Seminar

Co-infection with human immunodeficiency virus and tuberculosis

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INTRODUCTION

The World Health Organisation (WHO) declared the global tuberculosis (TB) epidemic to be a public health emergency in 1993. Despite signs that the epidemic may be slowing down, the actual number of TB cases continues to rise.[1] HIV and TB are closely associated; HIV promotes the progression from latent TB infection to active disease and TB is the leading infectious killer of people living with HIV. The fight against HIV/AIDS and TB remains among the higher priorities for WHO.

EPIDEMIOLOGY

It is estimated that more than one third of the world's population is infected with *Mycobacterium tuberculosis*. In 2005, there were an estimated 8.8 million new active TB cases and 1.6 million people died of TB.[2] Tuberculosis is a disease that thrives in conditions of poverty, malnutrition and limited access to healthcare. Developing countries bear the brunt of the global TB burden.

The TB burden in India remains high with an estimated incidence of 168 [107-228] per 100000 in a year of which an estimated 5.2% [3.0-8.0] are HIV-positive.[2] It is estimated that there are fourteen million TB cases in India, of which 3.5 million are sputum-positive. TB kills more than 2 million people annually and is the leading cause of death among adults (15-59 years) in Africa and Asia.[3] WHO estimates that there are 42 million HIV-infected people worldwide, with an estimated five million in India. The numbers are increasing worldwide.[3-4]

PATHOGENESIS OF INFECTION

Infection with *M. tuberculosis* is almost always acquired by inhalation. A cell-mediated immune response normally develops 6-10 weeks after the primary infection and is characterised by the formation of granulomas. In most affected individuals, the infection is contained in a state of dormancy (latent TB). These people remain well unless there is a breakdown of cell-mediated immunity.

HIV infects and destroys CD4+ T lymphocytes. Experimental evidence suggests that CD4+ T lymphocytes are essential in coordinating an effective cell-mediated immune response to *M. tuberculosis*.[5] Production of interferon-gamma as a result of activation of CD4+ and CD8+ cells results in the activation of macrophages and ultimately, in the control of *M. tuberculosis* replication. As the CD4+ function and counts decline during HIV disease, the likelihood of TB disease increases.

Disease due to *M. tuberculosis* occurs as a result of new infection or reactivation of latent infection. In an HIV-negative population, only up to 10% of people infected with *M. tuberculosis* develops TB; approximately 5% will develop primary infection in the first two years of exposure and 5% will develop disease due to reactivation of the latent infection at some time during their life. In an HIV-positive population, there is an increased risk of acquiring new TB infection.[6] Moreover, HIV-positive people are more likely to develop disease and less likely to contain the infection in a state of dormancy. Furthermore, it is estimated that HIV/TB co-infected individuals have an annual 5-10% risk of reactivation of latent *M. tuberculosis*.[7]

CLINICAL FEATURES

Infection and disease due to *M. tuberculosis* can occur at any stage of HIV infection. However, the features of the disease and the clinical presentation are influenced by the degree of immunosuppression. Patients with a well preserved CD4+ count are likely to present with symptoms and signs similar to nonHIV-infected patients, for example, with pulmonary infection and symptoms of cough, night sweats and weight loss. Patients with more advanced immunosuppression often present with more atypical symptoms and signs. Atypical pulmonary infection without cavitation and extrapulmonary and disseminated TB are more common as the CD4+ count falls.[8] Symptoms may be nonspecific or absent and it may be difficult to distinguish from HIV disease or other opportunisitic infections. Disseminated TB may be manifested by lymphadenopathy, hepatosplenomegaly and/or weight loss; fever may be absent.

Extrapulmonary tuberculosis, and in particular, tuberculous meningitis, is more common in HIV-positive patients presenting with TB and should be suspected in such patients.[9]

Clinicians should have a high index of suspicion for TB in symptomatic HIV-positive patients.

DIAGNOSIS

Microscopy and culture

The diagnosis of tuberculosis ultimately rests on the detection of *M. tuberculosis*, either by microscopy or culture of the appropriate body fluid or tissue. As with HIV-negative patients, cases of suspected pulmonary TB should have three early morning sputum samples examined for acid-fast bacilli and sent for TB culture. Absence or reduction in cavitation in HIV-positive patients results in lower numbers of bacilli expectorated; thus, the sensitivity of sputum examination in HIV-postive patients is lower with more advanced immunosuppression.[10] Often these patients will be sputum smear-negative. Bronchoscopy is recommended if sputum smears are negative. Definitive diagnosis of pulmonary TB in heavily immunosuppressed individuals is often made only when culture results are positive.

Radiology

In patients with a well preserved CD4+ count, chest X ray appearences are similar to nonHIV-infected individuals with classic changes such as upper lobe infiltrates and cavitation. The appearances can be more atypical in more immunosupressed patients. The chest X-ray can be normal in these patients or may reveal diffuse infiltrates or miliary pattern. Although computed tomography (CT) scan is a more sensitive investigation to detect pulmonary or hilar abnormaility, it is by no means specific for the diagnosis of pulmonary TB.

Tuberculin skin testing[11-13]

The tuberculin skin test (TST) interpretation is not always straightforward and the TST is not specific for the detection of *M. tuberculosis*. Previous bacille Calmette-Guérin (BCG) vaccination or exposure to environmental (atypical) mycobacteria can result in false positive results. False negative results may occur with chronic illness (including TB itself) and with immunosupression. The sensitivity of TST is reduced in HIV infection, particularly in advanced disease. Moreover, anergy to TST in a high TB prevalence area should alert the clinician to the possiblity of HIV disease. The British HIV Association (BHIVA) do not recommend the use of TST in patients with suspected HIV/TB co-infection or as a screening test for TB in HIV-positive patients.[11]

Interferon and Molecular tests

Trial data for the use of interferon tests in HIV positive individuals is accumulating.[12,13] However, currently there is insufficient evidence to support a recommendation for their use in this population. The use of tests based on PCR and related DNA techniques allows rapid and specific detection of M.tuberculosis antigens. However, these tests are limited by their poor sensitivity. Molecular techniques also enable the identificaion of nontuberculous mycobacteria and the identification of antibiotic resistance mutations. Rapid detection of rifampicin resistance using molecular techniques is recommended by the British Thoracic Society (BTS) and BHIVA in patients whose clinical course suggests drug resistance. These should be used as an adjunct to standard laboratory techniques.[11]

TREATMENT

Antituberculous therapy

Treatment guidelines for HIV-infected patients are the same as those for uninfected individuals. If directly observed treatment (DOT) is not possible, self-administered treatment with a fixed dose drug combination is preferred to improve the compliance. BTS and BHIVA guidelines state that all cases of TB in HIV-positive patients should be treated with standard daily quadruple antituberculous therapy, with an initial phase of isoniazid, rifampicin, pyrazinamide and ethambutol for two months and a

continuation phase with rifampicin and isoniazid for four months, once susceptibilities are known. Directly observed treatment regimens lasting three days per week with appropriate dose adjustment can be used, but less frequent intermittent treatment regimens are contraindicated in HIV patients because of unacceptably high rates of relapse. One recent retrospective study suggested that the standard antituberculous treatment regimen may result in worse outcomes, relapse and increased mortality in HIV-positive compared to HIV-negative patients.[11] However, there is currrently no randomised controlled trial data to recommend a universal longer treatment course in HIV-positive patients. As with HIV-negative TB cases, a continuation phase is recommended for ten months in central nervous system infection. Data on drug-resistant TB is limited but guidelines for HIV-negative patients need to be followed.

Antiretroviral therapy

The use of HAART reduces the risk of developing TB disease amongst HIV-postive patients. The effect of HAART on the risk of TB disease amongst HIV-positive patients has been examined in several studies. In patients given HAART, the risk of TB disease was up to 80% lower than in patients not on antiretroviral therapy. The protective effect of HAART was greatest in those with advanced immunosuppression but was not apparent in those with CD4+ counts >350 cells/μL.[14-17] The combination of antituberculous treatment and HAART reduces mortality in co-infected patients.[18,19]

Medication interactions and toxicity

Interactions between antiretroviral and antituberculous medications arise through shared routes of metabolism and are often a result of enzyme induction or inhibition. The isoform CYP3A4 of the P450 family is involved in the metabolism of many drugs including protease inhibitors (PIs) and nonnucleoside inhibitors (NNRTIs). Rifampicin is a potent inducer of this enzyme and will result in reduced levels of PIs and NNRTIs. In turn, PIs may reduce the metabolism of rifampicin and increase its concentration and potential for toxicity. Enyme inhibitors such as low dose ritonavir reduce the enzyme-inducing effect of rifampicin. Currently, PI-containing regimens are not recommended with concurrent antituberculous therapy. Rifabutin is a less potent inducer of CYP3A4 and is recommended as a substitute for rifampicin if an alternative (nonPI-containing) antiretroviral regimen is not available. Rifabutin seems to be equivalent to rifampicin, but there is an absence of long-term data.

Hence, rifampicin remains the drug of choice. Concerning NNRTIs, BHIVA recommends an efavirenz dose of 800mg/day in patients weighing over 50 kg and the standard dose of 600mg/day in patients with weights below 50 kg. The combination of neveripine and daily rifampicin is not recommended. Therapeutic drug monitoring (TDM) for PIs and NNRTIs may be of value in patients experiencing adverse effects or where drug regimes are complex. There are no major interactions with nucleoside/nucleotide reverse transcriptase inhibitors.

Rifampicin also results in reduced levels of other drugs that are dependent on the P450 system, such as antifungals, *e.g*, fluconazole.

Overlapping toxicity profiles can complicate care, *e.g.*, rashes with NNRTIs, rifampicin and co-trimoxazole, and peripheral neuropathy with isoniazid and stavudine.

Immune reconstitution inflammatory syndrome (IRIS)/paradoxical reactions

Some HIV/TB co-infected patients when started on HAART, will develop an exacerbation of symptoms, signs or radiological manifestations of tuberculosis. The exact aetiology of these reactions is uncertain, but it is presumed that they are a consequence of HAART-related reconstitution of the immune response to *M. tuberculosis* antigens. There is no standardised definition for IRIS but these reactions are characterised by worsening of or appearance of new signs, symptoms,or radiographic manifestations of TB that occur after the initiation of HAART, and not the result of TB treatment failure or the result of another disease process. IRIS does not seem to be associated with any particular drug class or antiretroviral regimen. Most patients with IRIS have advanced HIV infection and low CD4+ counts at the initiation of HAART. Treatment is supportive and corticosteroids may be required.

Starting HAART

The decision as to when to start HAART in patients with TB is not straightforward. There is a balance to be struck between the risk of IRIS with HAART and further immunosuppression without it. The potential for drug interactions and toxicities complicates the situation further. Current BHIVA and BTS guidelines state that patients with CD4+ counts >200 cells/μL should complete antituberculous therapy before starting HAART. For patients with CD4+ counts between 100 and 200 cells/μL, it is recommended to defer treatment until after the intensive phase of antituberculous therapy (two months). For patients with CD4+ counts <100 cells/μL,

there is a lack of data to support deferred or immediate HAART. It is recommended that patients in this group should be started on HAART as soon as is practical.

RELAPSE AND TREATMENT FAILURE

TB relapse is defined as a patient who has previously become culture-negative while receiving therapy, but becomes culture-positive again after the completion of treatment, or has clinical or radiographic deterioration consistent with tuberculosis. Most relapses occur within the first 6-12 months following the completion of therapy. If patients received treatment by directly observed therapy (DOT) programs, then relapse is nearly always due to a drug-susceptible organism. However, the risk of acquired drug resistance is high in patients who have self administered therapy. Microbiological confirmation of relapse is vital to enable testing for drug resistance.

Treatment failure is defined as the presence of positive cutures after four months of appropriate antituberculous therapy. After three months of antituberculous therapy, 90-95% of patients should have negative cultures and should have clinically improved. Treatment failure may result from patient nonadherence, malabsorption of drugs, drug resistance and biological variation. Two or more drugs to which the organism is thought to be susceptible should be added/substituted in any new regimen.

Multidrug resistance

Multidrug resistant TB (MDR-TB) is TB that is resistant to at least rifampicin plus isoniazid. It occurs when drugs are mismanaged or misused. Patient noncompliance, inadequate doses or duration of drug therapy, poor supply or quality of drugs are important factors in the development of MDR strains. The emergence of MDR-TB is responsible for contributing to the increased mortality and morbidity of TB. WHO estimates that there were 500,000 cases of MDR-TB worldwide in 2004 and that 2.5%[1-5] of new TB cases in India were MDR. MDR-TB cases seem to be closely associated with HIV.[20]

Extensively drug-resistant TB (XDR-TB) is defined as MDR-TB plus resistance to a flouroquinolone plus one of three injectable second-line drugs (capreomycin, kanamycin, amikacin) and results in extremely limited treatment options and worse outcomes. XDR-TB has an even stronger association with HIV. In one recent observational study in South Africa, all cases of XDR-TB were found to be co-infected with HIV and there was an almost 100% mortality.[21]

PREVENTION

Infection control

Any patients admitted to the hospital with suspected TB should be isolated from other patients. In areas where there are HIV-positive inpatients, suspected pulmonary TB cases should ideally be treated in negative pressure cubicles and every effort should be made to maintain respiratory isolation. TB in HIV-positive patients is also transmissible to HIV-negative people. TB is a notifiable disease and public health departments must be informed of new cases. Screening of close contacts of smear-positive cases for evidence of TB infection should be performed and chemoprophylaxis offered if appropriate.

Chemoprophylaxis

Chemoprophylaxis may be given either to prevent reactivation of latent TB into active disease (primary prophylaxis), or to prevent recurrence in patients who have previously been treated for TB (secondary prophylaxis). Although some studies have shown a short-term benefit in primary prophylaxis, BHIVA guidelines do not recommend routine chemoprophylactic therapy for HIV-infected patients although there is data that co-trimaxozole may be effective in a large population setting.[22] Close contacts of people with smear-positive TB should be followed up and offered chemoprophylaxis. Otherwise, patients at risk should be followed up and monitored closely. There is no randomised control trial evidence to suggest that secondary prophylaxis prevents the reactivation of TB or new tuberculous infection and is therefore not recommended.

Vaccination

The BCG vaccination is a live, attenuated strain of *Mycobacterium bovis*. In HIV-negative people, the degree of protection afforded by vaccination is controversial and is influenced by the age at vacccination and prior exposure to nontuberculous mycobacteria. The efficacy in HIV-negative people is approximately 50%, but it is more effective in preventing disseminated and meningeal disease in infants and children. Vaccination with BCG carries a risk of disseminated disease and side effects such as regional and extraregional lymphadenopathy. The risks of disseminated BCG disease increase with the degree of immunosupression and are well recognised in HIV-positive patients. Current WHO guidelines are that people with symptomatic HIV disease should not receive BCG vaccination. There is however, limited evidence to suggest that BCG vaccination may be given to HIV-positive infants

at birth, if the risks of TB are deemed to outweigh the risks of disseminated BCG.

Directly observed therapy and patient education

Directly observed therapy (DOT) is recommended by the WHO and CDC for the treatment of TB in HIV patients. It is recommended that all patients with MDR-TB take DOT. There are no published data on the utility and efficacy of combined HAART and TB DOT. The superiority of DOT over self-administered therapy for the treatment of TB in developing countries is yet to be proven. Encouraging and monitoring patient adherence to therapy, providing information and support for patients should minimise transmission of TB.

CONCLUSION

Tuberculosis and HIV co-infection remains a complex disease where there are hurdles to cross at each stage. Diagnosis and treatment are complex and involve a clear understanding of innovative laboratory methods as well as complex drug-drug interactions. The epidemiology clearly shows that the HIV and TB epidemics go hand in hand and indeed, fuel each other. Thus, prevention can not be underplayed. This review brings us up to date on the current thoughts on this co-infection and hopefully encourages more research in this area.

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Multiple choice questions

1. Which of the following statements best describes the effect of HIV on the development of TB disease:
   a. In an HIV-positive population, up to 10% of people infected with M. tuberculosis develop TB
   b. CD4+ T lymphocytes are not involved in the control of M. tuberculosis replication
   c. There is an increased risk of acquiring new TB infection in HIV-positive individuals
   d. HIV/TB co-infected individuals have an annual risk of reactivation of latent M. tuberculosis of 25%

2. Which of the following statements best describes the clinical presentation of TB in HIV-positive patients?
   a. Patients with a well preserved CD4+ count are likely to present with symptoms and signs similar to nonHIV-infected patients
   b. Patients with a CD4+ counts <100 cells/µL are unlikely to present with extrapulmonary TB
   c. The presentation of TB disease is not influenced by the level of the CD4+ count
   d. Pulmonary infection with cavitation is the typical presentation of TB in patients with a low CD4+ count

3. Which statement best describes the diagnosis of TB in HIV-positive patients?
   a. The sensitivity of the sputum smear examination is not affected by the degree of immunosuppression
   b. Anergy to the Tuberculin Skin Test (TST) in a high TB prevalence area should alert the clinician to the possiblity of HIV disease
   c. The TST is recommended as a screening test for TB in HIV-positive patients
   d. PCR and DNA amplification techniques have largely surpassed microscopy and culture for the diagnosis of TB

4. Which of the following statements best describes the treatment of HIV/TB coinfection?
   a. All cases of pulmonary TB should be considered for prolonged antituberculous therapy
   b. HAART reduces the risk of developing TB disease amongst HIV-positive patients by up to 25%
   c. The protective effect of HAART in reducing the risk of TB disease is greatest in those with advanced immunosuppression
   d. The protective effect of HAART in reducing the risk of TB is not influenced by the degree of immunosuppression

5. Which of the following statements concerning the treatment of HIV/TB co-infection is false?
   a. PI-containing HAART regimens are recommended for patients being treated with concurrent antituberculous therapy
   b. There are no major interactions with NRTIs and rifampicin
   c. Interactions between antiretroviral and antituberculous medications arise through shared routes of metabolism
   d. The combination of neveripine and daily rifampicin is not recommended

6. Which of the following statements best describes initiation of HAART in HIV/TB co-infection?
   a. HAART should be initated at diagnosis of TB
   b. Patients with CD4+ counts of 100-200 cells/µL should complete antituberculous therapy before starting HAART
   c. The development of IRIS does not seem to be associated with any particular drug class or antiretroviral regimen
   d. IRIS often occurs following completion of antituberculous therapy

7. Which of the following statements concerning drug-resistant TB is false?
   a. There is an association between MDR-TB and HIV
   b. MDR-TB is TB resistant to at least rifampicin plus isoniazid
   c. An estimated 2.5% of new TB cases in India in 2004 were MDR
   d. XDR-TB has not been reported in HIV-positive patients

8. Which of the following statements concerning the prevention of TB is true?
   a. TB in HIV-positive patients is not transmissable to HIV-negative people
   b. Primary antituberculous chemoprophylactic therapy is routinely recommended for HIV-positive patients
   c. Secondary chemoprophylaxsis has not been shown to prevent reactivation of TB and is not recommended in HIV-positive patients
   d. BCG vaccination should be routinely offered to HIV-positive patients

9. Which of the following statements is true ?
   a. Interferon tests should be performed to diagnose HIV-TB co-infection.
   b. The gamma interferon test has been shown to be neither sensitive nor specific in HIV positive individuals.
   c. Gamma interferon tests work on the same principle as the skin tests.
   d. Both the Quantiferon-gold and Ellispot tests are enzyme-linked immunoassays.

10. Which one of the following sttements is correct?
    a. TB-HIV coinfection can be prevented by early treatment of HIV.
    b. There is no role for TB chemoprophylaxis
    c. IRIS is commonly seen in patients with high CD4 counts
    d. Molecular tests are the most sensitive tests in the diagnosis of TB in the HIV-TB co-infection setting.

Answers: 1 - c, 2 - a, 3 - b, 4 - c, 5 - a, 6 - a, 7 - d, 8 - c, 9 - c, 10 - a