HIV-TB co-infection: Epidemiology, diagnosis & management

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Accepted February 17, 2005

HIV/AIDS pandemic has caused a resurgence of TB, resulting in increased morbidity and mortality worldwide. HIV and Mycobacterium tuberculosis have a synergistic interaction; each accentuates progression of the other. Clinical presentation of TB in early HIV infection resembles that observed in immunocompetent persons. In late HIV infection, however, TB is often atypical in presentation, frequently causing extrapulmonary disease. These factors coupled with low sputum smear-positivity, often result in a delayed diagnosis. HIV-infected patients respond well to the standard 6-month antituberculosis treatment regimens, although mortality is high. Antituberculosis treatment is complicated by frequent drug-interactions with highly active antiretroviral therapy (HAART) and adverse drug reactions are more common among HIV-infected patients. Guidelines for the management of patients co-infected with HIV and TB are still evolving. Timely institution of antituberculosis treatment using the directly observed treatment, short-course (DOTS) strategy and HAART markedly improves the outcome of HIV-infected patients with TB.

Key words Acquired immunodeficiency syndrome (AIDS) - directly observed treatment short-course (DOTS) - highly active antiretroviral therapy (HAART) - HIV-TB co-infection - human immunodeficiency virus (HIV) infection - tuberculosis (TB)

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), since the time of its initial description more than two decades ago, has relentlessly spread all around the globe showing no sign of abatement. In 2004, there were 4.9 million new infections and 3.1 million deaths due to HIV/AIDS, largely in the sub-Saharan Africa and South-East Asia. Unfortunately, these are the parts of the world where tuberculosis (TB) has been flourishing unhindered since ages, forming a deadly synergy. Advent of the HIV/AIDS pandemic has led to a dramatic increase in the number of TB cases worldwide. Globally, 9 per cent of all new TB cases (31% in Africa) in adults were attributable to HIV/AIDS, as were 12 per cent of the 1.8 million deaths from TB, in the year 2000. As a result of HIV/AIDS, incidence rates of TB in certain countries have gone up by >6 per cent per year, crippling the already overburdened health care resources. Considering the fact that about a third of the world’s population is infected with Mycobacterium tuberculosis, more than a half of which lives in countries ravaged by HIV/AIDS, the gravity of the situation becomes evident.

TB is a leading cause of morbidity and mortality in patients with HIV/AIDS. HIV and TB are also intricately linked to malnutrition, unemployment, alcoholism, drug abuse, poverty and homelessness. The direct and indirect costs of illness due to TB and HIV are enormous, estimated to be more than 30 per cent of the annual household income in developing
countries and have a catastrophic impact on the economy in the developing world. Thus, co-infection with HIV and TB (HIV-TB) is not only a medical malady, but a social and an economic disaster and is aptly described as the “cursed duet”.

EPIDEMIOLOGY OF HIV-TB

According to the recent estimates by the WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS), nearly 39.4 million people were living with HIV/AIDS, worldwide; more than a half of them in sub-Saharan Africa and nearly about a fifth in South and South-East Asia. In India, the overall prevalence of HIV infection is less than 1 per cent and India continues to be in the category of low prevalence countries. However, this blurs the actual picture of the epidemic in a vast, populous country like India. As per estimates, about 5.1 million people were infected with HIV in the year 2003, in India.

Prevalence of TB in patients with HIV infection

In contrast to western countries, where Pneumocystis jiroveci pneumonia was the commonest AIDS-defining illness, in developing countries TB is the most common life-threatening opportunistic infection (OI) in patients with HIV/AIDS with about 25 to 65 per cent patients with HIV/AIDS having tuberculosis of any organ. By the end of 2000, about 11.5 million people were co-infected with HIV and M. tuberculosis, globally; 70 per cent of co-infected people were in sub-Saharan Africa, 20 per cent in South-East Asia and 4 per cent in Latin America and the Caribbean. TB accounts for about 13 per cent of all HIV-related deaths worldwide. Of the 5.1 million HIV-infected people in India, about half of them are co-infected with M. tuberculosis; approximately 200,000 of these co-infected persons will develop active TB each year in association with HIV infection.

HIV seroprevalence in Patients with TB

In sub-Saharan Africa, HIV seroprevalence rates among patients with TB are high, ranging from 24 to 67 per cent. In Asia, the rate of HIV infection among TB patients has been lower. Studies from India have reported HIV-seropositivity rates ranging from 0.4 to 20.1 per cent. In certain cities such as Chennai and Mumbai, a higher prevalence has been observed. There has been a steady increase in HIV seroprevalence rates over the years. In Pune, the HIV seroprevalence rate was observed to have steadily increased from 3.2 per cent in 1991 to 20.1 per cent in 1996, among patients with pulmonary TB (PTB). HIV seroprevalence rate at a tertiary care referral hospital at New Delhi was reported to have increased from 0.4 per cent (1994-1999) to 9.4 per cent (2000-2002). The occurrence of localised epidemics and/or selection bias could be the cause of this large regional variation in reported rates of HIV-seropositivity among patients with TB.

HIV-TB: A BIDIRECTIONAL INTERACTION

HIV infection is the strongest of all known risk factors for the development of TB. HIV-infected persons are at markedly increased risk for progressive disease following primary TB infection, as well as reactivation of latent tuberculosis infection (LTBI). HIV infection also increases the risk of subsequent episodes of TB from exogenous reinfection (Fig.2). The estimated annual risk of reactivation among those co-infected with HIV and TB is about 5 to 8 per cent with a cumulative lifetime risk of 30 per cent or more compared to a cumulative lifetime risk of 5 to 10 per cent in HIV-negative adult patients.

Th1 type immune response characterised by adequate cell-mediated immunity is the crucial host
defence against \textit{M. tuberculosis} \textsuperscript{34}. HIV infection primarily affects those components of host immune response responsible for cell-mediated immunity. Thus in HIV infected individuals with LTBI, the fine balance between \textit{M. tuberculosis} and the host immunity gets tilted in favour of the former, resulting in reactivation \textsuperscript{35}. Moreover, the infection is poorly contained following reactivation, resulting in widespread dissemination causing extrapulmonary disease. This is corroborated by experimental findings that when peripheral blood lymphocytes of patients with HIV-TB are exposed to \textit{M. tuberculosis} \textit{in vitro}, they produce decreased amounts of Th1 type cytokines, as compared with HIV-negative patients with TB \textsuperscript{36,37}.

The interaction between HIV and TB in persons co-infected with them is bidirectional and synergistic. The course of HIV infection is accelerated subsequent to the development of TB and the inverse relationship between HIV viraemia and CD4+ count gets shifted to the right \textsuperscript{38}. Compared with CD4+-count-matched HIV-infected controls without TB, the relative risk of death and development of other OIs is higher in HIV-TB co-infected patients \textsuperscript{39}. Accelerated HIV progression is partly attributable to the increased systemic immune activation in patients with HIV-TB \textsuperscript{40}.

Further, increased HIV replication has been demonstrated locally, at sites of disease affected by TB such as affected lung and pleural fluid, in patients with HIV-TB \textsuperscript{41,42}. Moreover, the genetic diversity of the locally replicating HIV viral population is higher than the circulating population and the local immune activation also favours the development of latent HIV infection of macrophages and dendritic cells, thereby potentially enhancing dissemination of HIV \textsuperscript{38,42,43}. Thus in HIV-infected persons with active TB, the sites of active TB infection act as epifoci of HIV replication and evolution independent of systemic HIV disease activity. \textsuperscript{38} The proximate molecular mechanisms of increased HIV replication in patients with HIV-TB are increasingly being understood; increased levels of proinflammatory cytokines such as tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and chemokines such as monocyte chemotactic protein 1 (MCP1) result in transcriptional activation of HIV genes through activation of nuclear factor-\(\kappa\)B (NF-\(\kappa\)B) and mitogen-activated protein (MAP) kinase pathways \textsuperscript{38} (Fig.3).

**HIV/AIDS AND DRUG-RESISTANT TB**

In early 1990s, several institutional outbreaks of multidrug-resistant (MDR) TB among HIV-infected patients drew attention to the problem \textsuperscript{44-48}. However, HIV infection \textit{per se} does not appear to be a predisposing factor for the development of MDR-TB. Recent studies have found that drug-resistant TB including MDR-TB is no more common among people infected with HIV \textsuperscript{49,50}. Inspite of this, several factors such as (i) increased susceptibility to TB, (ii) increased opportunity to acquire TB due to over crowding, exposure to patients with MDR-TB due to increased hospital visits, and (iii) malabsorption of antituberculosis drugs resulting in suboptimal therapeutic blood levels in spite of strict adherence to treatment regimen, potentially increase the chances of MDR-TB in persons with HIV/AIDS, if not adequately addressed \textsuperscript{51}. Acquired rifamycin mono-resistance has also been described in HIV-TB patients treated with rifapentine \textsuperscript{52}.

**CLINICAL, RADIOGRAPHIC AND PATHOLOGIC FINDINGS**

Unlike other opportunistic infections which occur at CD4+ counts below 200/mm\(^3\), active TB occurs throughout the course of HIV disease \textsuperscript{27}. Clinical presentation of TB in HIV-infected individuals depends on the level of immunosuppression resulting from HIV infection. In patients with relatively intact immune function (CD4+ count > 200/mm\(^3\)), pulmonary TB (PTB) is more frequently seen than extrapulmonary TB (EPTB) \textsuperscript{53,54} (Table II). In these patients, chest radiographic findings include upper lobe infiltrates and cavitation, similar to those in HIV-negative individuals with PTB \textsuperscript{55}. Sputum smears are often positive for acid-fast bacilli (AFB) in these patients. As immunosuppression progresses, EPTB becomes increasingly common (Fig. 4). In contrast to HIV-negative patients with EPTB, the disease is often disseminated involving two or more non-contiguous organs concomitantly, in patients with HIV/AIDS \textsuperscript{11}. 
Chest radiographic findings in patients with advanced HIV disease are characterised by frequent lower lobe involvement, air-space consolidation similar to bacterial pneumonia and absence of cavitation\textsuperscript{55}; sputum smears are seldom positive for AFB. Intrathoracic lymphadenopathy is often evident in these patients, resembling primary TB, regardless of the prior TB exposure status\textsuperscript{57}. A miliary pattern of involvement is also associated with severe immunosuppression\textsuperscript{57}. Interestingly, a considerable proportion of patients (10 to 20\%) with advanced immunosuppression may have apparently normal-looking chest radiographs, yet \textit{M. tuberculosis} can be demonstrated or isolated from their sputum or bronchoalveolar lavage fluid\textsuperscript{55,58,59}. However, computed tomography (CT) demonstrates abnormalities such as pulmonary nodules, tuberculoma and intrathoracic lymphadenopathy in these patients\textsuperscript{55}.

In developing countries, EPTB is the commonest cause of pyrexia of unknown origin (PUO) among HIV-infected patients\textsuperscript{60}. Common forms of extrapulmonary involvement include extrathoracic lymph node TB, pleural effusion, meningitis and abdominal TB (Fig. 4). In advanced HIV/AIDS, lymph node involvement is characterised by poor granuloma formation with abundant AFB, in a background of neutrophils and florid necrosis\textsuperscript{57}. In contrast to HIV-negative patients in whom pleural effusion due to TB often resolves spontaneously, it is progressive and remains culture-positive for \textit{M. tuberculosis} for prolonged period of time in patients with HIV/AIDS\textsuperscript{61}. In addition, pleural fluid shows abundant mesothelial cells in these patients, a finding reflecting poor inflammatory response due to HIV/AIDS\textsuperscript{62}.

TB meningitis is accompanied by TB elsewhere in the body in most of the patients with HIV-TB and the cerebrospinal fluid (CSF) is often acellular; at times, CSF may be completely normal both in cellular and biochemical characteristics\textsuperscript{63,65}. In patients with acellular CSF, meningeal signs may not be evident clinically\textsuperscript{65}. Apart from these differences, intracerebral mass lesions are more commonly present in HIV-infected patients with TB meningitis\textsuperscript{66}. Hepatosplenic focal lesions and intraabdominal lymphadenopathy are more common in HIV-infected patients with abdominal TB; on the other hand, ascites and omental thickening are less common when compared to HIV-negative patients with abdominal TB\textsuperscript{67}. In patients with advanced HIV/AIDS, mycobacteraemia is commonly demonstrable\textsuperscript{68,69}. Cutaneous lesions appearing as small papules or vesiculopapules are more commonly found in HIV-infected patients with miliary TB\textsuperscript{70}. These are called tuberculosis cutis miliaris disseminata, tuberculosis cutis acuta generalisata and acute miliary tuberculosis of the skin.

Severe weight loss is a common presenting feature of HIV-infected patients presenting with TB\textsuperscript{71}. Many patients with AIDS, particularly in Africa, develop severe wasting and this has been called “slim disease”\textsuperscript{74}. Since these patients usually have chronic diarrhoea, the condition was thus thought to be a consequence of HIV-enteropathy. However, at

### Table II. Clinical presentation of TB in HIV-infected patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Late HIV infection*</th>
<th>Early HIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary: extrapulmonary disease</td>
<td>50:50</td>
<td>80:20</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Often resembles primary TB</td>
<td>Often resembles post-primary TB</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrathoracic lymphadenopathy</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Lower lobe involvement</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Cavitation</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Tuberculin anergy</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Sputum smear positivity</td>
<td>Less common</td>
<td>Common</td>
</tr>
<tr>
<td>Adverse drug reactions</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Relapse after treatment</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>

\* CD4+ T-lymphocyte count <200/mm\textsuperscript{3}

Adapted from references 6 and 54
autopsy, nearly half of HIV/AIDS patients who died with “slim disease” were found to have disseminated TB as compared with just over a quarter of those dying without such wasting, suggesting that cryptic disseminated/miliary TB may be an important cause of wasting in these patients.

**DIAGNOSIS**

**HIV testing in patients with TB**

Even though it is recommended that all patients with active TB should be tested for HIV infection, compliance with this recommendation is poor even in developed nations. Selective HIV testing of TB patients is considered unwise because physicians often fail to identify the risk factors for HIV transmission. Even when patients are questioned for risk factors, it has been observed that, up to 5 per cent of patients with TB, without any of the risk factors, had HIV infection. Though HIV is a major risk factor for the development of TB, HIV testing is not a component of the Revised National Tuberculosis Control Programme (RNTCP) in India. The lack of co-ordination between the voluntary counselling and testing centres (VCTCs) and the directly observed treatment short-course (DOTS) centres in India, is a cause of concern and calls for increasing the collaboration between the RNTCP and the National AIDS Control Organization (NACO).

**Diagnosis of TB in HIV/AIDS**

Diagnosis of TB in HIV-infected patients is often difficult due to several reasons: (i) frequently negative sputum smears, (ii) atypical radiographic findings, (iii) higher prevalence of EPTB especially at inaccessible sites, and (iv) resemblance to other opportunistic pulmonary infections. However, the diagnostic approach to suspected TB in a HIV-infected individual is similar to that in immunocompetent patients, except that invasive diagnostic procedures are more often required to establish the diagnosis. Universal precautions need to be followed meticulously. CT scan and magnetic resonance imaging (MRI) have facilitated the detection and characterisation of occult foci of EPTB. Attempts should be directed towards arriving at a bacteriological diagnosis, since multiple pathogens often coexist, and it is not possible to distinguish from atypical mycobacterial infections based on clinical and radiological findings alone. Peripheral blood cultures need to be performed to detect mycobacteraemia. Automated and semi-automated
Fig. 2. Natural history of *Mycobacterium tuberculosis* infection in immunocompetent and HIV-infected individuals. LTBI, latent TB infection; PTB, pulmonary TB; EPTB, extrapulmonary TB; SS, sputum smear.
liquid culture systems considerably reduce the delay in obtaining culture results\textsuperscript{79}. Several molecular diagnostic techniques based on detection of \textit{M. tuberculosis} specific DNA or ribosomal RNA sequences by polymerase chain reaction (PCR) have been developed in the recent past\textsuperscript{79}. However, the appropriate use of these tests in the diagnosis of active TB, especially in patients with HIV/AIDS needs to be defined\textsuperscript{27}. Messenger RNA (mRNA) based PCR techniques may be useful in assessing the response to treatment\textsuperscript{80} and detection of mutations in the rpo-B gene might be useful for rapid drug susceptibility testing\textsuperscript{79}.

**TREATMENT OF HIV-TB CO-INFECTION**

Availability of highly active antiretroviral therapy (HAART) has significantly improved the outcome of HIV/AIDS, in terms of prevention of OIs as well as mortality\textsuperscript{81}. Specifically, benefit in terms of prevention of TB has been demonstrated in South Africa\textsuperscript{82} and outcome of patients with HIV-TB co-infection has improved over the years, attributable to improvements in antiretroviral and antituberculosis treatment\textsuperscript{83}. Thus understandably, both antituberculosis treatment and HAART are indispensable in the management of patients with HIV-TB. However, substantial pharmacokinetic interactions occur between the rifamycin component of antituberculosis treatment and antiretroviral drugs especially, protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)\textsuperscript{84}. Moreover, short-course antituberculosis regimens used in immunocompetent patients are not so well studied in the setting of HIV co-infection\textsuperscript{85}.

The key therapeutic principles underlying the treatment of HIV-TB are, (i) treatment of TB always takes precedence over the treatment of HIV infection, (ii) in patients who are already on HAART, the same has to be continued with appropriate modifications both in HAART and antituberculosis treatment, and (iii) in patients who are not receiving HAART, the need and timing of initiation of HAART have to be decided after assessing the short-term risk of disease progression and death, based on CD4+ count and type of TB, on an individualised basis\textsuperscript{86-89}.

There is no evidence regarding the appropriate time for initiating HAART in patients with HIV-TB\textsuperscript{87}. A retrospective study found that in severely immunosuppressed patients with HIV-TB, early initiation of HAART was associated with reduced mortality and disease progression\textsuperscript{90}. British HIV Association (BHIVA) recommends that if CD4+ counts are >200/mm\textsuperscript{3}, HAART can be started after completion of antituberculosis treatment, if indicated; if CD4+ counts are 100-200/mm\textsuperscript{3}, HAART can be started after 2 months of TB treatment and when CD4+ counts are <100/mm\textsuperscript{3}, HAART has to be initiated as soon as possible after starting antituberculosis treatment\textsuperscript{87}. Guidelines laid by the WHO for use in resource-limited settings are depicted in Fig.5\textsuperscript{89}.

Of all rifamycins, rifabutin induces hepatic cytochrome CYP3A4 the least and is the preferred rifamycin for concurrent administration with HAART\textsuperscript{84}. In such a case, ritonavir and hard-gel formulation of saquinavir (PIs) and delavirdine (NNRTI) should not be used; dosages of indinavir and nelfinavir need to be increased to 1000 mg q8h and 1250 mg q12h, respectively and that of rifabutin has to be decreased to 150 mg/day, since PIs inhibit the metabolism of rifabutin and increase the rate of uveitis associated with rifabutin\textsuperscript{91}. In resource-limited settings where rifabutin is not available, ritonavir-boosted saquinavir (SQV/r) is the recommended PI and efavirenz at increased dosage (800 mg/day) is the preferred NNRTI to be given along with two nucleoside reverse transcriptase inhibitors, for concurrent administration with rifampicin containing antituberculosis regimens\textsuperscript{88}.

Principles of antituberculosis treatment in the setting of HIV-TB are identical to those for HIV-negative adults with two exceptions\textsuperscript{85,87}. In HIV-infected patients with TB caused by or presumed to be caused by susceptible strains of \textit{M. tuberculosis}, DOTS should be initiated with isoniazid, rifampicin/ rifabutin, pyrazinamide and ethambutol for the first 2 months followed by rifampicin and isoniazid for the subsequent 4 months. Since rifampicin monoresistance has been observed in HIV-infected patients with CD4+ count less than 100/mm\textsuperscript{3}, guidelines\textsuperscript{85} suggest that patients with advanced HIV
Fig. 3. Effect of TB on HIV infection: At the site of active TB infection, macrophages infected with *M. tuberculosis* (*Mφ-Mtb*) express tumour necrosis factor-α (TNF-α), which along with monocyte chemotactic protein 1 (MCP 1), transcriptionally activates HIV-1 replication (1). The long terminal repeat (LTR) of HIV contains two NF-κB sites. TNF-α induced HIV replication is mediated by increased activation of NF-κB in mononuclear cells. NF-κB, either alone or in concert with other transcription factors, enhances the transcriptional activation of HIV-1. *Mφ-Mtb* may also cause further cycles of infection in CD4+ T-lymphocytes and monocytes (2). *Mφ-Mtb* also transactivate HIV-1 replication in newly recruited latently infected CD4+ T-lymphocytes (3). Differentiation of monocytes into dendritic cells may facilitate transmission of HIV-1 to the CD4+ T-lymphocytes; differentiation into Mφ may promote establishment of latent HIV-1 infection. Thus, the events occurring during Mtib antigen presentation at the site of active TB infection, result in increased viral replication, plasma viraemia, viral genotypic diversity and CD4+ T-lymphocyte loss. ICAM, intercellular adhesion molecule; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; TNF-α, tumor necrosis factor-α. Source: reference 38.
Fig. 4. Relative proportion of various forms of TB in immunocompetent (a) and HIV-infected individuals (b). PTB, pulmonary TB; EPTB, extrapulmonary TB; LNTB, lymph node TB; MTB, miliary TB; DTB, disseminated TB; TBM, meningeal TB; ABDTB, abdominal TB; GUTB, genitourinary TB. Reproduced with permission from reference 56.
disease should not receive twice weekly regimens, but should be treated with daily or three times weekly therapy in the continuation phase. Six months is considered to be the minimum duration of treatment for adults with HIV-TB. If there is evidence of a slow or suboptimal response, prolongation of the continuation phase to 7 months (a total duration of 9 months) should be employed.

The initial response to 6-month therapy in HIV co-infected TB patients is good and the rate of recurrences is also similar to that of HIV-negative patients if rifampicin is administered for at least 6 months. However, higher recurrence rates have been observed in some studies, and were probably due to re-infection rather than treatment failure. Extended post-treatment isoniazid (INH) therapy has been shown to decrease the risk of recurrence in patients who had symptomatic HIV disease before the diagnosis of TB.

Role of corticosteroids

Clear guidelines do not exist regarding corticosteroid use in HIV-TB. Studies done in HIV-negative patients suggest that adjuvant corticosteroid administration is essential in patients with adrenal failure and is beneficial in those with meningal and pericardial TB and those developing immune reconstitution inflammatory syndromes (IRIS). A randomised controlled trial (RCT) conducted in Zimbabwe found a significant mortality benefit with 6 wk of prednisolone therapy in HIV-infected patients with pericardial TB. Whereas, another larger RCT of prednisolone in HIV-infected patients with pleural TB, found no significant mortality benefit. Moreover, it was observed that prednisolone treated patients had significantly higher incidence of Kaposi’s sarcoma. Likewise, subgroup analysis of a large RCT of prednisolone in TB meningitis found no beneficial effect of adjuvant steroid therapy on death or disability among HIV-infected patients. The clinician should weigh the relative merits of corticosteroid administration against the risk of immunosuppression and decide on their utility in each patient, individually.

Adjunct therapies in HIV-TB

Several immunomodulatory agents have been tried as adjunctive therapy in the treatment of HIV-infected patients with TB. These include M. vaccae vaccination, thalidomide, and pentoxyphylline. None of these agents were found to confer any meaningful benefit. Interestingly, a phase-1 study of adjunctive etanercept (TNF receptor-Fc chimera) therapy in patients with HIV-TB, found an insignificant trend towards better response in terms of weight gain, sputum culture conversion, cavity closure and CD4+ recovery.

Adverse drug reactions

HIV-infected patients are more prone to develop adverse reactions to antituberculosis drugs and need to be carefully monitored. The risk of adverse drug reactions (ADRs) increases with advanced immunosuppression and majority of the ADRs occur in the first two months of treatment. These include skin rash, usually caused by thiacetazone and sometimes by rifampicin and streptomycin, gastrointestinal disturbances and drug-induced hepatotoxicity among others. Thiacetazone can cause fatal ADRs and hence is contraindicated in HIV-infected patients. HIV-infected patients are more prone to develop isoniazid-induced peripheral neuropathy and all HIV-TB patients receiving isoniazid should be given pyridoxine supplementation (10-25 mg/day). Rifampicin reduces the effectiveness of oral contraceptive pills and patients should be advised to use other forms of contraception.

Immune reconstitution inflammatory syndromes

Paradoxical reactions, also called immune restoration syndromes or immune reconstitution inflammatory syndromes (IRIS) have been reported in 32 to 36 per cent of patients with HIV-TB, within days to weeks after the initiation of antiretroviral treatment. At times these can be delayed, occurring after several months. Manifestations range from isolated instances of fever to increased or initial appearance of lymphadenopathy, new or worsening pulmonary infiltrates, serositis, cutaneous lesions, and
Fig. 5. World Health Organization guidelines on timing of antiretroviral treatment in patients with HIV-TB. OI, opportunistic infection. Source: reference 89.
new or expanding central nervous system mass lesions. Consequently, some patients may develop acute renal failure or acute respiratory distress syndrome (ARDS). IRIS can be brief or prolonged with multiple recurrences.

These pose a diagnostic problem and have to be distinguished from TB treatment failure, and other OIs common among HIV-infected patients. Recent evidence suggests that CD4+ T-lymphocyte percentage and ratio of CD4+ to CD8+ T-lymphocytes, rather than CD4 + T-lymphocyte count, were the only factors independently associated with IRIS, suggesting that unbalanced T-cell response may be a key factor in the pathogenesis of IRIS. In general, antiretroviral therapy should not be interrupted if IRIS occurs. Nonsteroidal anti-inflammatory drugs may provide some relief, but some patients require adjunctive corticosteroid administration.

OUTCOME

The mortality of HIV-infected patients with TB is comparatively higher than that of HIV-negative TB patients. The mortality depends upon the type of disease and the degree of underlying immunosuppression. In HIV-infected patients with TB meningitis, mortality is about 60-70 per cent, despite adequate treatment. However, with adequate antituberculosis therapy, occurrence of TB has been found to have no independent effect on mortality in hospitalised HIV-infected patients. Other OIs which often go undiagnosed are a common cause of death in patients with HIV-TB, especially those dying later during antituberculosis treatment. In a study from south India, the median survival in HIV-infected patients with PTB and EPTB was found to be 45 and 40 months, respectively. Earlier studies from Uganda and Europe have documented a median survival of 22 to 24 months in HIV-infected patients with TB.

PREVENTION OF HIV-TB

All newly detected HIV-infected patients should undergo a tuberculin skin test and prophylactic therapy should be offered to those patients with LTBI (induration ≥ 5 mm). Treatment of LTBI substantially reduces the risk of developing active TB in HIV infected patients and has also been shown to reduce the mortality. The protection offered lasts for 2.5 to 3 yr.

However, in practice, especially in India, for reasons not well understood, treatment of LTBI is not widely offered. This is partly due to apprehension regarding inadvertent monotherapy of active TB and therapeutic nihilism on the part of physicians regarding the effectiveness of prophylactic treatment for fixed duration in a country where TB is endemic. Reliably ruling out active TB is likely to prove a bottleneck while implementing this strategy as a part of national programme, and operational research is urgently required in this aspect, in India.

The additional benefits of using IFN-γ assays based on M. tuberculosis specific peptides, early secretory antigen 6 (ESAT6) and culture filtrate protein 10 (CFP10) to diagnose LTBI in HIV-infected patients and lifelong prophylactic treatment with isoniazid to prevent reinfection, need to be evaluated in future studies.

While persons known to be HIV-infected should never be given bacille Calmette-Guerin (BCG), which is a live attenuated vaccine, the WHO advocates that routine immunisation of infants should nevertheless continue in areas with a high incidence of TB and HIV infection. Prior BCG vaccination offers modest protection against all forms of TB, independent of HIV status; however, HIV infection nullifies the protection offered by BCG against the development of EPTB. This is in contrast to HIV-negative patients in whom BCG vaccination offers maximum protection against the development of extrapulmonary TB such as meningitis and miliary TB.

Conclusions

Globally, HIV/AIDS pandemic is threatening to destabilise the control of TB. Treatment of HIV-TB co-infection requires strong commitment and a focussed approach. Appropriate use of HAART to preserve immunity and treat HIV infection, ensuring
high levels of coverage and compliance is required to prevent TB. The DOTS strategy is useful to ensure cure of TB in patients with HIV/AIDS. A strong co-ordination between the national TB and the AIDS control programmes is required for effective management of HIV-TB patients.

References


5. Sharma SK, Mohan A. Co-infection of human immunodeficiency virus (HIV) and tuberculosis: Indian perspective. Indian J Tuberc 2004; 51 : 5-16.


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