HIV and Tuberculosis

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ABSTRACT

Tuberculosis is a major public health problem worldwide for centuries. TB is one of the commonest opportunistic infections in HIV infected patients and is of particular importance because it is contagious by respiratory route, readily treatable and potentially preventable by chemoprophylaxis. TB was endemic before the HIV epidemic in India. The growing HIV epidemic has breathed a new life in to the old enemy. The interaction between TB and HIV is lethal. TB adds to burden of illness of HIV infected people and shortens their life-expectancy, while the HIV epidemic spurs the spread of TB. TB in HIV infected patients raises important issues, like atypical presentations, drug - drug interactions, paradoxical worsening, MDR-TB and associated polymicrobial infections (e.g. MTB, *Pneumocystis carinii* pneumonia (PCP), CMV, candida colonization and bacterial infections etc.) particularly in advanced disease.

EPIDEMIOLOGY

Around one out of three people on earth are infected with the germ that can lead to tuberculosis. Prevalence is highest in condition of poverty and overcrowding. In some of the developing world's poorest and most overcrowded cities, up to 80% of the adults carry the TB germ.[1] In the year 2000, the revised estimates of global HIV/TB burden indicate that 9% out of a total 8.3 million new TB cases in adults (15-49 years) were attributable to HIV infection. There were an estimated 1.8 million deaths from TB, of which 12% were attributable to HIV. **Tuberculosis** was the immediate cause of 11% of all adult AIDS deaths.[2] There are more than 52,000 deaths per week attributable to TB and more than 40% are in Southeast Asia. Of the nearly 6 million adults living with HIV in the South-East Asia region, about 40-50% is likely to be infected with TB.

Etiology

M. tuberculosis is the commonest organism responsible for human diseases. Infection by MAC and other atypical mycobacteria is uncommon. Co-infection is common in young males. Hispanic, Blacks, prisoners and persons living in groups are more vulnerable to tuberculosis.

PATHOGENESIS

Effect of HIV on tuberculosis

HIV-infected persons are at markedly increased risk for progressive primary or reactivation of latent tuberculosis[3,4] and for second episodes of tuberculosis from exogenous reinfection.[5] Susceptibility to tuberculosis is related to the pattern of cytokines produced by T lymphocytes. T1 lymphocytes, which produce interferon-γ, are central to antimycobacterial immune defenses, and fatal mycobacterial disease develops in children who lack the interferon-γ receptor.[6] Peripheral-blood lymphocytes from HIV-infected patients with TB produce less interferon-γ as compared with lymphocytes from HIV-negative patients with tuberculosis on exposure to M.TB.[7] These findings suggest that the reduced T1 response in HIV-infected patients contributes to their susceptibility to tuberculosis. HIV is the most powerful known risk factor for reactivation of latent MTB infection to active TB disease. Annual risk of progressing to active TB disease from latent MTB infection in HIV infected patient ranges from 5% to 15%, compared 7% to 10% lifetime risk for progressing to active TB disease among people without HIV infection.[8] Individuals with preexisting HIV infection who become newly infected with MTB carry a higher risk of progression to active TB. In addition, there is an increased risk of TB transmission to the general community, whether or not HIV-infected and concomitant emergence of strains of multidrug-resistant MTB.[8]

Effect of TB on HIV

M. tuberculosis probably increases HIV replication by inducing macrophages to produce tumor necrosis factor-α, interleukin-1, and interleukin-6.[9,10] Patients with TB have higher plasma HIV-1 RNA levels and a more rapid progression of HIV disease than comparable patients without TB. The host immune response to MTB enhances HIV replication and might also accelerate the natural progression of HIV disease. Mortality in HIV-infected patients with TB matched for CD4+ cell counts is twice that in HIV-infected patients without TB.[11] In this population most

deaths are caused by progression of HIV disease, rather than by TB itself. Thus, people with HIV/TB co-infections carry higher risks of other opportunistic diseases. Increased HIV RNA levels in HIV/TB co-infected patient decreases with successful therapy of tuberculosis. The degree of immunosuppression is the most important predictor of survival in HIV-infected patients with tuberculosis. Negative tuberculin skin tests, prior opportunistic infections, and low CD4 cell counts are associated with increased mortality.

CLINICAL FEATURES

Tuberculosis can occur at any point in the course of HIV infection. If TB occurs in the early stages of HIV infection, the clinical features are more like typical pulmonary tuberculosis, commonly with upper lobe cavitations, and the disease resembles that seen in pre-HIV era.[12] As immunodeficiency advances, HIV-infected patients present with atypical pulmonary disease resembling primary pulmonary tuberculosis or extra-pulmonary and disseminated disease. The pulmonary TB in advanced HIV disease commonly presents with mediastinal lymphadenopathy and lower lobe involvement. Pulmonary cavitations and granuloma formation in tissues is less common in presence of marked immunosuppression. In the extra-pulmonary disease the commonly involved sites are lymph nodes (peripheral, mediastinal, abdominal), pleura, pericardium, spleen, liver, kidneys, intestine, meninges, brain parenchyma, joint, bone marrow and disseminated disease involving multiple sites are common. Visceral lesions and intra-abdominal lymphadenopathy with necrosis characterize the clinical presentation of abdominal tuberculosis in HIV-infected patients, while ascites and omental thickening the characteristic of abdominal tuberculosis in HIV-negative patients are absent.[13] The clinical presentation of tuberculous meningitis is similar in HIV-infected patients and in immunocompetent patients, except that intracerebral mass lesions are more common in HIV-infected patients.[14] Whether patients have pulmonary/extrapulmonary or both diseases, almost all patients have systemic manifestations of tuberculosis (fever, anorexia, weight loss, night sweats, and cough). In addition to manifestations of tuberculosis one should look for other OIs commonly seen in HIV infected patients like oral thrush, PCP, diarrhea, OHL, seborrheic dermatitis etc.

DIAGNOSIS

Tuberculin test

Though useful for measuring the prevalence of tuberculous infection in a community, it has limited value for the diagnosis of TB infection in adults in India, though it can be used as an adjunct to diagnose childhood TB. In HIV infected persons induration of 5mm or more is considered as positive.[15] In HIV and TB co-infection there is a reduction in the proportion of those reacting to PPD as the CD4 count falls, from 50%-90% in those who have a CD4 count of >500 cells down to 0% - 20%, in those patients who have AIDS or advanced HIV infection and a CD4 count of <200cells/cmm. This limits the tuberculin test as a diagnostic tool. Specific non-reactivity to PPD is difficult to distinguish from the general poor immune responsiveness seen in HIV patients. The results of anergy testing using a panel of antigens gives inconsistent and ambiguous results and is no longer recommended for routine use in TB screening programme of HIV infected persons.[16-18]

Sputum Microscopy:

It is the cornerstone of diagnosis of TB even in high HIV-prevalence areas. Patients suspected of having TB should have three consecutive morning sputum specimens examined for acid-fast bacilli (AFB). HIV-infected, smear positive patients tend to excrete significantly fewer organisms per ml of sputum than HIV- negative patients, which can lead to AFB being missed if the appropriate number of sputum samples as well as high power fields is not examined by microscopy. Approximately 5 percent of HIV-infected patients with pulmonary tuberculosis have positive results on acid-fast staining of sputum, despite normal chest radiographs.[12]

Chest X-Ray

In all HIV infected patients chest radiograph should be done at the time of first evaluation, regardless of PPD status. In addition chest radiograph should be done in all persons suspected of active tuberculosis and in all persons with a newly positive PPD.[15] No radiographic pattern is pathognomonic of TB, although the classical hallmarks of the disease are cavitation, apical distribution, pulmonary fibrosis, shrinkage and calcification as seen in patients with well-preserved immune function. However, as immune suppression worsens, chest X-rays more often show atypical findings such as pulmonary infiltrates affecting the lower lobes, intrathoracic lymphadenopathy, military tuberculosis and rarely a normal chest radiograph.[19] Disease other than TB can cause both the classical and atypical chest X-ray findings, and if sputum smears are negative, other conditions have to be considered in the differential diagnosis. Important HIV-related pulmonary diseases, which may be confused with pulmonary tuberculosis, are bacterial pneumonia, *Pneumocystic carinii* pneumonia, Kaposi's sarcoma, fungal infections and nocardiosis.

Extra-Pulmonary Tuberculosis

Extrapulmonary disease has been reported in up to 70% of HIV-related TB cases when the CD4 lymphocyte count is less than 100. The definitive diagnosis of extrapulmonary TB is often difficult because of the paucity of diagnostic facilities, and at times difficulty in accessing the affected tissue for intervention. HIV-related TB lymphadenopathy can occasionally be acute and resemble an acute pyogenic bacterial infection. Fine needle aspiration cytology of the lymph node and histopathological examination of lymph nodes biopsy for macroscopic caseation, typical tuberculous granulomas, examination of direct smears from the cut surface for AFB and culture of specimen can make diagnosis. In TB meningitis, the examination of CSF is a useful tool. The CSF must always be subjected to an India-ink preparation to exclude cryptococcal meningitis. Pericardial TB is not rare and may be diagnosed presumptively on the characteristic radiological appearance. Evidence of tuberculosis elsewhere may provide circumstantial evidence in favor of the diagnosis. A pericardial tap and examination of pericardial fluid may also provide very useful information. However it should be undertaken only in appropriately well-equipped facility. Ultrasonography or CT scan examination of abdomen are

useful in finding out lymphadenopathy, infiltrations in spleen and liver, ascites, thickening of bowel wall seen in HIV infected TB patient. CT scans of other organ (brain, chest) are helpful in identifying lesions of tuberculosis. Mycobacteremia occurs in patients with disseminated as well as disease localized to the lungs. Blood cultures and bone marrow examination for acid-fast bacilli should be performed whenever suspicion of tuberculosis is strong.[15] Biopsy for histopathological examination, cultures and other diagnostic tests will be indicated based on site of infection.

TREATMENT OF TUBERCULOSIS

Aims of TB treatment

Treatment of tuberculosis has benefits to the individual and also to the community. The aims of TB therapy are:

i. To cure the patient of TB and
ii. To minimize the transmission of *Mycobacterium tuberculosis* to community.

Effective TB treatment also helps in reducing progressions of HIV infection.

Recommendations for the treatment of tuberculosis in HIV infected adults are similar to those for HIV uninfected adults.

Treatment Regimen

The treatment regimen for all adults with previously untreated tuberculosis should consist of two phases;

Phase 1: A two-month initial phase of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB).

Followed by phase 2, a continuation phase of treatment is given for either 4 or 7 months.

Seven-month continuation phase

Seven month continuation phase is recommended for certain groups: e.g.

i. Patients with cavitary pulmonary tuberculosis caused by drug susceptible organisms and whose sputum culture obtained at the time of completion of 2 months of treatment is still positive.
ii. Patients with drug susceptible organisms whose initial phase of treatment did not include PZA.
iii. A ten-month continuation phase for patients with CNS involvement e.g. meningitis, tuberculomata.

Treatment for a defined number of days without accounting for the number of doses taken can result in undertreatment. Treatment endpoint is based on the total number of doses taken—not solely on the duration of therapy e.g. 1) A 6 month daily (given 7 days/week) regimen should consist of at least 182 doses of INH and RIF, and 56 doses of PZA. 2) If the drugs are administered by DOT at 5 days/week, the minimum number of doses is 130. It is recommended that all of the doses for the *initial* phase to be taken within 3 months and those for the 4 month *continuation* phase to be taken within a 6 month period. Thus 6-month regimen should therefore be completed by 9 months.

Few recommendations:

1. Intermittent treatment regimens are contra-indicated in HIV infected patients because of unacceptably high rates of relapse.
2. Adherence strategies including directly observed therapy (DOT) are especially important for patients with HIV related tuberculosis.
3. Look for drug malabsorption in advanced HIV infection, drug-drug interactions with antiretrovirals especially PIs, NnRTI and fluconazole.

Hepatotoxicity is a common and potentially serious adverse event. It is defined as:

1. A serum AST or ALT level of more than three times the upper limit of normal in the presence of symptoms, or
2. A serum AST or ALT greater than five times the upper limit of normal in the absence of symptoms.

As resolution of the hepatitis may be prolonged and until the cause of the hepatitis is identified then, if necessary, it would be reasonable to treat with two or more antituberculosis medications without significant risk of hepatotoxicity, such as EMB, SM, amikacin /kanamycin, capreomycin, or a fluoroquinolone.

Monitoring of serum AST (or ALT) and bilirubin and any symptoms should be performed frequently. Once the AST level drops to less than two times the upper limit of normal and symptoms have significantly improved, then first-line medications can be restarted in stepwise manner.

SPECIAL ISSUES IN THE TREATMENT OF HIV

When to start HAART

The optimal time to start HAART in TB/HIV patients is not known. Delaying the ART until completion of TB treatment simplify the management, but it can result in HIV related co morbidity and even death in patients with low CD4 count.[20] Physicians have to balance the risk of HIV progression if HAART is delayed against the risk of having to discontinue therapies because of toxicities, side effects, paradoxical reactions or unforeseen drug-drug interactions if HAART is started with potential risk of microbiological and virological failure.[21] Patients with HIV disease and a CD4 cell count of greater than 200/microL cells have a low risk of HIV disease progression or death during the subsequent 6 months of tuberculosis treatment. CD4 cell count should be monitored three monthly for such patients. Antiretroviral therapy should be offered once tuberculosis treatment completed. For patients who develop TB with CD4 counts between 50-200cells/mm^3, ART should be started once TB therapy has been tolerated by patient. ART can be safely started in such group after completion of TB treatment if patients are free from OI and keeps a good health with periodic CD4 cell monitoring. Patient with very low CD4 cell counts (under 50cells/mm^3) or with other severe HIV related diseases, two months is probably too long to wait because of the high risk of HIV-associated events. ART should be started in these patients as soon as TB therapy is tolerated.[22]

Which regimen should be used?

New antiretroviral combination regimens have dramatically improved the prognosis for HIV-infected patients but have complicated the management of tuberculosis due to drug-drug interactions. Rifampin induces the activity of cytochrome P-450 CYP3A, which lowers the concentrations of HIV-protease inhibitors and non-nucleoside reverse-transcriptase inhibitors to subtherapeutic levels. Low trough plasma levels of these antiretroviral drugs are associated with incomplete viral suppression and the emergence of drug resistance.[21] Therefore, concomitant administration of rifampin with these drugs is not recommended.

There are four ARV options for patients receiving a rifampicin based TB regimen. [1] Triple NRTI regimens (including ABC) involve no drug interactions with antituberculous therapy and require no dose adjustments. One has to be very cautious about hypersensitivity reactions occurring with use of ABC. Other triple NRTI regimens not including ABC, e.g. ZDV/ddI/3TC, may also be considered, but antiviral potency may be less and peripheral neuropathy and hepatotoxicity may complicate management.[22]

[2] ZDV (or d4T)/3TC/EFZ is another option for patients receiving rifampicin. Although levels of EFZ are reduced in the presence of rifampicin, but in two studies presented at 10th conference on retrovirus and opportunistic infections regarding concomitant use of RMP with EFV clinical, immunological and microbiological outcome was not affected.[23,24] Nevirapine is not recommended as rifampicin reduces drug exposure to nevirapine by 31%, and dose adjustment for NVP co-administered with rifampicin have not been established.[25] Moreover, there is theoretical concern about combined hepatotoxicity of NVP and TB medications.

[3] The only recommended PI-containing combination for patients receiving rifampicin is ZDV/3TC/SQV/r or d4T/3TC/SQV/r where dosage of ritonavir should be at least 400mg BID. There is very limited published information, but data emerging from clinical trials support this choice.[26]

[4] Drug interaction is less pronounced for some protease inhibitors with rifabutin, a semisynthetic derivative of rifampicin. However, while rifabutin appears efficacious for the treatment of TB, it is not generally available in resource-limited settings.

PARADOXICAL REACTION/ IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

Some patients after starting antituberculosis treatment will develop an exacerbation of symptoms, signs, or radiological manifestations of tuberculosis. This has been well described in patients without HIV infection, but appears to occur more commonly in HIV positive patients that occur after initiation of HAART and are not the direct result of TB treatment failure or another disease process. They are often defined as transient but can last many months. IRIS occurs within a median of 15 days after HAART with the rapid rise in CD4 cells. IRIS does not appear to be associated with any particular antiretroviral regimen or drug class. Most patients with IRIS have advanced HIV infection; its relationship to the initiation of antiretroviral therapy suggests that, as the immune system recovers from profound immunosuppression, abnormal responses toward mycobacterial antigens occur.[27]

Paradoxical worsening of disease developed in up to 36% of the patients receiving ART and ATT simultaneously as compare to 7% of patients who received ATT alone.[21] IRIS most often presents with fever and increased or new lymphadenopathy. The skin over the nodes is often inflamed and the nodes can spontaneously rupture. Pleural and pericardial effusions, ascites, new chest infiltrates, psoas abscess, cutaneous lesions and new or expanding central nervous system tuberculoma have also been described as have worsening pulmonary lesions. Reactions occur within a median of 15 days after HAART. Other OIs must be ruled out in patents with strong suspicion of paradoxical reaction. These are usually self-limiting and generally last 10 to 40 days. However few life-threatening IRIS (intracranial tuberculoma, meningitis with raised intracranial pressure, pulmonary opacities lead to ARDS) requires high dose corticosteroids to control symptoms. Prednisone or methylprednisolone have been used at a dose of about 1 mg/kg and gradually reduced to a reducing regimen after 1 to 2 weeks.

TREATMENT OF LATENT TB INFECTION

The treatment of latent TB reduces the risk for active TB in HIV-infected patients, although the durability of this effect may be limited by high rates of reinfection with TB.[28-30] Preventive therapy for TB may not be feasible in many resource-limited settings because of the difficulty in excluding active disease. TB preventive therapy is therefore recommended in areas where diagnostic testing, such as chest X-rays can exclude active TB and where PPD skin testing is feasible. Once active tuberculosis has been ruled out, chemoprophylaxis is recommended for all HIV-infected persons with a positive tuberculin skin test (induration of 5 mm or more in diameter), a previous positive tuberculin skin test without prior chemoprophylaxis against tuberculosis, or recent close contact with potentially infectious patients with tuberculosis.[21] There have been several short-term controlled trials in HIV positive persons showing the protective effect of chemoprophylaxis. A protective effect of isoniazid is found only in those who are tuberculin skin test positive. The preferred regimens for treatment of latent tuberculosis infection include:

i. INH 300mg/day for a total of 9 months
ii. INH 900mg 2x/week for a total of 9 months
iii. Rifampicin/rifabutin + PZA daily for 2 months.

While using rifampicin containing regimen for prophylaxis drug interaction of RMP with PIs and NNRTIs should be kept in mind. So 9 months course of INH is better or rifabutin in modified dose with PZA can be used. RMP/PZA was favored initially due to short course, but there have been subsequent reports of severe hepatotoxicity including 6 deaths attributed to this regimen, although none of the patients had concurrent HIV infection. Due to high risk of hepatitis this regimen is recommended for HIV infected patient who are not expected to complete the 9 month INH regimen, but these patients should be seen every 2 weeks and have CBC and LFTs monitored at baseline, 2, 4, and 6 weeks.[31] Most important measure to prevent severe hepatitis is to instruct patients to stop taking medications immediately if hepatitis symptoms occur. Treatment of patients

with INH resistant strain should include rifampin/rifabutin with PZA. Choice between rifampin/rifabutin depends on current HAART. Chemoprophylaxis for an HIV-infected person exposed to a patient with multidrug-resistant tuberculosis should include at least two drugs with activity against the drug-resistant isolate. In India, however, the issue of INH prophylaxis is complicated due to the following reasons:

(a) Difficulty in excluding active TB disease in those with HIV/TB co-infection. (b) In a country like India where the burden of TB is high, chemoprophylaxis may not prevent the reinfection. (c) Widespread use of INH for chemoprophylaxis may contribute to an increase in INH resistance. (d) PPD skin test may not be feasible and is also not reliable in severely immunocompromised patients.

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