PAEDIATRIC TB/HIV CO-INFECTION – ‘AN UNCOMPROMISING DUET THAT MAKES CHILDREN SUFFER AND PARENTS CRY’

South Africa carries a high proportion of the global burden of TB and HIV.

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Of the global burden of 9.4 (8.9 – 9.9) million incident cases of tuberculosis (TB) in 2009, childhood TB accounted for 11% (884 000 cases).1 South Africa had the seventh highest burden of TB with an annual incidence of 600/100 000. During the same period childhood HIV infection carried a significant burden of disease in sub-Saharan Africa (SSA) with 1.8 million cases present in this region. Despite the presence of highly effective strategies for the prevention of mother-to-child transmission of HIV infection, an estimated 665 000 new childhood infections still occur globally each year. South Africa, with its massive scaling up of the provision of antiretroviral therapy has reduced the HIV mother-to-child transmission rate to just 3.5% among HIV-infected pregnant women. Furthermore, an estimated 60% of its 240 000 HIV-infected children are receiving ARV therapy and this is likely to reduce the incidence of TB and the rate of HIV-related TB deaths.2 The influence of HIV on TB in infants below 1 year of age is well described in a prospective study by Hesseling et al., who reported a rate of culture-confirmed TB of 1 596 per 100 000 in HIV-infected and 65.9 per 100 000 in HIV-uninfected infants.3 The incidence of pulmonary and extrapulmonary TB was 24.2-fold (95% CI, 17.1 - 34.7) higher in HIV-infected compared with uninfected infants.4 Among the HIV-infected group 32.7% died and 19.2% of these patients did not receive HAART. The risk of acquiring TB is 10% per annum in HIV-infected children while for an HIV-uninfected child it is 10% per lifetime.

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Antiretroviral therapy reduces the incidence of TB in HIV-infected children. Volari et al. have shown a reduction in mortality by 76% and the halving of the incidence of TB (from 20.2 to 8.3 per 100 patient years) with early initiation (7 weeks) compared with late initiation (6 months) of ARVs.5 A Kenyan study evaluating the incidence of TB in 6 535 HIV-infected children during 1994 - 2006 showed an 85% reduction in incident TB in ART-treated children compared with those not on combination ART (cART).6

Pathogenesis of TB

Cell-mediated immunity, specifically that mediated by CD4+ T cells, is important for the control of both HIV and TB infection. HIV-infected individuals with depleted CD4+ T cells are more likely to acquire infection, less capable of controlling replication of Mycobacterium tuberculosis, progress rapidly from primary infection to TB disease, and develop reactivation disease from latent TB infection. Infection with M. tuberculosis usually occurs via the respiratory tract. After infection, alveolar macrophages present mycobacterial antigens to CD4+ T cells. This results in the release of interferon-γ and other cytokines. In HIV-positive individuals there is poor granuloma formation, little or absent caseous necrosis, poor containment of mycobacteria with large organism loads and haematogenous dissemination.6

Impact of TB on HIV disease

The course of HIV infection is accelerated following the acquisition of TB infection. The development of TB is associated with increased HIV-1 replication and increased viral loads due to increased systemic immune activation as well as altered local cytokine milieu at sites of M. tuberculosis infection. Mycobacteria enhance HIV replication in tissues by inducing nuclear factor kappa-β, the cellular factor that binds to the promoter region of HIV. Mononuclear cell activation is a feature of active TB disease. Mononuclear cells that express HLA-DR are the most productive source of HIV replication. Dysregulation in β chemokines and their receptors has been described during TB; this may contribute to enhanced viral dissemination.7 Programmed cell death of T cells is increased at the time of diagnosis of pulmonary TB in HIV-infected patients and may be partly responsible for further loss of immune responses directed to HIV-1.8,9 TB provides a milieu of continuous cellular activation and changes in cytokine and chemokine circuits that are permissive of viral replication and expansion in situ.10

Congenital tuberculosis

The incidence of congenital TB has increased 5-fold since the onset of the HIV epidemic. There has been a parallel 10-fold increase in the incidence of TB in HIV-infected pregnant women compared with HIV-uninfected (774/100 000 v. 74/100 000). Perinatal transmission of TB (in utero, during delivery or postpartum) occurs at a rate of 10 - 15% and increases 5 - 6-fold if appropriate care is not provided for the mother. Infants with immature immune systems are vulnerable to rapid progression of HIV infection3 and rapid progression to TB disease after infection. Postnatal transmission of M. tuberculosis is through inhalation. It is estimated that at least 50% of infant TB cases are from a maternal TB source case.3 Congenital TB usually manifests in the first 3 weeks of life but can occur later. Difficulties in diagnosis include the nonspecific presentation, challenges in obtaining sputum samples and the low yield of bacteriological confirmation in the majority.10 Even in the absence of HIV, 50% of infants infected with M. tuberculosis will progress to disease in the first year of life, with many developing disseminated forms of the disease.11
Diagnosis
The diagnosis of TB in HIV-infected children is difficult. A history of recent contact with an infectious TB-infected source case is extremely useful. The risk of acquiring *M. tuberculosis* infection is determined by the proximity, duration and infectivity of the exposure. The risk of transmission of an infectious pulmonary TB source case with close contact is between 60% and 80% for sputum acid-fast bacilli (AFB) smear-positive and 30 - 40% for smear-negative source cases. Parents are often the source of transmission of TB to their infants. The characteristic clinical features of TB, e.g. fever for longer than 2 weeks, persistent cough for longer than 2 weeks and failure to thrive in the preceding 3 months are less useful in HIV-infected than uninfected children (sensitivity 51.2% v. 82.3%). Radiographic manifestations of TB overlap with other HIV-associated lung conditions such as bacterial pneumonia and lymphocytic interstitial pneumonia.

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The poor sensitivities of the tuberculin skin test (TST) of just 26% in HIV-infected children make confirmation of the diagnosis of TB difficult. The interferon gamma release assays, quantiferon gold in tube and Elispot measuring specific antigens, i.e. early secretory antigens target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) have sensitivities of 17% and 52% in HIV-infected children respectively. The interferon gamma release assays, the Genotype MTBDRsl assay, can rapidly detect genetic mutations for drug resistance-related of strains of XDR-TB in >85% of cases. In December 2010, WHO endorsed an automated PCR based assay, the Gene-Expert MTB/RIF diagnostic test for the detection of *M. tuberculosis* and drug resistance in less than 2 hours – this technique is being phased in South Africa currently.

Anti-tuberculosis therapy
Current IUA-TLD and WHO recommendations for the management of TB in HIV-infected children are the same as for HIV-uninfected children, with standard 6-month short-course of rifampicin-based therapy. Children must be reviewed at the end of this period to ascertain if cure has been achieved, otherwise longer duration of treatment is warranted. Careful attention should be paid to correct dosing, especially with weight gain during successful therapy. Culture and sensitivity should be requested, especially if the source patient is a retreatment case or is known to have drug resistance.

Combination antiretroviral therapy (cART)
When to start cART in children with TB
Issues of age, pill burden, overlapping adverse drug reactions, drug interactions, development of immune reconstitution inflammatory syndrome (IRIS), progression of immunosuppression and outcome contribute to the decision-making process. Recent data from a HIV/TB co-infected adults in Durban has shown a 56% reduction in risk of deaths in patients with early initiation of cART (<4 weeks) compared with deferring cART until completion of anti-TB therapy. This benefit was predominantly seen among patients with very low CD4 counts. In the Camelia trial, initiating cART after 2 weeks of anti-TB therapy was associated with reduced deaths in adults with advanced HIV disease as opposed to those initiating cART at week 8 (17.8 % v. 27.3%). In pregnancy, the early initiation of cART and anti-TB therapy will reduce transmission of both diseases to the newborn infant. In children, little data exist on the timing of cART. A major concern with the early introduction of cART in patients on anti-TB therapy is the overlapping toxicity and the possibility of precipitating IRIS, especially in children with severe immune suppression. However, early initiation (<2 weeks after anti-TB therapy) of cART is advocated, especially in those HIV-infected children with low CD4 counts (<200 cell/µl). All other newly diagnosed co-infected children should commence cART during the continuation phase of the TB therapy as soon as the patient can tolerate the medication.

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Children on cART who develop TB
The differential diagnoses include re-infection or reactivation TB, primary TB or IRIS. Initially, cART treatment failure should be ruled out and adherence ensured. In those on abacavir, lamivudine and efavirenz/nevirapine without treatment failure, ensure that the dose of NVP/EFV is at the higher end of the dosing schedule. Co-administration of cART and anti-TB therapy carries an increased risk for hepatotoxicity, so monitoring of liver enzymes is essential. In patients on abacavir, lamivudine and lopinavir/ritonavir, additional ritonavir (to achieve a lopinavir:ritonavir of 1:1 instead of 4:1 in the syrup and tablet formulations) is required to overcome the enzyme inducing effect of rifampicin.

Adverse drug-effects
Anti-TB drugs and cART have similar toxicities. These include nausea (ddI, AZT,
Although bacilli Calmette-Guérin (BCG) vaccination could lead to disseminated Mycobacterium bovis disease in the presence of immunosuppression, the current national policy in South Africa to vaccinate all newborns with BCG should continue because of the large overall burden of TB to both HIV-infected and uninfected children.

**Outcome**

Mortality rates are higher among HIV-infected than uninfected TB co-infected children (13.4% v. 1.5%).

There is lower cure rate of approximately 60% in HIV-infected children in a study by Palme et al.

References available at www.cmej.org.za

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**TB chemoprophylaxis in HIV-infected children**

Chemoprophylaxis with isoniazid is effective in preventing progression of TB infection to disease in adults. It is critically important to exclude active TB before preventive therapy is instituted. Current evidence of the value of universal isoniazid preventive therapy (IPT) prior to or in the absence of documented exposure to a source case (pre-exposure IPT) seems contradictory. Zar and colleagues showed a benefit in mortality a double-blind study comparing INH with placebo (11 (8%) v. 21 (16%) (hazard ratio 0.46, 95% confidence interval 0.22 - 0.95, \( p=0.015 \)) in HIV-infected children with limited access to ART in Cape Town. The incidence of TB was also lower in the INH group (5 cases, 3.8%) than in placebo (13 cases, 9.9%) (hazard ratio 0.28, 0.10 - 0.78, \( p=0.005 \)). A large multi-centre trial of more than 500 HIV-infected and 800 HIV-exposed uninfected infants between 3 and 4 months of age in South Africa and Botswana showed no benefit of pre-TB exposure IPT when compared with placebo. The difference could be explained by the variance in patient populations and study protocols. WHO supports IPT for HIV-infected children with TB infection after the first year of life, and meticulous identification of TB exposure coupled with a high index of suspicion for TB below a year of age. The Centers for Disease control recommends prophylaxis for all HIV-infected individuals with a tuberculin skin reaction >5 mm. The South African policy on IPT states that INH should be given to all HIV-infected children in contact with a TB index case and in children with TB infection where active disease is excluded.

It is estimated that at least 50% of infant TB cases are from a maternal TB source case.

**BCG vaccination**

The use of BCG in HIV-infected children has recently been shown to be associated with an increased incidence of 400 - 800 per 100 000 cases of disseminated BCGosis. The safety committee of WHO have recommended that BCG vaccine should not be used in children who have symptomatic HIV disease.