

Co-infection of *Mycobacterium tuberculosis* and Human Immunodeficiency Virus

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ABSTRACT

Co-infection with Human Immuno Deficiency Virus (HIV) and *Mycobacterium tuberculosis* is common, particularly in the developing world. Tuberculosis (TB) is commonly found in HIV-positive individuals, who are at increased risk of both reactivation of latent infection and acquisition of new infection. As the degree of immunosuppression increases, the risks of developing TB disease also increase. HIV infects and destroys CD4+ T lymphocytes. As the CD4+ function and counts decline during HIV disease, the likelihood of TB disease is increased. In an HIV positive population, there is an increased risk of acquiring new TB infection. HIV/TB co-infected individuals have an annual 5-10 percent risk of reactivation of latent *Mycobacterium tuberculosis*. The highly active antiretroviral therapy (HAART) reduces the risk of developing TB by 80 percent amongst the HIV-positive patients compared with the patients not on antiretroviral therapy (ART). Most patients with immune reconstitution inflammatory syndrome (IRIS) have advanced HIV infection and low CD4+ counts at the initiation of HAART. The emergence of multi-drug resistance (MDR) strains of *M. tuberculosis* is a world wide problem and more alarming. The highest rates of multidrug resistance tuberculosis (MDR-TB) have been documented in Nepal (48%) and Gujarat of India (33.8%). WHO recommends that all patients in this condition should take directly observed treatment (DOT). To combat HIV/AIDS, effective global strategies must be highly linked with TB control strategies. (*J Infect Dis Antimicrob Agents* 2010;27:45-52.)

INTRODUCTION

Tuberculosis (TB) is the leading cause of morbidity and mortality in untreated people living with the HIV in Africa.^{1,2} Patients infected with HIV are

at increased risk, up to 10 percent per year, of reactivating latent *Mycobacterium tuberculosis* infection, and of accelerated progression to TB disease after infection.^{3,4} In addition, HIV appears to increase

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the rate of TB re-infection and recurrent disease.^{5,6} During the last decade, TB case notification rates have risen sharply in the areas of high HIV prevalence, such as sub-Saharan Africa, largely attributable to the HIV epidemic.⁷⁻⁹ WHO declared the global TB epidemic to be a public health emergency in 1993. Despite signs that the epidemic may be slowing the number of TB cases continues to rise. The fight against HIV/AIDS and TB remains among the higher priorities for WHO¹⁰ and recommends that affected countries implement collaborative programmatic TB/HIV activities, including ART, as part of health problems regarding the burden of the disease.^{11,12}

Epidemiology

It is estimated that more than one third of the world's population is infected with *Mycobacterium tuberculosis*. Globally there were an estimated 709000 new HIV positive TB cases in 2006. In 2005, there were 8.8 million new active TB cases and 1.6 million people died of TB. The African region accounts for 85 percent of estimated cases, India for 3.3 percent, the European region for 1.8 percent and other countries for 9.4 percent. In South East Asia only 4 percent of notified TB cases were tested for HIV. This region carries the highest burden of tuberculosis and the second highest burden of HIV in the world and leading causes of death among adults of 15-59 years.¹³⁻¹⁶ TB is the cause of death for one out of every three people with AIDS worldwide. The spread of the HIV epidemic has significantly impacted the TB epidemic. One-third of the increase in TB cases over the last five years can be attributed to the HIV epidemic.¹¹

Among the 9.27 million incident cases of TB in 2007, an estimated 1.37 million (14.8%) were HIV-positive. Of these 9.27 million new cases, an estimated 44 percent or 4.1 million (61 per 100,000 population) were new smear positive cases. India, China, Indonesia,

Nigeria and South Africa rank first to fifth in terms of the total number of incident cases. The global number of incident HIV-positive TB cases is estimated to have peaked in 2005, at 1.39 million. In 2007, as in previous years, the African Region accounted for most (79%) HIV-positive TB cases, followed by the South-East Asia Region (mainly India) with 11 percent of total cases. South Africa accounted for 31 percent of cases in the African region.¹⁷

The estimated and reported cases of HIV/AIDS in Nepal are about 70,000 and 6,990 as of June 30, 2006.¹⁸ TB/HIV co-infection is a rising trend. It was observed that in 1992-1998, out of 14 AIDS cases 78.5 percent had TB whereas during 1998-2002, out of 442 AIDS cases 80.76 percent had TB. Symptoms like weight loss (98.4%), fever (93.4%) and diarrhoea (74.3%) have been contributing for the majority of the presentation of HIV/AIDS. In Nepal very few numbers of People Living with HIV/AIDS (PLWHA) are undergoing ART; only 336 as of August 2006.^{19,20}

Pathogenesis

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 characterized by the formation of granulomas.

HIV infects and destroys CD4+ T lymphocytes which are essential in coordinating an effective cell-mediated immune response to *M. tuberculosis*.¹⁵ 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.²¹

TB due to pathogen *M. tuberculosis* occurs as a result of new infection or reactivation of latent

infection. In an HIV-negative population, only up to 10 percent of people infected with *M. tuberculosis* develop TB; approximately 5 percent will develop primary infection in the first two years of exposure and 5 percent 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. Furthermore, it is estimated that HIV/TB co-infected individuals have an annual 5-10 percent risk of reactivation of latent *M. tuberculosis*.^{15,22}

Clinical features

TB is potentially one of the most easily treated opportunistic infections occurring in HIV-positive people and the chemotherapy required is widely available, even in most of the developing world. However, the disease picture is often atypical, which can lead to delay in diagnosis.

Infection and disease with *M. tuberculosis* can occur at any stage of CD4+ count. The nature, clinical presentation and investigative features of TB depend on the degree of HIV-related immunosuppression. In patients with early HIV disease and a well-maintained CD4 count, the clinical picture is essentially very similar to that in the HIV-negative population and the classical presentation of cough, fever and weight loss is common. As the degree of immunosuppression increases, the clinical presentation becomes increasingly atypical and non-specific. The difficulty with diagnosis is compounded by the fact that fever and weight loss can be common symptoms of HIV disease alone. The risks of disseminated disease become higher as the CD4 count falls. A clear association has been reported between low CD4 count and an increased frequency of extra-pulmonary TB, positive blood cultures for *M. tuberculosis* and intra-thoracic adenopathy on chest X-ray Central nervous system involvement is more

common in HIV-positive patients than HIV- negative patients.²¹

Symptoms may be non-specific or absent and it may be difficult to distinguish from HIV disease or other opportunistic infections.²² Extra pulmonary tuberculosis, and in particular, tuberculosis meningitis, is more common in HIV-positive patients presenting with TB and should be suspected in such cases.²³

Diagnosis

Diagnosis of tuberculosis is difficult in HIV positive patients since they often present with atypical symptoms and are susceptible to pulmonary infections that mimic tuberculosis. Sputum collection may not be possible even in patients with pulmonary involvement since a productive cough is not always present. In HIV positive patients, blood smear and culture for acid fast bacilli - not specific for TB therefore not necessarily diagnostic tool can be used for testing drug sensitivity.²³ Moreover, the sensitivity of sputum examination in HIV-positive patients is lower with more advanced immunosuppression.

The tuberculin skin test response is also often reduced in HIV/AIDS due to T cell suppression so again not sensitive. Previous Bacille Calmette-Guérin (BCG) vaccination or exposure to environmental (atypical) mycobacteria can result in false positive results whereas false negative results may occur with chronic illness including TB itself and with immunosuppression. The sensitivity of test is reduced in HIV infection; particularly in advanced disease.²⁵⁻²⁷

In patients with a well preserved CD4+ count, chest X-ray appearances are similar to non-HIV-infected individuals with classic changes such as upper lobe infiltrates and cavitation. The use of tests based on PCR and related DNA techniques allow rapid and specific detection of *M. tuberculosis* antigens. Molecular techniques also enable the identification of

non-tuberculous mycobacteria and the identification of antibiotic resistance mutations. These should be used as an adjunct to standard laboratory techniques.^{19,21}

Treatment

In anti-tuberculosis therapy, treatment guidelines for HIV-infected patients are the same as those for uninfected individuals. If DOT is not possible, self-administered treatment with a fixed dose drug combination is preferred to improve the compliance. The British HIV Association (BHIVA) guidelines state that all cases of TB in HIV-positive patients should be treated with standard daily quadruple anti-tuberculous 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. DOT 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.²⁷

Household contacts of an infectious TB case are a high priority for TB screening and treatment, especially if they are living with HIV and those who are found to have active TB disease need prompt treatment. The first priority for HIV-positive TB patients is to initiate TB treatment, followed by cotrimoxazole and ART. ART should be initiated for all people living with HIV with active TB disease irrespective of CD4 cell count. TB treatment should be started first, followed by ART as soon as possible and within the first 8 weeks of starting TB treatment. The rationale for starting ART soon after TB diagnosis is that case-fatality among HIV-TB patients occurs mainly in the first 2 months of TB treatment.

ART regimen contains two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI).

The preferred NRTI backbone is zidovudine (AZT) or tenofovir disoproxil fumarate (TDF), combined with either lamivudine (3TC) or emtricitabine (FTC). For the NNRTI, world health organization (WHO) recommends either efavirenz (EFV) or nevirapine (NVP).

Because of concerns related to teratogenicity, efavirenz should not be used in women of childbearing potential without adequate contraception, nor should it be used for women who are in the first trimester of pregnancy. Alternatives are also needed for patients who are intolerant to efavirenz or are infected with a strain of HIV that is resistant to NNRTIs. For those who are unable to tolerate EFV or who have contraindications to an EFV-based regimen, AZT + 3TC + NVP or TDF + 3TC or FTC + NVP or a triple NRTI regimen (AZT + 3TC + ABC or AZT + 3TC + TDF) is recommended; the choice of regimen should be based on available regimens within countries.

Mild to moderate IRIS is relatively common in one third of patients with TB started on ART. However, it is relatively rare in its severe forms. The syndrome can present as fever, enlarging lymph nodes, worsening pulmonary infiltrates, or exacerbation of inflammatory changes at other sites generally within 3 months of the start of ART and is more common when CD4 cell count is low (<50 cells/mm³). Most cases resolve without intervention and ART can be safely continued.²⁸

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. The IRIS reactions are

characterized 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.²⁹

Multidrug resistance

Estimate of drug resistance is extremely important in epidemiology and control of tuberculosis. The emergence of strains of *M. tuberculosis* that are resistant to anti-TB drugs is a world wide problem and more alarming is the fact that the highest rates of MDR has been reported from Nepal (48%), Gujarat (India) (33.8%), New York (30.1%), Bolivia (18.3%) and Korea (14.5%). Isoniazide and rifampin resistance was found to be 0.6 percent in England and Wales during 1982-1991³⁰ while prevalence of MDR cases was found to be 4 percent in Western Cape Town.³¹ Multiple drug resistance has been defined by many workers as the simultaneous resistance to isoniazid and rifampin with or without resistance to other drugs by many of the workers. The treatment of MDR - TB cases is not only very difficult but also very expensive.^{30,31,33}

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.²⁹

MDR occurs when drugs are mismanaged or

misused. Patient non-compliance, 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 the increased mortality and morbidity of TB cases.^{14,15,33} Extensively drug-resistant TB (XDR-TB) has an even stronger association with HIV. It has been transmitted to HIV co-infected patients with high mortality.^{31,34-36} Because of the increasing of MDR, resulting from noncompliance to treatment and the high incidence of TB in crowded care facilities like hospitals and prisons with poor health conditions, especially in regions in which prevalence of HIV infection is high, establishing priorities urges to combat TB.

Prevention

TB patients are best isolated from other patients (non-TB) if possible and in particular immunosuppression including HIV/AIDS. Isolation to the TB- suspected a patient admitted in a hospital is an essential step. 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. Screening of close contacts of smear-positive cases for evidence of TB infection should be performed.

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-trimoxazole may be effective in a large population setting. 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 tuberculosis infection and is therefore not recommended.³⁷

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 vaccination and prior exposure to non-tuberculous mycobacteria. The efficacy in HIV-negative people is approximately 50 percent. The risks of disseminated BCG disease increase with the degree of immunosuppression and are well recognized 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.

DOT is recommended by the WHO and Center for Disease Control for the treatment of TB in HIV patients. It is recommended that all patients with MDR-TB take DOT. The superiority of DOT over self-administered therapy for the treatment of TB in developing countries is yet to be proven.²⁹ Encouraging and monitoring patient towards the therapy, providing relevant information and support to the patients should minimize *Mycobacterium tuberculosis* infection.

CONCLUSIONS

HIV/AIDS has become one of the greatest public health threats in the last 500 years. To combat it, effective global strategies must be tightly linked to TB control strategies. Due to HIV, infected patients have high chances of developing TB. TB control is an exercise in vigilance; the goal of controlling and

eventually eliminating TB requires a targeted and continuous effort to address the prevention and treatment needs for those most at risk, including HIV-infected individuals. Efforts to eliminate TB are therefore essential to reducing the global toll of HIV. The epidemiology clearly shows that the HIV and TB epidemics go hand in hand and TB is a diagnostic marker for AIDS, patients with HIV and TB disease but fighting TB/HIV co-infection and drug resistant TB is one of the greatest challenges. Growing multiple drug resistance among tubercle bacilli warrants urgent attention in tuberculosis control programme. Moreover, these must include advanced treatment paradigms, such as HAART, both in order to prolong lives and to help prevent the rates of new TB infections from increasing catastrophically, conceivably beyond all hope of control. The problem of TB/HIV is an issue of critical importance, which needs to be seriously addressed by all countries. This review brings up to date on the current thoughts on this co-infection and hopefully encourages more research in this area of molecular epidemiology of TB in association with HIV/AIDS which allows to tuberculosis control units to carry out the epidemiological studies to monitor TB transmission and efficacy of TB and HIV/AIDS control programs that can be significant for clinical impact.

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