et al* 2007). Hypercalcemia is a strange but frequent manifestation in TB-related IRIS. It is probably related to increased production of 125 dihydroxy cholecalciferol in functioning granulomas. A simple way of demonstrating IRIS is restoration of DTH response to PPD. Interferon gamma secretion and cell mediated immune

response to mycobacteria are restored leading to restoration of DTH skin test response to mycobacterial antigens. Thus HAART reverses the impact of HIV on the host granulomatous response to mycobacteria. But the rapidly compensating inflammatory response damages the tissues that characterize IRIS. (Lawn *et al* 2005)

The differential diagnoses include treatment failure, progression of TB, superadded infections and drug reaction. The best way to tackle IRS is to rule out and treat common, endemic causes of fever first. Most IRIS responds to non-steroidal anti-inflammatory drugs (NSAIDs) along with continuation of ART. A course of steroids (Prednisolone 1 mg/kg body weight) tapered over 4–6 weeks may be required when fever/constitutional symptoms prevail despite NSAID treatment or life-threatening symptoms occur. Thalidomide and pentoxifylline have also been tried as anti-inflammatory agents (Lawn *et al* 2005). Rarely, ART needs to be terminated.

14. Preventive therapy (Chemoprophylaxis) for TB in India

Several randomized clinical trials in HIV-infected persons have shown that the incidence of TB can be reduced by 40–60% by preventive therapy (Woldehanna and Volmink 2004; Mohammed *et al* 2007). The standard regimen is Isoniazid for 12 months, though several short-course regimens like 2RZ and 3RH have been tried and found to be equivalent. However, adverse reactions tend to be higher with multi-drug regimens and the 2RZ regimen is no longer recommended because of a high incidence of hepatotoxicity, including several fatal cases in HIV un-infected persons (Narita *et al* 2002). Standard recommendations in USA, UK etc include giving preventive therapy to all PPD-positive (>5 mm) HIV positive persons, after ruling out active TB.

Presently, there is no national policy regarding TB preventive therapy for HIV positive persons in India. A clinical trial being conducted at the Tuberculosis Research Centre, Chennai is investigating two different regimens: a 6-month regimen of ethambutol and INH vs. a 3-year regimen of INH alone, in order to establish the ideal duration of therapy. In a TB-endemic country like India, consideration must be given to providing preventive therapy to HIV-infected persons regardless of Mantoux status. This is because the prevalence of TB in the community is high with a constant risk of exposure as well as the fact that the Mantoux test has many pitfalls in interpretation. TB preventive therapy should form part of the care and support package for HIV+ persons that includes co-trimoxazole prophylaxis, nutritional counseling and supplementation and anti-retroviral treatment. It needs to be delivered through integrated counseling centres or anti-retroviral treatment centres, where HIV+ individuals are followed over the long term.

15. Coordination between TB and AIDS control programs

At the national level, there is a concerted effort to achieve coordination between the designated microscopy centre (DMC) of the RNTCP and the integrated counselling and testing centers (ICTC) of the HIV/AIDS control program. The objective is to promote early diagnosis and treatment of TB in HIV infected individuals and vice versa. All ICTC clients with suggestive symptoms are referred by the counselor to the nearest microscopy centre for investigations to rule out TB. In 2007, approximately 5% of all diagnosed TB cases in India came from ICTCs, demonstrating that these are excellent sites for active TB case finding (RNTCP report 2008). Further, the yield of cases was similar (approximately 20%) from HIV infected and uninfected clients. Counselors need ongoing training to improve their knowledge about TB diagnosis and treatment. One of the programmatic limitations encountered is the lack of investigations for extrapulmonary TB at peripheral health facilities; another is the distance between DMCs and ICTCs in some districts. The system works much better when both are located in the same site.

Till a few months ago, TB patients were offered HIV testing only when the physician suspected HIV, due to co-existing symptoms or signs (selective testing). Recently, the National AIDS Control Organization has taken a decision to routinely offer HIV testing to all diagnosed TB patients in the high-prevalence states. Our study on 4000 TB patients demonstrated that over 2/3rds were willing to undergo an HIV test and the major barrier to acceptance was patients not perceiving themselves to be at risk (Thomas *et al* 2007). If patients are counseled and explained the importance of having an HIV test, when they are diagnosed with TB, most will accept the test.

With increasing availability of ART across the country, diagnosis of HIV is beneficial to the individual as he/she can be referred to the nearest ART centre for evaluation and initiation of antiretroviral treatment, if indicated. Tuberculosis clinics, therefore, form an important entry point for HIV diagnosis, care and support. Further, the counseling that patients receive as part of the process of testing will help prevent new infections in the future. Coordination and cross-talk between these two government health programs is crucial not only to improve the outcome of HIV-infected TB patients but also to control the burden of tuberculosis in India.

References

- Ackah A N, Coulibaly D, Digbeu H, Diallo K, Vetter K M, Coulibaly I M, Greenberg A E, De Cock K M 1995 Response to treatment, mortality and CD4 lymphocyte counts in HIV infected persons with tuberculosis in Abidjan, Cote d'Ivoire; *Lancet* **345** 607–610
- Agarwal S P and Chauhan L S 2005 *Tuberculosis control in India* (Elsevier, a division of Reed Elsevier India Private Limited)
- Ahmad Z and Shameem M 2005 Manifestations of Tuberculosis in HIV Infected Patients; *JIAACM* **6** 302–305
- Andrews J R, Shah N S, Gandhi N, Moll T, Friedland G; Tugela Ferry Care and Research (TF CARES) Collaboration 2007 Multidrug-resistant and extensively drug-resistant tuberculosis: implications for the HIV epidemic and antiretroviral therapy rollout in South Africa; *J. Infect. Dis. (Suppl. 3)* **196** S482–S490
- Antonucci G, Girardi E, Raviglione M C, Ippolito G 1995 Risk factors for tuberculosis in HIV-infected persons: A prospective cohort study; *JAMA* **274** 143–148
- Arora V K and Kumar S V 1999 Pattern of opportunistic pulmonary infections in HIV sero-positive subjects: observations from Pondicherry, India; *Indian J. Chest Dis. Allied Sci.* **41** 135–144
- Burman W J and Jones B E 2001 Treatment of HIV-related Tuberculosis in the Era of Effective Antiretroviral Therapy; *Am. J. Respir. Crit. Care Med.* **164** 7–12
- Cohen K, van Cutsem G, Boule A, McIlleron H, Goemaere E, Smith P J and Maartens G 2008 Effect of rifampicin-based antitubercular therapy on nevirapine plasma concentrations in South African adults with HIV-associated tuberculosis; *J. Antimicrob. Chemother.* **61** 389–393
- De Cock K M, Soro B, Coulibaly I M and Lucas S B 1992 Tuberculosis and HIV infection in sub-Saharan Africa; *JAMA* **268** 1581–1587
- de Jong B C, Israelski D M, Corbett E L and Small P M 2004 Clinical management of tuberculosis in the context of HIV infection; *Annu. Rev. Med.* **55** 283–301
- Deivanayagam C N, Rajasekaran S, Senthilnathan V, Krishnarajasekhar R, Raja K, Chandrasekar C, Palanisamy S, Samuel Dinesh A, Jothivel G and Elango S V 2001 Clinico-radiological spectrum of tuberculosis among HIV sero-positives - a Tambaram study; *Indian J. Tuberc.* **48** 123–127
- Driver C R, Munsiff S S, Li J, Kundamal N and Osahan S S 2001 Relapse in persons treated for drug susceptible tuberculosis in a population with high co-infection with Human Immunodeficiency virus in New York City; *Clin. Infect. Dis.* **33** 1762–1769
- Emergence of XDR-TB WHO concern over extensive drug resistant TB strains that are virtually untreatable 2006; accessed from <http://www.who.int/mediacentre/news/notes/2006/np23/en/print.html> on 25/05/08
- Fee M J, Oo M M, Gabayan A E, Radin D R and Barnes P F 1995 Abdominal tuberculosis in patients infected with the human immunodeficiency virus; *Clin. Infect. Dis.* **20** 938–944
- Finlay A F, Walt M V, Holtz T H, Thorpe L E, Wells C D and Weyer K 2004 Treatment outcome of patients with multidrug resistant tuberculosis in south Africa using a standardized regimen, 1999–2000 (abstract 584); in *Program and abstracts of the infectious diseases* (Society of America 2004 Annual Meeting Alexandria, VA: infectious Disease society of America) p. 155
- Gil-Setas A, Torroba L, Fernandez J L, Martinez-Artola V and Olite J 2004 Evaluation of the MB/BacT system compared with Middlebrook 7H11 and Lowenstein-Jensen media for detection and recovery of mycobacteria from clinical specimens; *Clin. Microbiol. Infect.* **10** 224–228

- Harries A D, Hargreaves N J, Jindani A, Enarson D A, Meher D and Salaniponi F M 2001 Deaths from tuberculosis in Sub-Saharan African countries with a high prevalence of HIV -1; *Lancet* **357** 1519–1523
- Havir D V and Barnes P F 1999 Tuberculosis in patients with human immunodeficiency virus infection; *N. Engl. J. Med.* **340** 367–373
- Jindani A, Nunn A J and Enarson D A 2004 Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomized trial; *Lancet* **364** 1244–1251
- Kejarawal D, Sarkar N, Chakraborti S K, Agarwal V and Roy S 2001 Pyrexia of unknown origin: a prospective study of 100 cases; *J. Postgrad. Med.* **47** 104–107
- Kumarasamy N, Vallabhaneni S, Flanigan T P, Mayer K H and Solomon S 2005 Clinical profile of HIV in India; *Indian J. Med. Res.* **121** 377–394
- Lawn S D, Bekker L G and Miller R F 2005 Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals; *Lancet Infect. Dis.* **5** 361–373
- Lawn S D, Butera S B and Shinnick T M 2002 Tuberculosis unleashed: the impact of HIV infection on the host granulomatous response to mycobacterium tuberculosis; *Microbes Infection* **4** 635–646
- Lawn S D, Myer L, Bekker L G and Wood R 2007 Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa; *AIDS* **21** 335–341
- Lawn S, Myer L, Bekker L G and Wood R 2007 *Early mortality among patients with HIV associated TB in Africa: Implications for the time to initiate ART* (Conference on Retroviruses and Opportunistic Infections: Abstract 81)
- Lee J J, Suo J, Lin C B, Wang J D, Lin T Y and Tsai Y C 2003 Comparative evaluation of the BACTEC MGIT 960 system with solid medium for isolation of mycobacteria; *Int. J. Tuberc. Lung Dis.* **7** 569–574
- Long R, Maycher B, Scalcini M and Manfred J 1991 Chest roentgenogram in pulmonary tuberculosis patients seropositive for HIV type I; *Chest* **99** 123–127
- Lucas S B, De Cock K M, Hounnou A, Peacock C, Diomande M, Hondé M, Beaumel A, Kestens L and Kadio A 1994 Contribution of tuberculosis to slim disease in Africa; *BMJ* **308** 1531–1533
- Manabe Y C, Campbell J D, Sydnor E and Moore R D 2007 Immune reconstitution inflammatory syndrome: risk factors and treatment implications; *J. Acquir. Immune Defici. Syndr.* **46** 456–462
- Manosuthi W, Mankatitham W, Lueangniyomkul A, Chimsuntorn S and Sungkanuparph S 2008 Standard-dose efavirenz vs. standard-dose nevirapine in antiretroviral regimens among HIV-1 and tuberculosis co-infected patients who received rifampicin; *HIV Med.* **9** 294–299
- Manosuthi W, Sungkanuparph S, Thakkinstian A, Rattanasiri S, Chaovavanich A, Prasithsirikul W, Likanonsakul S and Ruxrungtham K 2006 Plasma nevirapine levels and 24-week efficacy in HIV-infected patients receiving nevirapine-based highly active antiretroviral therapy with or without rifampicin; *Clin. Infect. Dis.* **43** 253–255
- McIlleron H, Meintjes G, Burman W J and Maartens G 2007 Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome; *J. Infect. Dis. (Suppl. 1)* **196** S63–S75
- Miranda A, Morgan M, Jamal L, Laserson K, Barreira D, Silva G, Santos J, Wells C, Paine P and Garrett D 2007 Impact of antiretroviral therapy on the incidence of tuberculosis: the Brazilian experience, 1995–2001; *PLoS ONE* **2** e826
- Mohammed A, Myer L, Ehrlich R, Wood R, Cilliers F and Maartens G 2007 Randomised controlled trial of isoniazid preventive therapy in South African adults with advanced HIV disease; *Int. J. Tuberc. Lung Dis.* **11** 1114–1120
- Nahid P, Gonzalez L C, Rudoy I, De long B C, Unger A and Kawamura L M 2007 Treatment outcomes of patients with HIV and tuberculosis; *Am. J. Respir. Crit. Care Med.* **175** 1196–1206
- Narita M, Ashkin D, Hollender E S and Pitchenik A E 1998 Paradoxical worsening of tuberculosis following Antiretroviral therapy in patients with AIDS; *Am. Crit. Care* **158** 157–161
- Narita M, Kellman M, Franchini D L, McMillan M E, Hollender E S and Ashkin D 2002 Short course rifampicin and pyrazinamide treatment for latent tuberculosis infection in patients with HIV infection: the 2 year experience of a comprehensive community based programme in Broward county, Florida; *Chest* **122** 1292–1298
- National AIDS Control Organization 2007 *Antiretroviral therapy guidelines for HIV-infected adults and adolescents including post-exposure prophylaxis* (Section A7)
- Park M M, Davis A L, Schluger N W, Cohen H and Rom W N 1996 Outcome of MDR –TB patients, 1983–1993: prolonged survival with appropriate therapy; *Am. J. Respir. Crit. Care Med.* **153** 317–324
- Ramachandran R, Swaminathan S, Somasundaram S, Asgar V N, Paramesh P and Paramasivan C N 2002 Mycobacteremia in tuberculosis patients with HIV infection; *Indian J. Tuberc.* **50** 29–31
- Rieder H L 1999 *Epidemiological basis of tuberculosis control* First edition [International Union against Tuberculosis and Lung Diseases (UNION)] pp 50–52
- Rupali P, Abraham O C, Zachariah A, Subramanian S and Mathai D 2003 Aetiology of prolonged fever in antiretroviral-naïve human immunodeficiency virus-infected adults; *Natl. Med. J. India* **16** 193–199
- Sahn S A and Neff T A 1974 Miliary tuberculosis; *Am. J. Med.* **56** 494–505
- Sharma S K, Mohan A and Kadhiravan T 2005 HIV-TB co-infection: epidemiology, diagnosis & management; *Indian J. Med. Res.* **121** 550–567
- Singh S, Gopinath K, Shahdad S, Kaur M, Singh B and Sharma P 2007 Nontuberculous mycobacterial infections in Indian AIDS patients detected by a novel set of ESAT-6 polymerase chain reaction primers; *Jpn. J. Infect. Dis.* **60** 14–18
- Singh S, Sankar M M and Gopinath K 2007 High rate of extensively drug-resistant tuberculosis in Indian AIDS patients; *AIDS* **21** 2345–2347
- Steingart K R, Henry M, Ng V, Hopewell P C, Ramsay A, Cunningham J, Urbanczik R, Perkins M, Aziz M A and Pai M 2006 Fluorescence versus conventional sputum smear

- microscopy for tuberculosis: a systematic review; *Lancet Infect. Dis.* **6** 570–581
- Swaminathan S, Deivanayagam C N, Rajasekaran S, Venkatesan P, Padmapriyadarsini C, Menon P A, Ponnuraja C and Dilip M 2008 Long term follow up of HIV-infected patients with tuberculosis treated with 6-month intermittent short course chemotherapy; *Natl. Med. J. Indian* **21** 3–7
- Swaminathan S, Narendran G, Menon P A, Padmapriyadarsini C, Arunkumar N, Sudharshanam N M, Ramesh Kumar S and Chandrasekhar S 2007 Impact of HIV infection on radiographic features in patients with pulmonary tuberculosis; *Indian J. Chest Dis. Allied Sci.* **49** 133–136
- Swaminathan S, Paramasivan C N, Ponnuraja C, Iliayas S, Rajasekaran S and Narayanan P R 2005 Anti-tuberculosis drug resistance tuberculosis in South India; *Int. J. Tuberc. Lung Dis.* **9** 896–900
- Swaminathan S, Ramachandran R, Baskaran G, Paramasivan C N, Ramanathan U, Venkatesan P, Prabhakar R and Datta M 2000 Risk of development of tuberculosis in HIV infected patients; *Int. J. Tuberc. Lung Dis.* **4** 839–844
- Swaminathan S, Subbaraman R, Venkatesan P, Subramanyam S, Ramesh Kumar S, Mayer K H and Narayanan P R 2008 Tuberculin skin test results in HIV-infected patients in India: Implications for latent tuberculosis treatment; *Int. J. Tuberc. Lung Dis.* **12** 168–173
- TB/HIV, A Clinical Manual, WHO 2004 accessed from <http://libdoc.who.int/publications/2004/9241546344.pdf> on 25/05/2008
- Thomas A, Ramachandran R, Rehman F, Jaggarajamma K, Santha T, Selvakumar N, Krishnan N, Mohan N S, Sundaram V, Wares F and Narayanan PR 2007 Management of multi drug resistance tuberculosis in the field: Tuberculosis Research Centre experience; *Indian J. Tuberc.* **54** 117–124
- Thomas B E, Ramachandran R, Anitha S, Swaminathan S 2007 Feasibility of routine HIV testing among TB patients through a Voluntary, Counseling and Testing Centre (VCTC); *Int. J. Tuberc. Lung Dis.* **11** 1296–1301
- WHO Smear Negative Algorithm 2006 Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents; Accessed from http://www.who.int/tb/publications/2006/tbhiv_recommendations.pdf
- William R and Stuart G 2004 *Tuberculosis* (New York: Lippin Cott Williams and Wilkins)
- Williams-Bouyer N, Yorke R, Lee H I and Woods G L 2000 Comparison of the BACTEC MGIT 960 and ESP culture system II for growth and detection of mycobacteria; *J. Clin. Microbiol.* **38** 4167–4170
- Woldehanna S and Volmink J 2004 Treatment of latent tuberculosis infection in HIV infected persons; *Cochrane Database Syst. Rev.* **1** CD000171
- World Health Organization 2006 Initiating First-Line ART in Relationship to Starting Anti-TB Therapy; accessed from <http://www.womenchildrenhiv.org/wchiv?page=charts-00-13> on 25/05/2008
- World Health Organization 2008. *Global tuberculosis control: surveillance, planning, financing*. WHO report 2008. WHO/HTM/TB/2008.393. Geneva

ePublication: 15 October 2008