HIV & TB “The Deadly Duo”

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INTRODUCTION INCIDENCE & IMPORTANCE

WHO estimates that more than 7 million people, 98% of whom are in the developing world are co-infected with HIV and TB. The situation is explosive, leading to unprecedented public health crises. Both diseases are devastating but the devastation of the TB /HIV co-epidemic surpasses the devastation of either disease on its own. An estimated 1.4 million new cases of HIV-TB occurred in 2008, representing 15% of the total global burden of TB. In addition, an estimated 5,00,000 HIV-TB deaths accounted for 26% of global HIV/AIDS mortality.

India accounts for one-fifth of the world’s new TB cases. Every year 1.8 million people of the country develop TB and 3, 70,000 people die of it. In India, the estimated prevalence of HIV in the adult population is 0.36% and 2.5 million people are living with HIV/AIDS. At present, about 5% of new TB cases in India occur in people with HIV co-infection.

An HIV infected person has weak immunity and falls an easy prey to tuberculosis, a disease whose bacilli spreads easily through the air and is breathed unsuspectingly by all around. An HIV positive person infected with TB is 30 times more likely to become sick with TB than someone infected with TB who is HIV negative. Tuberculosis is the only major opportunistic infection in HIV infected which can spread through the air from a HIV positive person to a HIV negative person. TB thus spreads much more quickly to otherwise healthy populations.

HIV-TB: A Vicious cycle

TB is one of the most virulent opportunistic infections and it appears relatively early in the course of the HIV infection than other opportunistic infections. In one study, the median CD4+ cell count t presentation of TB was 326/l. As it is one of the first opportunistic infection to appear in HIV-infected people, TB may be one of the earlier signs of HIV infection.

Th1 type immune response characterized by adequate cell-mediated immunity is the crucial host defense against M. tuberculosis. HIV infection primarily affects those components of host immune response responsible for cell-mediated immunity. There is progressive depletion & dysfunction of CD4 lymphocytes and impaired macrophage function leading to impaired phagocytosis, Intracellular killing, altered cytokine production and defective antigen presentation Advanced HIV infection reduces number and causes dysfunction of alveolar macrophages hence high proportion of those infected develop active disease. Moreover, the infection is poorly contained following reactivation, resulting in widespread dissemination causing extrapulmonary disease.

In HIV infected, TB may be due to endogenous reactivation or exogenous infection. Endogenous reactivation involves reactivation of latent TB infection. HIV is the most potent risk factor for reactivation of latent tuberculosis. The risk of reactivation of latent TB infection in HIV negative is <1% per year (10% lifetime) and in HIV positive is ~ 7-10% per year (apprx 50-100% lifetime). Incidence of TB is 100 times more in HIV infected than in general population. Patient with HIV infection may also have exogenous infection with mycobacterium tuberculosis. 40% of HIV patients exposed
to TB develop active disease within weeks and progresses rapidly and relentlessly on a downhill course.

Untreated TB infection can accelerate the course of HIV infection. Immune activation from TB enhances both systemic and local HIV replication and plasma HIV RNA level increases. 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. The CD4+T lymphocyte count falls and Immune suppression increase leading to myriad opportunistic Infections (OI) and increased morbidity & mortality due to OI. After ATD, HIV viral load decrease but never to baseline. Patients with HIV/TB co infection have been shown to have two times higher mortality than other HIV patient when matched to CD4+ level.

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-α (TNF-α) and chemokines such as monocyte chemotactic protein 1 (MCP1) result in transcriptional activation of HIV gene through activation of nuclear factor κB (NF-κB) and mitogen-activated protein (MAP) kinase pathways.

**CLINICAL MANIFESTATIONS**

The clinical manifestations of TB in HIV infected are quite varied and generally show different presentations as a function of CD4+ T cell count. In early stages the presentations of TB in TB-HIV co-infection is the same as HIV-negative but in late stages, extra-pulmonary and disseminated forms are more common. TB progresses faster in HIV-infected people. In Early stages with CD4 > 200 /mm3, typical presentations of pulmonary reactivation occurs in which patient presents with fever, cough, dyspnea on exertion, weight loss, night sweats and a chest X ray showing focal infiltrates and cavitations involving upper lobes. Sputum smears are often positive for acid-fast bacilli (AFB) in these patients. (Table I)

In patients with lower CD 4+ cell counts, disseminated disease is more common. Chest radiographic findings in these patients may reveal diffuse or lower lobe bilateral reticulonodular infiltrates consistent with military spread, air-space consolidation similar to bacterial pneumonia and absence of cavitations. There may be pleural effusion and hilar and /or mediastinal lymphadenopathy. Infection may be present in brain, bone, meninges, gastro intestinal tract, lymph nodes and viscera. Sputum smears are seldom positive for AFB. In patients with advanced HIV/AIDS, mycobacteraemia is commonly demonstrable. Cutaneous lesions appearing as small papules or vesiculopapules are commonly found. Severe weight loss is a common presenting feature of HIV-infected patients presenting with TB. Many patients with AIDS, particularly in Africa, develop severe wasting and this has been called “slim disease”.

**DIAGNOSIS**

What is most unfortunate is the fact that TB goes unrecognized or incorrectly treated in as many as two thirds of all HIV positive people with TB. HIV associated TB is more difficult to diagnose due to several reasons including frequently negative sputum smears, atypical radiographic findings, higher prevalence of EPTB especially at inaccessible sites and 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. ATD must 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 liquid culture systems (BACTEC) considerably reduce the delay in obtaining culture results. Several molecular diagnostic techniques based on detection of M. tuberculosis specific DNA or ribosomal RNA sequences by polymerase chain reaction (PCR) have been developed. IFN-γ assays based on M. tuberculosis specific peptides, early secretory antigen 6 (ESAT6) and culture filtrate protein 10 (CFP10) are increasingly being used for diagnosis.

Tuberculin skin testing is not of much use. Tuberculin reactivity is reduced fourfold in HIV infection. The reactivity declines with increasing immune suppression, from 40-70 % in early HIV infection to 10-30% in advanced cases. Since the reaction decline with immune suppression, 5mm induration is considered significant in HIV infection. Some have advocated reducing it to 2mm.

HIV testing is recommended in all patients with active TB. However 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.

TREATMENT

TB in HIV is more likely to be fatal if left untreated. It is the only major AIDS-related opportunistic infection that poses a risk to HIV-negative people. Fortunately, response to TB treatment in HIV positives is good. It is imperative that treatment and care are carried out with the same zeal through measures required to tackle TB under any other circumstances. Curing TB can improve and prolong the life of a HIV positive person. It can also protect other HIV positive people from contacting TB and reduce the risk of multidrug resistant TB.

Although treatment of TB can improve the quality of life in HIV positive people and prolong their life, it cannot prevent the progression to AIDS. Hence, antiretroviral therapy (ART) is also vitally important. Thus both antituberculosis treatment and HAART are indispensable in the management of patients with HIV-TB. However, substantial pharmacokinetic interactions occur between the rifampicin component of antituberculosis treatment and antiretroviral drugs especially, protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Given the variability in yield from smear microscopy and difficulty in diagnosis, empiric treatment may be initiated and continued in HIV-infected persons in whom TB is suspected until all diagnostic work-up (smears, cultures, or other identification results) is complete. When active TB is diagnosed or suspected, a multi-drug anti-TB treatment regimen should be immediately started. Excellent TB cure rates have been obtained using the DOTS strategy.

Both NACO and RNTCP advice standard DOTS therapy for treatment of TB-HIV co-infection. However all cases are taken as seriously ill. Duration of therapy remains the same. 12 month of therapy is recommended for miliary TB , bone and joint disease and TB meningitis.

If patient is HAART naive, CD4+ cell count should be done for decision regarding initiation of HAART. If CD4+ cell count is > 350 cells, ATD should be started and HAART should be deferred till completion of ATD. If CD4+ cell count is < 200 cells, ATD should be started followed by HAART in 2-3 weeks (as soon as patient tolerates ATD). In patients with CD4 count between 200 and 350, patient should be reassessed after 8 week of ATD therapy. In case of extrapulmonary tuberculosis if CD4<350 ART should be started after 2 weeks of ATD therapy.

The CDC- IDSA recommendations are slightly different .For patients with a CD4+ count <100 cells/µL, HAART should be started after ≥ 2 weeks of TB treatment. For persons with a CD4+ count of 100-200 cells/µL, HAART should be delayed until the end of the 2-month intensive phase of anti-TB treatment . In those with a sustained CD4+ count >200 cells/µL, HAART could be started during the anti-TB maintenance phase and for those with a CD4+ count >350 cells/µL, after finishing anti-TB treatment.

The treatment of TB can be complicated by drug interactions with the rifamycins and overlapping toxicities associated with antiretrovirals (ARVs) and anti-TB drugs when therapy for both infections is concomitantly administered. Both Riampicin and rifabutin induce CYP3A enzymes, and although rifabutin is not as potent as Riampicin, it is a substrate, leading to reduced serum concentration of PIs ( by 75-95%)
and non-nucleoside reverse transcriptase inhibitors (by 20-55%) when these agents are concomitantly administered with the rifamycins.

If patient is on rifampicin based ATD, efavirenz based HAART regimen should be considered. Rifampicin excluded ATD may be used if there are no options, but treatment response and survival is poor.

Clear guidelines do not exist regarding corticosteroid use in HIV-TB. Adjuvant corticosteroid administration is essential in patients with adrenal failure and is beneficial in those with meningeal and pericardial TB and those developing immune reconstitution inflammatory syndromes (IRIS). However, recent trials have shown equivocal results. 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.

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. Thiacetazone can cause fatal ADRs and hence is contraindicated in HIV-infected patients. ATD induced hepatitis occurs fourfold

<table>
<thead>
<tr>
<th>Preferred Therapy, Duration of Therapy, Chronic Maintenance</th>
<th>Alternative Therapy</th>
<th>Other Options / Issues</th>
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<tbody>
<tr>
<td><strong>Empiric treatment should be initiated and continued in HIV-infected persons in whom TB is suspected until all diagnostic work-up is complete (AH)</strong></td>
<td><strong>Treatment for drug-resistant TB:</strong></td>
<td>Directly Observed Therapy (DOT) is recommended for all HIV patients undergoing treatment for active TB (AH)</td>
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<td></td>
<td><strong>Resistant to INH:</strong></td>
<td>Initial phase of TB treatment may also be administered 5 days weekly (40 doses) (AH), or TIW (24 doses) (BH) by DOT</td>
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<td>For CNS disease: Corticosteroid should be initiated as early as possible and continue for 6-8 weeks (AH)</td>
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<td><strong>Discontinue INH (and streptomycin, if used)</strong></td>
<td>Rif is not recommended for patients receiving HIV protease inhibitors (PI) due to its induction of PI metabolism (EH)</td>
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<td><strong>(RIF or RFB) - EMB + PZA for 6 months (BH); or</strong></td>
<td>Rifapentine given once weekly can result in development of resistance in HIV patients and is not recommended (EH)</td>
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<td><strong>(RIF or RFB) - EMB for 12 months (preferably with PZA during at least the first 2 months) (BH)</strong></td>
<td>Therapeutic drug monitoring should be considered in patients receiving rifampicin and interacting ART</td>
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<td><strong>A fluoroquinolone may strengthen the regimen for patients with extensive disease (CIH)</strong></td>
<td>Paradoxical reaction that is not severe may be treated with non-steroidal anti-inflammatory drugs (NSAIDs) without a change in anti-TB or HIG therapy (BH)</td>
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<td><strong>Resistant to Rifamycin</strong></td>
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<td><strong>INH + PZA + EMB + a fluoroquinolone for 2 months, followed by 10-16 additional monthly doses with INH + EMB + fluoroquinolone (BIH)</strong></td>
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<td><em><em>Amikacin or capromycin may be included in the 1</em> 2-3 months for patients with rifampycin resistance &amp; severe disease (CIH)</em>*</td>
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<td><strong>Multidrug resistant (MDR, i.e. INH &amp; RIF resistant) or extensively drug resistant (XDR, i.e. resistance to INH &amp; RIF, fluoroquinolone &amp; at least 1 injectable agent) TB:</strong></td>
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<td><strong>Therapy should be individualized based on resistance pattern and with close consultation with experienced specialist (AIH)</strong></td>
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higher than seronegative patient. 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).

**Immune reconstitution inflammatory syndromes (IRIS)**

IRIS has been reported in 32 to 36 per cent of patients with HIV-TB, within days to weeks after the initiation of antiretroviral treatment. 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. These pose a diagnostic problem and have to be distinguished from TB treatment failure, and other OIs common among HIV-infected patients. Risk factors for TB presenting as IRIS include early initiation of antiretroviral therapy (ART) within 2 months of starting antitubercular therapy (ATD), low CD4, presence of extrapulmonary TB especially of the CNS, disseminated TB and high viral load. 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.

**HIV - MDR TB & XDR TB**

Development of multi drug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) is increasingly being seen in the treatment of TB in HIV. Worldwide, there were an estimated 500,000 new MDR-TB cases in 2007 MDR-TB and XDR-TB can occur in HIV due to poor compliance to ATD, Use of Rifabutin prophylaxis for MAC, Large pill burden and malabsorption of drugs due to associated diarrhoea. Poor immune response in HIV patients leads to increased rapidly dividing bacilli and spontaneous mutations leading to increased resistance. As far as possible, MDR TB and XDR-TB should be managed by specialized units having a facility for quality controlled drug sensitivity testing and experienced in handling such cases.

**PREVENTION OF HIV-TB**

Several randomized controlled trials in HIV-infected persons have shown that the incidence of TB can be reduced by 40-60% by preventive therapy. The standard regimen of preventive therapy is isoniazid (INH) for 12 months after ruling out active TB. The protection offered lasts for 2.5 to 3 yr.

All newly detected HIV-infected patients should undergo a tuberculin skin test and prophylactic therapy should be offered to those patients with Latent TB (induration > 5 mm). However, in India, treatment of latent TB is not widely offered. This is partly due to apprehension regarding inadvertent monotherapy of active TB and lack of national policy regarding TB preventive therapy for HIV +ve persons. Isoniazid resistance is also widespread in India (30%).

Regarding Bacille Calmette-Guerin (BCG) vaccination, while persons known to be HIV-infected should never be given (BCG), as it is a live attenuated vaccine, the WHO advocates that routine immunization of infants should continue in areas with a high incidence of TB and HIV.

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