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. The incidence of pulmonary and extrapulmonary TB was 24.2-fold (95% CI, 17 - 34) higher in HIV-infected compared with uninfected infants.[3] 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.[4] 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).[5]

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] 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*.[9]

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 infection[4] 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.[3] 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.[11,12] Parents are often the source of transmission of TB to their infants. The characteristic clinical features of TB, i.e. 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%).[13] Radiographic manifestations of TB overlap with other HIV-associated lung conditions such as bacterial pneumonia and lymphocytic interstitial pneumonia.[14]

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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. A negative TST and negative IGRA test would help exclude the diagnosis of TB and unnecessary treatment in almost a third of cases.

Samples for the microbiological identification of TB depend on the site of disease. Pulmonary TB is identified by finding acid-fast bacilli on induced sputum, bronchoalveolar aspirates and gastric aspirates. The measurement of the lipoarabinomannan (LAM) in a urine sample appears to be promising to confirm a diagnosis in disseminated TB, but further studies are required.

Molecular diagnosis based on nucleic acid amplification techniques (NAAT) have a sensitivity approaching 100% in detecting *M. tuberculosis* in smear-positive specimens with a sensitivity of 70% in smear-negative samples, and a result can be obtained in 1 - 2 days.[16] Isoniazid and rifampicin resistance can be detected within 2 days with a line probe assay, the Hain test. In a large study conducted in the National Health Laboratory service (NHLS), a comparison of the drug susceptibility on conventional testing with molecular testing showed sensitivity, specificity, positive predictive value, negative predictive value of 99%, 100%, 100%, 100%, respectively. Sensitivity for INH resistance was less optimal at 82% (72 - 92%). The latest version of the line probe assays, the Genotype MTBDRsl assay, can rapidly detect genetic mutations for drug resistance-related of strains of XDR-TB in >85% of cases.[15] 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 IUATLD 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.[16] 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%).[17] 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.[18] 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,

ritonavir, PZA), peripheral neuropathy (d4T, ddI, INH), rash (NVP, abacavir, INH) and hepatitis (rifampicin, NVP, PI). The use of fixed-drug combination (FDC) of ARTs and anti-TB therapy may make recognition of specific causes for the ADRs difficult. However, the overall benefit of FDC outweighs this risk.

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.[19] 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.[20,21] 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.[22] The Centers for Disease control recommends prophylaxis for all HIV-infected individuals with a tuberculin skin reaction >5 mm.[23] 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.[24]

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. 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%).25 There is lower cure rate of approximately 60% in HIV-infected children in a study by Palme *et al.*[26]

References available at www.cmej.org.za

In a nutshell

- Tuberculosis (TB) is the commonest opportunistic infection in HIV-infected children worldwide.
- TB accelerates the progression of HIV disease while HIV infection increases the severity of TB manifestations in a co-infected child.
- The risk of diagnostic delay and error is commoner in HIV-positive than in HIV-negative children due to overlapping clinical and radiological features.
- Interferon gamma assays add little to the diagnosis of TB in HIV-infected children.
- Newer molecular testing methods are likely to revolutionise the diagnosis of childhood TB by providing a rapid diagnosis, but do have limitations and they are currently only used to diagnose MDR TB.
- Early treatment of TB among HIV-infected children with low CD4 counts has a significant impact on outcome. HIV-positive children have lower cure rates and higher mortality compared with HIV-negative children on standard anti-TB therapy.
- INH prophylaxis is beneficial in HIV-infected children with latent TB infection, although its role in all HIV-infected children is uncertain.
- Active TB disease must be excluded prior to initiating INH prophylaxis.
- The incidence of congenital TB has increased substantially among babies born to HIV-infected mothers.
- Active screening and management of the pregnant women for TB and HIV infection will reduce the transmission of both diseases.
- Bacille Calmette-Guérin (BCG) vaccination may lead to disseminated *Mycobacterium bovis* disease in the HIV-infected child but due to high overall burden of TB, the current national policy is to vaccinate all newborns with BCG.

SINGLE SUTURE

Extra weight hinders IVF success

Carrying excess weight could make life even harder for women who are trying to conceive via IVF. Obesity is associated with an increased risk of miscarriage but its effect on assisted reproduction wasn't known. To investigate, Tarek El-Toukhy at Guy's and St Thomas's Hospital in London, and colleagues, followed 413 women who had had IVF between 2006 and 2010. The group noted the women's BMI before treatment – a figure between 25 and 29.9 is classed as overweight, while over 30 is obese. Around 44% of women who were obese had a miscarriage compared with 19% of those at a healthy weight. Around 33% of women who were overweight but not obese miscarried.

Being overweight can alter hormone levels that affect the egg and its environment, El-Toukhy says. The UK's National Institute of Health and Clinical Excellence says that women with a BMI over 30 who opt for IVF should be informed of the potential difficulties. But 'we shouldn't stop at 30, we should aim for a BMI as close as possible to the healthy range,' El-Toukhy says.

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