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HIV-TB Coinfection: Nuts and Bolts

GAUTAM AHLUWALIA

EPIDEMIOLOGICAL *NUTS AND BOLTS* - *What is the Gravity of the Problem for India?*

In patients with human immunodeficiency virus (HIV) infection, tuberculosis (TB) is a very important cause of morbidity and mortality. As such, India constitutes one-third of the global TB burden with one death reported every minute due to TB. Each infectious patient results in 10-15 new infections every year. In fact, TB kills more women than all causes of maternal mortality and is responsible for 25% of all avoidable deaths in developing nations. No wonder, the impact of TB is greatest on the developing countries. On the other hand, there are reports that India has the maximum number people living with HIV/AIDS (PLWHA) in the world. Moreover, the majority of people afflicted with HIV and TB are in the economically active age groups. It is being predicted that if India does not cap the HIV/AIDS epidemic, it would affect the economy of the nation in the coming years[1-3].

TB is the leading cause of death in HIV patients. The mortality of TB in HIV patients is two fold to four fold more than in HIV negative patients. TB is the cause of death in one out of three PLWHA. TB also accelerates HIV infection by increasing viral load by five to seven fold. TB is not only the most common opportunistic infection (OI), it also increases risk of other opportunistic infections[3-5].

TB shares a deadly synergism with HIV and increases the risk by 150 times for developing active TB. Individuals infected with tubercle bacilli have a 10% lifetime risk of developing active disease. The risk increases to 10% per year if they are co-infected with HIV. Consequently, many countries in developing world with a high prevalence of HIV are encountering an epidemic of TB also. In Thailand, 40% of patients with TB are co-infected with HIV also. If we do the same extrapolation in India, 50-60% HIV patients will develop active TB[2,6].

There have been some very important recent developments in the interplay between HIV-TB. We need to realize their implications before it is too late in our country. In an important study in South African miners, it was observed that HIV doubles the rate of active TB within 1 year of seroconversion irrespective of higher CD4 count in these patients. This is contrary to the classical view that HIV accelerates TB when CD4 count is low[7]. Similarly, in Tanzania, HIV patients with normal chest radiograph who were otherwise asymptomatic had active TB detected by sputum culture and the symptoms of TB developed much later[8]. These observations have serious implications for disease detection and screening program for TB in HIV. Most guidelines do not have sputum culture to screen for latent TB before antiretroviral therapy (ART) due to financial and logistical limitations. Consequently, we may fail to identify a substantial number of HIV-infected persons with 'subclinical but active TB'.

ART has significantly improved the outcome of HIV/AIDS in terms of prevention of non-tubercular opportunistic infections. In a recent study form UK, 17% patients developed active TB when started on ART[9]. These facts may have all the more catastrophic implications as reflected in ART cohort collaboration study involving 20,000 patients. Though there was improved viral load/immunological response with ART, but there was no reduction in all cause mortality at 1 year with an increase in combined AIDS-related death risk in more recent years largely because of increased incidence of TB[10].

IMMUNOLOGICAL *NUTS AND BOLTS* - *Who is 'Responsible' for this Intricate Interplay Between HIV and TB?*

Cytokines, TB and HIV form a hub and spoke model, in which the two spokes viz. TB and HIV integrate with the hub viz. cytokines. In fact, cytokines are the future of medical science and are having an impact on all diseases.

The key components of the immune response in TB include T lymphocytes and alveolar macrophages. CD4+ T lymphocytes, especially the T-helper type 1 (Th1) subclass, are the major effector cell in cell-mediated immunity of TB or the 'policeman' responsible for controlling TB. When *Mycobacterium tuberculosis* reaches the lower respiratory tract, the initial defense against infection is alveolar macrophage. The organism is engulfed by the macrophage through a complicated process of phagocytosis. Subsequently, macrophage-lymphocyte interactions involve Thl and natural killer lymphocytes that secrete INF-α in response to mycobacterial antigens, which activates alveolar macrophages to produce a variety of mediators including reactive oxygen and nitrogen species that are involved in growth inhibition and killing of mycobacteria. These cellular interactions are mediated by Thl cytokines. Macrophages can also secrete interleukin (IL)-12, another Thl cytokine, in a posi-tive feedback loop to amplify this process.[11]

In HIV, CD4+ T cell depletion removes the 'policeman' of TB control in the lung resulting in dissemination of *Mycobacterium tuberculosis*. Consequently, disseminated tuberculosis (DTB) and extrapulmonary tuberculosis (EPTB) are more common. On the other hand, the activated macrophages also release proinflammatory cytokines, such as tumor necrosis factor and IL-1, which enhance HIV replication. The mycobacteria and their products also enhance HIV replication by inducing nuclear factor kappa-B, the cellular factor that binds to promoter regions of HIV. Therefore, the fact that HIV-TB interplay is a bidirectional response anchored by the cytokines has improved our understanding of the natural progression and clinical course of HIV and TB. In fact, sites of active TB infection act as epifoci of HIV replication independent of HIV disease activity. The genetic diversity of locally replicating HIV strains is also more. These findings have renewed our impetus for prevention, early recognition and effective treatment for both diseases[11].

Interestingly, in HIV patients, ART improves immunity against *Mycobacterium tuberculosis* by increasing the function and number of CD4+ lymphocytes. Nevertheless, there is a potential disadvantage to HAART-induced improved immunity against *Mycobacterium tuberculosis.* The heightened granulomatous response facilitates clearing of mycobacterial organisms, but the granulomatous inflammation results in immune reconstitution inflammatory syndrome (IRIS) or so called "paradoxical reactions" in HIV patients co-administered antituberculosis therapy (ATT) and highly-active ART (HAART). The paradoxical reactions or "HAART attacks" are defined as worsening of disease characterized by fever, worsening chest infiltrates on radiography and peripheral or mediastinal lymphadenopathy. However, paradoxical reactions have been shown to be more temporally related to initiation of ART than ATT. Most HIV patients who experience paradoxical reactions con-vert their Mantoux test from negative to strongly positive, which is a sign of improved CD4+ cell number and function[11].

It has also been observed that numerous cases of sarcoidosis have been reported in HIV patients who have been started on ART in the west[11]. The pathogenesis of this condition is likely to be very similar to the paradoxical reactions seen in ART-treated patients with TB. It is likely the antigen(s) that causes sarcoidosis is present in HIV patients with a low CD4 count. However, CD4 lymphocyte count is inadequate to mount a significant Th1-induced granulomatous response until ART therapy is administered.

CLINICAL *NUTS AND BOLTS* - *How are the Clinical Features of TB Different in HIV?*

The clinical manifestation of TB in HIV depends on the degree of immunosuppression. In fact, TB is the commonest cause of fever of unknown origin in HIV reactive patients. In patients with a higher CD4 count (>200/μL), classical PTB is more common than EPTB in a ratio of 4:1. The chest radiograph reveals classical upper lobe cavitary apical disease. However, when CD4 count decreases (<200/μL), EPTB/DTB becomes more common. The clinical features include hilar and/or mediastinal lymphadenopathy, diffuse lower lobe reticulonodular infiltrates, miliary TB and pleural effusion. As compared to HIV negative patients, pleural effusion in HIV never resolves spontaneously and the acid-fast bacilli (AFB) culture may be positive for prolonged periods Moreover, there is abundance of mesothelial cells reflecting impaired inflammatory response. In lymph node TB, there is paucity of granulomas and abundant AFB in a milieu of neutrophils and necrosis[12,13].

Visceral lesions and intra-abdominal lymphadenopathy with necrosis characterize the clinical profile of

abdominal TB in HIV patients. In contrast, ascites and omental thickening are characteristic of abdominal TB in HIV-negative patients. Moreover, wasting syndrome or cachexia due to diarrhea also called HIV enteropathy is due to DTB in about 50% patients[12,13]. Intracerebral mass lesions are more common in HIV patients with TB meningitis. However, CSF may be acellular with normal proteins again indicating an impaired immune response[12,13].

DIAGNOSTIC *NUTS AND BOLTS* - *Why is Diagnosis of TB in HIV More Problematic?*

The diagnostic armamentarium of sputum and chest radiograph, the 2 most easily accessible and important investigations have limitations when it comes to TB in HIV. There are less chances that HIV patients will have a positive sputum smear for AFB, which is the sheet anchor of TB control program in India and reflects 'infectiousness' of the disease. The CXR may reveal abnormalities non-specific for TB and mimic frequent other co-morbid opportunistic infections. Moreover, 1 in 5-10 HIV patients may have normal CXR where TB is detected by sputum culture. The presence of EPTB would entail advanced 'costly' investigations like ultrasound, computed tomography and magnetic resonance imaging. The gold standard investigation in diagnosis of TB in HIV is mycobacteriological diagnosis including AFB culture and/or polymerase chain reaction to exclude co-morbid pathogens and atypical mycobacteria. The implications in a resource-limited setting are again obvious[12,13].

MANAGEMENT *NUTS AND BOLTS* - *What is Important in the Management of HIV-TB?*

We need to appreciate that both antituberculosis therapy (ATT) and ART are indispensable in the management of patients with HIV-TB. Although ART co-administered with ATT leads to some peculiar problems, these issues can be easily overcome by making therapeutic modifications. ART substantially reduces mortality among HIV/TB co-infected patients and initiation of ART within 6 months of TB diagnosis is associated with greater survival.[14] It has also been documented that initiation of ART with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens {efavirenz (EFV) or nevirapine (NVP)} at 4-12 weeks of TB treatment in advanced AIDS is safe and effective.[15]

Rifamycins are the backbone of any effective ATT regimen. However, there are substantial pharmacokinetic interactions between rifamycins and NNRTI or protease inhibitor (PI). Rifamycins induce hepatic cytochrome CYP3A4. The least interaction is with rifabutin, which however is not available in a resource limited setting like India. The maximum interaction of NNRTI or PI is with rifampicin. Moreover, there is also the problem of similar adverse drug effects. The hepatotoxicity of NVP overlaps with hepatotoxicity of rifampicin (R), isoniazid (H) and pyrazinamide (Z). The other important issue involves compliance due to increased pill burden. Immune reconstitution inflammatory syndrome (IRIS) is another very important predicament when ATT and ART are co-administered[16].

There are two clinical situations to be addressed when management of TB in HIV is concerned[16].

a. *Active TB and HIV detected together:* The treatment of TB is the immediate priority and CD4 count may be used as a guide for adding ART. If CD4 count is less than 200/µL, start ATT first and add ART as soon as ATT is tolerated. This usually takes 2 weeks to 8 weeks. If CD4 count is between 200/µL and 350/µL, start ATT first and add ART after the intensive phase (8 weeks) of ATT. If CD4 count is more than 350/µL, treat TB first completely and defer ART.

   The principles of ATT are same as in HIV negative patients. DOTS can be used as the sheet anchor of ATT. The minimal duration of therapy is 6 months. However, if clinical and/or bacteriological response is slow, ATT should be given for nine months or for four months after the TB culture (if available) become negative.

b. *Active TB develops in patients already on ART:* In this clinical situation, the question to be answered is about ART failure, especially in our resource-limited settings where CD4/viral load facilities are limited. The rule of thumb is if TB develops less than 6 months of initiation of ART, then it is not ART failure. However, if TB develops after 6 months of starting ART, failure of ART should be considered.

The ART regimen should be decided as follows:

a. *HIV-TB detected together or TB develops within 6 months of initiation of ART:*

   The ART regimen to be administered is standard first line therapy [2 nucleoside reverse transcriptase inhibitors (NRTI) + 1 NNRTI (EFV)]. As rifampicin reduces EFV levels by 25%, the dose of EFV has to be increased depending on the weight of the patient. If weight is more than 60 kg, the dose of EFV should be increased to 800 mg from the standard dose of 600 mg. NVP should replace EFV in women of child bearing potential or if patients develop neuropsychiatric manifestations as a side effect of EFV. When

nevirapine is administered with ATT, the problem of hepatitis and skin reactions need to be viewed with greater caution. The liver function tests should be monitored more rigorously.

b. *TB develops after 6 months of initiation of ART:*

Ideally, treatment failure is diagnosed on the basis of CD4 counts and/or viral load, but in our resource-limited setting if these facilities are not available, patients developing PTB may not be considered as treatment failure. On the other hand, if patients develop EPTB/DTB, it should be considered as treatment failure. However, this empirical approach of deciding ART resistance has great limitations on the long-term prognosis of the patient.

The need for a correct identification whether ART failure is present or not is vital because in ART failure patients, NNRTI has to be replaced with PI. PI results in significant interaction with ATT as rifamycins decrease PI levels to sub-therapeutic concentrations. Though rifabutin is a 'relatively' good alternative as it has less interaction with PI, dose adjustments of rifabutin are still required to decrease its side effects like uveitis. Moreover, rifabutin is contraindicated in patients with total leukocyte count less than 1000/µL, and platelets less than 50,000/µL, which can be observed in patients with advanced AIDS. Of course, in a resource limited setting like India, cost is a very important limiting factor resulting in almost non-existent availability of rifabutin in our country. Therefore, the therapeutic modification done is rifampicin with a boosted PI (ritonavir-boosted lopinavir or ritonavir-boosted saquinavir), which is also an expensive proposition for the patients in India[16].

The appropriate management of both TB and HIV is important to prevent the increasing problem of drug resistance of both HIV and TB in these patients. Initially, it was multi-drug resistance TB (MDR-TB), but recently extensively drug resistant (XDR-TB) has also been described[17]. XDR TB is resistant to more than 3 second line ATT drugs as compared to MDR which is resistant to at least R and H, but second line drugs are effective in these patients. The implications of XDR TB on HIV-TB control are rather alarming especially for developing nations[18].

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