The Interaction of Tuberculosis and HIV in Africa

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Abstract
The interaction of Tuberculosis (TB) and HIV has deadly consequences around the world, especially in sub Saharan Africa. Diagnosis is challenging particularly in childhood in countries with limited resources. This review focuses on the epidemiology of co-infection, clinical presentation and management of affected patients.

Keywords: Tuberculosis; Africa

The Epidemiology of HIV-Tuberculosis Co-infection
HIV infection affects 34 million of the world population and Tuberculosis (TB) affects 15 million. The greatest burden of both diseases is in Sub Saharan Africa [1]. In high HIV prevalence countries in sub Saharan Africa TB notifications have increased over 20 years from 1990 to 2009 [2]. According to the WHO world report in 2009, HIV-associated TB cases accounted for 78% of the total cases in Africa yet in South East Asia it was only 13% [3]. Clearly high HIV prevalence rates are associated with high TB prevalence rates, to the extent that HIV infected people are 20 to 30 times likely to develop TB [4]. In addition, HIV-associated TB contributes disproportionately to TB-related deaths. In 2008, there was 37% estimated case fatality due to TB among HIV infected people while HIV uninfected accounted for 16% [3]. The probable reasons for such high case fatality rates include rapid progression of disease in HIV infected individuals and, delayed diagnosis of both HIV and TB. There is also a delay in accessing combination antiretroviral therapy and higher rates of multidrug resistant TB in HIV infected patients [3].

Africa is the world’s second largest and second most populous continent [5]. However, it remains the world’s poorest and underdeveloped continent. Sub-Saharan Africa has been the least successful region of the world in reducing poverty [6]. There has been rural urban migration resulting in slums, crowded housing, working places with poor ventilation, poor nutrition and health care. In addition, risky behaviours among commercial sex workers have fuelled the burden of both HIV and TB.

Does HIV alter the transmission of TB? It is interesting to note the paradox that HIV infected patients with pulmonary TB are less likely than uninfected to transmit TB. TB patients with advanced AIDS maybe less infectious than those without HIV. This could be due to the fact that they have less cavitary TB than HIV uninfected, reduced spumum bacillary burden, a weak cough and greater social isolation [4]. It is unclear how much HIV associated TB contributes to the transmission in the community and barriers to health care are associated with increased infectiousness.

The Clinical Management of HIV-TB Co-Infection
TB accelerates the progression of HIV in individuals. In Uganda, there was 3 times higher mortality of TB in HIV infected individuals with a CD4 count of less than 200 [7]. During antiretroviral therapy, TB incidence rates decrease with recovery of CD4 counts [8]. In patients with latent TB, HIV infection accelerates progression to reactivation TB with a risk of about 10 percent every year [9]. HIV infected patients also appear to be at a higher risk of re-infection, about 69% of TB recurrences in HIV infected Gold miners in South Africa were due to re-infection [10].

The clinical presentation of TB is different in HIV infected patients. Subacute systemic and respiratory symptoms are common. Pulmonary TB is the most common form of TB. Typical symptoms include fever, weight loss, cough and persistent diarrhoea [11]. Typical X-ray findings of TB in early HIV infection include right cavitary pneumonia, but in late HIV infection atypical TB signs include pleural effusion, lower or idle lobe infiltrates, mediastinal adenopathy, interstitial nodules and normal chest X-ray findings [11]. As the CD4 cell count declines, the frequency of cavitation in pulmonary TB decreases while extra pulmonary manifestations increase [4].

Diagnosing TB is challenging, the gold standard TB culture, can take up to 6 weeks. In resource constrained settings, the sensitivity of sputum microscopy to detect TB ranges from 20- 60 % [12]. HIV infected patients have a lower rate of sputum positivity when they have pulmonary tuberculosis. It is hoped that the introduction of the Xpert MTB/Rif assay, which is more sensitive than smear but less sensitive than liquid culture along with other emerging diagnostic techniques will improve TB diagnosis [13]. Interferon gamma release assays (IGRAS) detect cellular immune responses to MTB antigens. They are approved for the diagnosis of latent TB infection in HIV infected patients but lack specificity for the diagnosis of active TB [14]. In countries with high TB prevalence, the sensitivity and negative predictive value of the IGRAS are insufficient to rule out active TB infection in HIV infected patients. Indeterminate results are common for HIV infected patients with low CD4 counts [4].

TB drug treatment in HIV infected patients is the same as for HIV uninfected patients. The use of bactericidal Rifampin in both the initial and continuation phases of TB treatment is essential. It reduces the rates of treatment failure, TB relapse and drug resistance in HIV infected patients with pulmonary TB [4]. Rifampin and Rifabutin are potent inducers of the cytochrome P450 system. Combination of Rifampin

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with protease inhibitors, with or without Ritonavir is contraindicated. For integrase inhibitors and entry inhibitors, studies now indicate that Rifampin significantly accelerates the metabolism of Raltegravir and Maraviroc resulting in sub therapeutic levels of the antiretroviral drugs when administered at standard doses [15,16]. Rifabutin has less of an effect on Raltegravir metabolism and may be more appropriate for co administration [17]. The preferred combined regimen for the concomitant treatment of HIV and TB is Efavirenz-based antiretroviral with Rifampin-based TB treatment. The use of Nevirapine with Rifampin-based TB therapy can be an alternative, though its inferior for co infected patients who cannot take Efavirenz (first trimester of pregnancy or resistance) and if Rifabutin is not available [4]. It is also important to note that multi drug resistant TB is common in HIV infected individuals with low CD4 counts. This was noted in the Tugela Ferry outbreak, in South Africa [18]. Multidrug resistant TB, also resulted in higher mortality in HIV infected individuals.

Immune reconstitution inflammatory syndrome (IRIS) is a clinical deterioration after the initiation of anti-retroviral therapy in HIV infected individuals. It is due to inflammation associated with pathogens and tumours. TB associated IRIS has been described [19]. There are two clinical forms of TB-associated IRIS namely paradoxical and unmasking-TB associated IRIS. Paradoxical TB-associated IRIS is an exaggerated inflammatory response during TB treatment in a patient known to have TB while unmasking TB-associated IRIS is previously undiagnosed TB which is unmasked after the initiation of antiretroviral therapy. The risk factors of developing IRIS are as follows: less than 2 months of antiretroviral therapy, extra pulmonary or disseminated TB, low CD4 (<100) at the start of ART, viral load greater than 10^5log copies/ml, rise in CD4% and decreasing viral load [13]. The management of IRIS is mainly supportive and can include the use of corticosteroids. Delaying initiating ART in HIV infected patients with TB had been recommended until recently by expert opinion to prevent IRIS. In the SAPIT trial conducted in South Africa, the researchers found that starting ART during TB treatment reduced mortality by 56% compared with sequential therapy [20]. In this trial, the integrated therapy group started ART in less than 4 weeks or between 8 and 12 weeks after initiation of tuberculosis treatment. The comparison group delayed ART until 6 months after completion of tuberculosis treatment. In the CAMELIA trial in Cambodia, a comparison was made between mortality rates in patients with CD4 counts of less than 200 who were started on ART 2 weeks or 8 weeks after completion of tuberculosis treatment. There was a 34% reduction in the mortality rate in the 2 week versus 8 week group, however, rates of IRIS were 3 times higher [21]. The STRIDE ACTG 5221 trial enrolled co-infected patients with CD4 counts of less than 250 cells/microliter and randomized patients to an immediate (<2 weeks) or early (8-12 weeks) ART regimen. The composite endpoint of AIDS/death was similar in the 2 arms but in the subgroup of CD4 count less than 50 was reduced from 27% to 15% [22].

Conclusion

TB and HIV co-infected affect clinical presentation, diagnosis, treatment and outcomes of affected patients. This pandemic is mainly in Africa and efforts targeted at this region will enable health workers to cope and eventually manage the problem adequately, taking into account the current evidence. Improvements in TB screening and diagnosis are required. Treatment of latent TB infection is needed and in settings of high HIV prevalence Isoniazid preventive therapy can reduce TB incidence. Scientific advances are essential for an effective TB vaccine and simple anti-TB drug regimens are necessary.

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