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HIV/TB CO-INFECTION:THE CHALLENGES
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ABSTRACT

Tuberculosis (TB) is a major cause of morbidity and mortality worldwide. Each year, there are eight million new Mycobacterium tuberculosis complex (MTB) infections and three million TB-related deaths. The catastrophic effects of TB are borne disproportionately among the most vulnerable. The HIV pandemic has further increased the burden so that the risk of TB reactivation from latency is five to 15 percent in HIV/TB coinfection. Tuberculosis reactivation fuels further primary infections, creating a vicious cycle of increasing infection, disease, and deaths. In addition, drug-resistant TB exacerbates this increasingly common problem.

INTRODUCTION

Tuberculosis is one of the leading causes of morbidity and mortality in the world. Each year approximately eight million people acquire MTB infection, and three million people die from the disease. But, as is common with most infectious diseases, the poorest and most vulnerable populations pay the highest toll. The HIV pandemic has enlarged the population of susceptible individuals, resulting in a net increase in morbidity and mortality rates. Even before the AIDS pandemic, an estimated 50 percent of adults had MTB infection in sub-Saharan Africa, with an incidence of about 200 per 100,000 people. Nationwide notification rates and hospital-based studies suggest that the incidence of TB has more than doubled since the early 1980s in those countries where the rates of HIV are highest (4).

In 1997, global prevalence of MTB infection was 32 percent, accounting for 1.86 billion people. Eighty percent of all incident TB cases were found in 22 countries, with more than half the cases occurring in five Southest Asian countries. Nine of ten countries with the highest incidence rates were in Africa. Prevalence of MTB/HIV co-infection worldwide was 0.18 percent, and 640,000 incident TB cases (8%) had HIV infection. The global burden of TB remains enormous because of inadequate TB control in sub-Saharan Africa, and the high rates of MTB/HIV co-infection in African countries.

About a third of the 40 million people living with HIV are co-infected with M-tuberculosis. HIV is the most powerful known risk factor for reactivation of latent MTB infection to active TB disease, in which the annual risk of developing TB disease from MTB infection ranges from five to 15 percent. HIV-infected people who become newly infected by MTB carry higher risk of progression to active TB. Tuberculosis is the leading cause of death among people with HIV infection, accounting for a third of AIDS-related deaths worldwide. In addition, there is a concomitant emergence of multi-drug-resistant (MDR) strains of MTB to isoniazid (INH) and at least rifampin (RIF), among other anti-tuberculous agents.

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 (10). 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."

In contrast to western countries, where Pneumocystis jiroveci pneumonia was the most common 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 of patients with HIV/AIDS having tuberculosis of any organ (11).

CHALLENGES TO HEALTH CARE WORKER IN TB INFECTION

The combination of an increasing prevalence of TB, HIV, and multi-drug resistant tuberculosis (MDR-

TB) has led to increased hospitalisation of patients with infectious TB and to increased risk for MTB transmission to HCWs, other patients, and visitors. There have been two adverse effects: the rising prevalence of MDR-TB involved in outbreaks, and the high rates of morbidity and mortality among immunocompromised people, particularly those with AIDS.

Several factors influence the transmission of TB, including delayed or failed diagnosis in the source case; closed, re-circulating air systems with minimal fresh air ventilation; exposure of highly vulnerable individuals; and reduced efficacy or failure of chemotherapy from drug resistance among source cases.

Human immunodeficiency virus (HIV) infection is a potent risk factor for tuverculosis (TB). Not only does HIV increase the risk of reactivating latent Mycobacterium tuberculosis (MTB) infection, it also increases the risk of rapid TB progression soon after infection or reinfection with MTB. In persons infected with MTB only, the lifetime risk of developing TB ranges between 10 and 20%. In persons co-infected with MTBand HIV, however, the annual risk can exceed 10%. The TB burden in countries with a generalised HIV epidemic has therefore increased rapidly over the past decade, especially in the severely affected countries of Eastern and Southern Africa.

It is possible that, in addition to increasing individual susceptibility to TB following MTB infection, the increased burden of HIV-associated TB cases also increases MTB transmission rates at the community level, threatening the health and survival of HIV-negative individuals as well. In several countries HIV has been associated with epidemic outbreaks of TB, and many of the reported outbreaks involved multidrug-resistant strains responding poorly to standard therapy.

CLINICAL, RADIOGRAPHIC AND PATHOLOGIC FINDINGS

Unlike other opportunistic infections which occur at CD4+ counts below 200/mm, active TB occurs throughout the course of HIV disease. 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), pulmonary TB (PTB) is more frequently seen than extrapulmonary TB (EPTB). In these patients, chest radiographic findings include upper lobe infiltrates and cavitation, similar to those in HIV-negative individuals with PTB. Sputum smears are often positive for acid-fast bacilli (AFB) in these patients. As immunosuppression progresses, EPTB become increasingly common. 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

In developing countries, EPTB is the most common cause of pyrexia of unknown origin (PUO) among HIV-infected patients. Common forms of extrapulmonry involvement include extrathoracic lymph node TB, pleural effusion, meningitis and abdominal TB. In advanced HIV/AIDS, lymph node involvement is characterised by poor granuloma formation with abundant AFB, in a background of neutrophils and florid necrosis. In contrast to HIV-negative patients in whom pleural effusion due to TB often resolves spontaneously, it is progressive and remain culture-positive for M. tuberculosis for prolonged period of time in patients with HIV/AIDS. In addition, pleural fluid shows abundant mesothelial cell in these patients, a finding reflecting poor inflammatory response due to HIV/AIDS (15).

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. In patients with acellular CSF,meningeal signs may not be evident clinically. Apart from these differences intracerebral mass lesions are more commonly present in HIV-infected patients with TB meningitis. Hepatosplenic focal lesions an intra-abdominal lymphadaenopathy are more common in HIV-infected patients with abdominal TB; on the other hand, ascites and omental thicknening are less common when compared to HIV-negative patients with abdominal TB. In patients with advanced HIV/AIDS mycobacteraemia is commonly demonstrable Cutaneous lesions appearing as small papules or vesiculopapules are more commonly found in HIV-infected patients with miliary TB. These are called tuberculosis cutis miliaris disseminata, tuberculosis cutis acuta generalisata and acute miliary tuberculosis of the skin.

Chest radiographic findings in patients with advanced HIV diseases are characterised by frequent lower lobe involvement, air-space consolidation similar to bacterial pneumonia and absence of cavitations 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. A miliary pattern of involvement is also associated with severe immunosuppression. Interestingly, a considerable proportion of patients (10 to 20%) with advanced immunosuppression may have apparently normal looking chest radiographs, yet M. tuberculosis can be demonstrated or isolated from their sputum or bronchoalveolar lavage fluid. However, computed tomography (CT) demonstrates abnormalities such as pulmonary nodules tuberculoma and intrathoracic lymphadenopathy in these patients.

DIAGNOSIS

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.

Diagnosis of TB in HIV/AIDS

Diagnosis of TB in HIV-infected patients is often difficult due to several reasons (i) frequently negative sputum smear, (ii) atypical radiographic findings. (iii) Higher prevalence of EPTB especially at inaccessible sites, and (iv) resemblance to other opportunistic pulmonary infections (21). However, the diagnosis 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. 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.

Several molecular diagnostic techniques based on detection of M.tuberculosis specific DNA or ribosomal RNA sequences by polymerase chain reaction (PCR) have been developed in the recent past. However, the appropriate use of these tests in the diagnosis of active TB, especially in patients with HIV/AIDS need to be defined. Messenger RNA (mRNA)based PCR techniques may be useful in assessing the response to treatment and detection of mutations in the rpo-B gone might be useful for rapid drug susceptibility testing.

TREATMENT OF HIV-TB CO-INFECTION

Availability of highly active anti-retroviral therapy (HAART) has significantly improved the outcome of HIV/AIDS, in terms of prevention of OIs as well as mortality. Specifically, benefit in terms of prevention of TB has been demonstrated in South Africa and outcome of patients with HIV-TB co-infection has improved over the years, attributable to improvements in anti-retroviral and antituberculosis treatment. 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 anti-retroviral drugs especially, protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Moreover, short-course antituberculosis regimes used in immunocompetent patients are not so well studied in the setting of HIV co-infection.

The key therapeutic principle underlying the treatment of HIV-TB are:

(i) treatment of TB always takes precedence over 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 individuals basis.

There is no evidence regarding the appropriate time for initiating HAART in patients with HIV-TB. A retrospective study found that in severely immunosuppressed patients with HIV-TB, early initiation of HAART was associated with reduced mortality and disease progression. British HIV Association (BHIVA) recommends that if CD4+ counts are >200/mm, HAART can be started after completion of anti-tuberculosis treatment, if indicated; if CD4+ counts are 100-200/mm, HAART can be started after two months of TB and when CD4+ counts are <100mm, HAART has to be initiated as soon as

possible after starting anti-tuberculosis treatment. Guidelines laid by the WHO for use in resource-limited settings are available (28).

Of all rifamycins, rifabutin induces hepatic cytochrome CYP3A4 the least and is the preferred rifamycin for concurrent administration with HAART. In such a case, ritonavir and hard-gel formulation of saquinavir (PIs) and delaviridine (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 rifabutine. 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 transriptase inhibitors, for concurrent administration with rifampicin containing anti-tuberculosis regimes.

Principles of anti-tuberculosis treatment in the setting of HIV-TB are identical to those for HIV negative adults with two exceptions. In HIV infected patients with TB caused by or presumed to be caused by susceptible strains of M. tuberculosis DOTS should be initiated with isoniazid, rifampicin/ rifabutin, pyrazinamide and ethambutol for the first two months followed by rifampicin and isoniazid for the subsequent four months. The initial response to six 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 six months (31). 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[33].

Adverse drug reactions

HIV-infected patients are more prone to develop adverse reactions to anti-tuberculosis 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 rifamoicin 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 anti-retroviral 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 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, anti-retroviral therapy should not be interrupted if IRIS occurs. Non-steroidal 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 anti-tuberculosis 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 anti-tuberculosis treatment.

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 two and a half to three years.

However, in practice, especially in Kenya 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 progremme, and operational research if urgently required in this aspect in Kenya.

BCG VACCINATION

While persons known to be HIV-infected should never be given bacilli 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 o EPTB. This is in contrasts to HIV-negative patients in whom BCG vaccination offers maximum protection against the development of extrapulmonary TB such as meningitis and military TB.

CONCLUSION

The worldwide incident of TB is increasing currently, particularly in areas of the southern hemisphere where HIV epidemics are devastating because anti-retroviral therapies are not available. HIV-infected patients are at extremely high risk for progression from latent TB to active disease, and unusual clinical manifestations of TB should not be ignored in this high-risk group. Patients receiving HAART may have significant drug-drug interactions when rifampicin is used with PIs of NNRTIs, and risk developing severe paradoxical reactions attributable to immune restoration. Finally, the dramatic extension of anti-TB drug resistance, caused partially by the HIV epidemics, as seen currently in Southeast Asia, India, sub-Saharan Africa and South America, should be taken into account by international public health authorities.

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