ABSTRACT

The truth is Tuberculosis (TB) is not eradicated even now. The cure and prevention of TB are very clearly known before the HIV/AIDS era, but still we are not able to eliminate this ancient bug. Prior to 1950’s TB was incurable and after 1950’s it became curable and again now it is threatening to become incurable because of MDR/XDR-TB. The WHO STOP TB strategy, targets to eliminate TB as a public problem by 2050. Because of HIV epidemic, even the developed countries are experiencing the TB resurgence. Overlapping toxicities, drug-drug interactions, immune reconstitution syndrome (IRIS), pill burden and difficulty in integrating the management programmes of TB & HIV at national level, are the main hurdles. Coordinating & balancing these programmes at national level and bringing the simpler guidelines to grass route level (like ICTC & private practioners) are the most important factors in success to battle against this deadly duo.

INTRODUCTION:

Tuberculosis –the mother of AIDS is the most common opportunistic infection in HIV. Globally about one-third of HIV patients are co-infected with TB. About 5% of new TB cases in India occur in people HIV with infection. In endemic countries, TB infection is usually acquired in childhood. Because of robust immunity it remains as latent TB infection (LTBI). The life time risk of reactivation of latent TB, in HIV negative persons is 10% but in HIV positive persons the risk is 5%-10% yearly, leading to lifetime risk of 50% . In a study by Agarwal et al, 30% of HIV infected patients accessing highly active antiretroviral therapy (HAART) had concurrent active TB and treatment of both conditions together lead to an improved outcome .

HIV and TB interactions: HIV decreases macrophages and CD4 cells, which are the main cells that provide immunity. In HIV positive persons there is increased risk of primary TB, reactivation disease, rapid progression, increased incidence of extra pulmonary (EPTB) and disseminated TB and immune reconstitution TB on HAART. HIV infection increases the risk of developing active TB by a factor of 100. According to Dr. Havlir, within two weeks of becoming infected with HIV, a patient’s risk of getting TB goes up two-fold . The impact of TB on HIV-tuberculosis increases the viral load and quasispecies diversity. After ATT, the viral load decreases but never to baseline. Patients with HIV/TB have 2 times higher mortality when matched to CD4.

Clinical features: In patients with higher CD4 cell count, clinical picture often resembles post-primary TB. Chest X-ray typically shows upper lobe infiltrates, cavitation and pulmonary fibrosis. In patients with lower CD4 cells clinical features are atypical resembling those of primary TB and dissemination is common. Chest X-ray shows unilateral or bilateral infiltrates mainly in lower lobes and typical cavities are seen in only 25% of patients . Dissemination is more common in advanced disease; infection may be present in bone, brain, meninges, gastrointestinal tract, lymph nodes and viscera. Approximately 60-80% of patients have pulmonary disease, and 30-40% has extra pulmonary disease . HIV patients often present with prolonged fever, the commonest cause of which is tuberculosis. Careful search for enlarged lymph nodes in cervical, axillary (clinical examination), mesenteric area, abscess in spleen, bowel thickening (ultrasonography), hilar region (chest X-ray) and Potts spine is necessary. Pulmonary tuberculosis (PTB) is considered in WHO clinical staging III and EPTB in stage IV.

Investigations: Diagnostic tests are same as HIV negative patients. Mycobacterium tuberculosis should be differentiated from atypical mycobacteria, Histoplasmosis, Cryptococcosis, Sarcoidosis and Solid Malignant neoplasia. Diagnosis is made by clinical, radiological and microbiological grounds. The count of CD4 cells is to be correlated to TB/EPTB. Sputum examination for AFB and culture, chest x-ray, FNAC of lymph nodes, CSF analysis, pleural, pericardial, ascitic fluid analysis, blood culture, CT scan head, bone marrow biopsy and culture, ultrasonography of abdomen are some of the investigations. Yield of sputum AFB is same as in HIV negative, except in advanced cases were sputum negativity chance is more. According to Dr. Hamilton, conventional sputum examination for AFB catches only half of active cases . Microorganisms other than mycobacteria that display some acid fastness include species of Nocardia and Rhodococcus, Leginella micdadei and the protozoa Isospora and Cryptosporidium. AFB should be looked in FNAC aspirate of lymph nodes as granuloma is less likely to be present in advanced disease. In suspected cases when chest x-ray is normal (normal chest x-ray does not rule out PTB), HRCT thorax may show-miliary mottling and hilar lymphadenopathy,LDH and uric acid to be done in suspected cases of lymphoma. Fever, anemia,
HIV & TB - The "Deadly Duo"

**Table 1: ATT and ART Overlapping Toxicity:**

<table>
<thead>
<tr>
<th>Side effects</th>
<th>ATT</th>
<th>ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>Rifampicin, rifabutin, INH, pyrazinamide</td>
<td>NVPEFVABC</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Rifampicin, rifabutin, INH, pyrazinamide</td>
<td>NVP, PI's</td>
</tr>
<tr>
<td>Leucopena, anemia</td>
<td>Rifampicin, rifabutin</td>
<td>AZT</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>INH</td>
<td>d4T</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>Pyrazinamide</td>
<td>ddi</td>
</tr>
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raised serum alkaline phosphatase and hepatosplenomegaly may indicate mycobacterium avium complex (MAC) infection. Patients with AIDS at risk for developing disseminated MAC disease can be identified by acid-fast staining and culture of fecal specimens. The gold standard test for diagnosis TB is microscopy and culture identification of MTB after incubation of biological samples in liquid and solid media. Three consecutive morning specimens of entire volume urine must be collected in sterile containers after proper precautions in suspected cases of urogenital tuberculosis. Atypical mycobacteria usually grow faster than MTB and can be identified within two weeks of incubation. MTB PCR can be used, it is a rapid sensitive test, but sensitivity is decreased to 40-77% if sputum samples are negative for AFB. Biopsy samples are to be fixed in HOPE (Hepes glutamic acid buffer –mediated organic solvent protection effect) media (but not in formalin) for PCR.

**Latent tuberculous infection (LTBI):** For diagnosing LTBI, Mantoux test (MT) and interferon-γ assay are used. Mantoux test is of limited value in India. Cut-off value of 5 mm induration is considered positive in HIV. If the initial MT is negative the test should be repeated within 1-2 weeks. The two-steps MT may eliminate some false negative reactions. An initial negative MT may become positive if tested again after HAART due to immune reconstitution. As of today, two IFN-γ blood tests are available:ELISPOT (T-SPOT-TB Test) and ELISA (Quantiferon-Gold-in-tube Test). These tests are more sensitive and specific than MT for diagnosing MTB infection in patients with immunodeficiency, as the cross reactivity with previous BCG vaccination and Non-Tuberculous Mycobacteria is not likely to occur. These are one-step test and there is no need recall to read, but are costly, need to be processed in limited time.

**Treatment:** Standard DOTS (directly observed treatment-short course) regimen is advised to all patients based on category. Duration of therapy remains same as in HIV negative patients. Twelve months of therapy is recommended in miliary TB, bone and joint disease and tubercular meningitis. Cures rates are similar to HIV negative patients, but relapse is common.

If patient is ART (anti retroviral therapy) naïve, assess CD4 and (a) if CD4 is more than 350 cells, start DOTS. Here HAART can be deferred or started after completion of DOTS, if other AIDS defining illness are present. In these cases it is better to reassess the patients after 8 weeks of ATT (anti tuberculosis therapy) for HAART, (b) if the CD4 cell count is less than 350, start DOTS and after 2 months start HAART, (c) if the CD4 cell count is less than 200, first start DOTS then start HAART (within 2-3 weeks) as soon as possible (once the patient tolerates ATT). Early HAART is suggested as the mortality is high if only ATT is given.

If the patient is on ATT (rifampin based) then consider efavirenz (EFV) based HAART. Rifampicin is a CYP 3A4 inducer and it reduces nevirapine (NVP) level by 20-55%, PI’s level by 75-95% and EFV level by up to 20% . This leads to sup-optimal drug level and drug resistance.

Irrational use of ART and ATT can lead to drug resistance in both groups.

Administration of fluconazole with ATT (rifampicin) can cause hepatotoxicity. The dose of steroids (if indicated) should be increased by 33-50% with rifampicin and 25-33% with rifabutin.

In HIV-associated TB, rifampin monoresistance may develop with widely spaced intermittent treatment.

Following HAART regimens can be used with rifampin based DOTS:

1. AZT (zidovudine) + 3TC (lamivudine) + EFV
2. AZT + 3TC + TDF (tenofovir)
3. TDF + 3TC (or FTC-emtricitabine) + EFV
4. d4T (stavudine) + 3TC + EFV

Rifampicin excluded ATT can be used when there are no options, but treatment response and survival is poor; ATT duration is prolonged and relapse is common.

There is no need to start lead-in phase of NVP if switched from EFV (e.g. after completion of ATT). But stop rifampicin based ATT first (as its level persists for two weeks), continue EFV based HAART for 2 weeks. Then switch to NVP based HAART.

Rifabutin based ATT is recommended if NVP or PI based HAART is used. Rifabutin is a less potent inducer of CYP3A4 than rifampicin. Unlike rifampicin; it is also a substrate of the enzyme. Any CYP3A4 inhibitors will therefore increase the concentration of rifabutin although they have no effect on rifampicin metabolism. Most PI’s are inhibitors of CYP3A4 and when used with rifabutin, plasma concentrations of rifabutin and its metabolites may increase and cause toxicity. If patient is on PI based HAART or NVP based HAART (where EFV cannot be used/changed)-then rifabutin based ATT is used. Rifabutin dose is 300mg/d or thrice a week if used with NVP and if lopinavir/ritonavir is used the rifabutin dosage is 150mg thrice a week. Clarithromycin and fluconazole increases rifabutin levels and cause its toxicity. Uvietis and bone marrow depression are an indication to stop rifabutin. If patient develops PTB within six months of HAART, check ART adherence and start DOTS/ATT. Here IRIS is to be ruled out. If patient develops PTB after six months of HAART, then check CD4 and viral load to rule out ART failure. Adherence is to be checked before considering second line ART. EPTB after six months of HAART usually indicates ART failure. Overlapping toxicities of ATT & ART are shown in table 1.

**Treatment of LTBI:** Many studies have shown that IPT (isoniazid
preventive therapy) reduces TB incidence in HIV-infected patients and Cochrane review summarized this risk to be 32% in all HIV-infected patient regardless MT results. Despite WHO’s recommendation that IPT be offered to all HIV-infected patients in areas with a high tubercular burden, very few countries in high-burden areas utilize IPT. As a policy it is not recommended in India. There are certain difficulties-active TB has to be ruled out, primary drug resistance to isoniazid is high in our country (about 30%), toxicity, and poor adherence and there may be irrational use of INH monotherapy for active TB. INH is used in dose of 5mg/kg for 9-12 months.

MDR TB and HIV: Multi-drug resistance TB means resistance to INH and rifampicin.

The risk is same as seen in HIV negative patients. May arise due poor adherence, poor absorption (due to diarrhea). Duration of treatment is 18 months to 2 years after culture revert to negative. The case fatality in immunocompromised individuals infected by MDR strains has recently been reported to be approximately 40% and in immunocompromised individuals greater than 80%. In India about 1, 10, 132 new cases of MDR-TB cases emerged in 2006. The Government of India is planning to implement DOTS plus standard TB therapy. The drug regimens were well tolerated and delivered a 90% cure rate.

XDR-TB and HIV: Extensively drug resistant TB is defined as MDR-TB plus resistance to of fluoroquinolones and one of three injectables (capreomycin, kanamycin, amikacin). Mortality is very high. Poor prescription practice, use of fluoroquinolones as a routine antibiotic in PTB patient may lead to drug resistance. Fluoroquinolones are categorized in second line anti-TB drugs. These should be used unnecessarily e.g. Patient on first line ATT develops hepatitis. In 2006, 53 people in the province of KwaZulu Natal in South Africa were identified as having XDR–TB. Of these people 52 died within 25 days of TB diagnosed. The majority were HIV positive. Since then XDR TB isolates have appeared in every part of world. Population data demonstrated that in USA, Latvia and South Korea prevalence of XDR TB is 4%, 19% and 15% of all MDR TB cases respectively. Combination of HIV and XDR-TB is difficult to treat and needs expert care.

IRIS: It may occur in up to one third of patients who have been diagnosed as having TB and who have started ART. It typically presents within three months of initiation of ART but can occur as early as five days. Patient with TB-associated IRIS most commonly present with fever and worsening of pre-existing lymphadenopathy or respiratory disease. The symptoms occur more frequently (36%) when compared to paradoxical reactions seen in HIV negative patients (2%) in a study by Narita et al. Most cases resolve without any interventions and ART can safely continued. Serious reactions may require corticosteroids.

MAC (Mycobacterium Avium Complex): A clinical MAC syndrome consists of one or more of the following: persistent fever<38°C for more than one week, night sweats, diarrhea, weight loss or wasting, radiologically documented pulmonary infiltrate, hepaticomegaly, splenomegaly, anemia (hemoglobin <8.5 g/dl) and alkaline phosphatase more than twice the upper limit of normal. Diagnosis is considered probable if MAC is cultured from bronchopulmonary, gastrointestinal, skin surface or other non-sterile sites (as a sole pathogen) and histopathological confirmation of AFB/MAC is obtained from the tissue specimen from which the culture was obtained. The diagnosis is confirmed if MAC is cultured from normally sterile body fluid, tissue or organ. Mycobacteremia is common in MAC (80-90%) when compared to PTB (10-40%). Clarithromycin or azithromycin plus ethambutol combination is treatment of choice. A third or fourth drug e.g.-Ciprofloxacin and Rifampicin is/are sometimes added to prevent resistance. Suspect MAC if CD4 cell count is less than 50. Addition of clarithromycin to 4 drugs ATT if clinically suspected MAC in patients of confirmed PTB may be tried. Weekly dose of Azithromycin is used for chemoprophylaxis if CD4 cell count is less than 75.

INTEGRATING HIV-TB PROGRAMME:

Dr Freidland, in 5th IAS conference on HIV pathogenesis, treatment and prevention 2009 Cape Town, discussed about START study published in 2004. Here a pioneering effort was done to integrate HIV care and treatment into an existing TB program (DOTS -HIV/TB). HIV counseling and testing was introduced and those identified with HIV infection were given a once daily ART regimen plus standard TB therapy. The drug regimens were well tolerated and delivered a 90% cure rate.

At the national level in India, there are several efforts being attempted to achieve co-ordination between designated microscopy centre (DMC) and integrated counseling and testing centre (ICTC) of HIV/AIDS control programme. The objective is to promote early diagnosis and treatment of TB in HIV and vice versa. Recently National AIDS Control Organization has decided to routinely test the HIV status in all newly diagnosed TB patients in the high-prevalence states.

Some of the hurdles in combining ATT & HAART programmes are mentioned in table 2.

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