The interaction of HIV and tuberculosis in childhood

P M Jeena

The recognition of a case of childhood tuberculosis (TB) is a sentinel public event. It reflects a poor adult TB control programme, a marker of other diseases, e.g. HIV, provides a reservoir for future cases of TB, an opportunity to undertake contact tracing and a need for action in child health. Childhood TB accounts for 11% (884 000 cases) of the global burden of TB, with Africa accounting for 27% of the global cases despite having just 11% of the world's population. South Africa has the seventh highest global burden of TB with an incidence of 600/100 000.

Of the 2.8 million cases of childhood HIV disease, 2.2 million (> 80%) live in sub-Saharan Africa (SSA). There are 665 000 new childhood infections and 450 000 deaths (3%) globally from HIV each year despite effective strategies for the prevention of mother-to-child transmission. In SSA, only 6% of children deserving antiretroviral drugs receive therapy; consequently HIV disease accounts for 6% of all deaths in children younger than 5 years of age. In South Africa, of the 240 000 HIV-infected children only 10 - 15% receive treatment.

The incidence of TB in HIV-uninfected persons is 656/100 000 person years while in HIV-infected persons it is 4 381/100 000 person years. In South Africa, the incidence of both TB and HIV is increasing exponentially, with each epidemic fuelling the other (4.3- and 3.5-fold increase for TB and HIV respectively). The risk of acquiring TB is 10% per annum in HIV-infected children while for an HIV-uninfected child it is 10% per lifetime. The impact of HIV on TB prevalence is clearly seen with the increase in the prevalence of congenital TB, paucibacillary or smear-negative TB, extrapulmonary TB, reactivation and reinfection TB and immune reconstitution inflammatory syndrome (IRIS).

Diagnostic criteria for TB and HIV disease in childhood

The diagnosis of childhood TB has always been difficult to confirm; this is compounded in HIV-infected children. Several practical advances to assist in the diagnosis have recently been made. Contact with an infectious source TB case has been explored in terms of duration of exposure, degree of infectivity, drug susceptibility, and nutritional and immunological status of the index case. The recognition that 10 - 15% of acute pneumonia cases are due to TB and increased incidence of clubbing in HIV and TB co-infected children has allowed for a heightened suspicion of the diagnosis of TB. However, overlapping clinical and radiological features and poor sensitivities for the tuberculin skin test (TST) make confirmation of TB difficult. The TST has a sensitivity of 58% in HIV-uninfected and just 26% in HIV-infected children. Its sensitivity is affected by BCG, age, degree of immune suppression, poor nutrition and environmental mycobacterium. The T-lymphocyte-based immune releasing assays measuring specific antigens, e.g. early secretory antigen target 6 (ESAT 6), culture filtered protein 10 (CFP10) or Resat have shown promise in HIV-infected individuals. Two types of interferon-gamma releasing assays (IGRA) are commercially available, the Quantiferon TB Gold and the Elispot T-spot based assays. The former test appears to be superior to TST in HIV-uninfected children, but is less useful in HIV-infected children with low sensitivity (17%) and specificity (38%). The Elispot T test has a sensitivity of 52% in HIV-infected children. Further comparative studies are needed to confirm these findings. In comparison with the TST, the IGRA appears to be slightly better in detecting TB infection (51% v. 73 - 85%), although the combination of the IGRA and TST was useful in confirming a diagnosis of TB infection in 91.4% of children. A negative IGRA and TST would help exclude the diagnosis of TB and could reduce over-diagnosis by almost one-third.

As regards microbiological detection of *Mycobacterium tuberculosis*, the use of the radiometric mycobacterium liquid culture system (MGIT) has increased the yield of TB in a suitable specimen to 97% within 9.5 to 14 days; its value in HIV-infected children has not yet been evaluated. Histological findings on biopsy for TB in HIV-infected children include ill-defined caseous granulomas with epitheloid histiocytes.

Management of TB and HIV disease

Several major issues related to the combined use of anti-TB and antiretroviral therapy have been studied recently. Concerns relating to pill burden, adverse drug reactions, drug interactions and IRIS have been identified. The commencement of highly active antiretroviral therapy (HAART) in a child being treated for TB is best undertaken after the completion of anti-TB therapy, provided the child's condition allows this. This limits drug interactions and adverse effects between HAART and anti-TB drugs. In children with WHO stage 4 disease or a CD4 count within 5% of severe immunodeficiency (200 - 349 cells/µl) HAART should be commenced as soon as possible after the TB treatment is tolerated, i.e. during in the initiation phase of anti-TB treatment. Children with WHO

Department of Paediatrics and Child Health, University of KwaZulu-Natal, Durban
P M Jeena, MB ChB, FCP (Paed)

Corresponding author: *P M Jeena (jeena@ukzn.ac.za)*

stage 3 disease or with a CD4 count above 349 cells/µl or > 5% above severe immunodeficiency, HAART should be commenced during the maintenance phase of anti- TB therapy. In a child receiving HAART who develops TB, HIV treatment failure should first be ruled out. After this one should decipher whether reinfection/reactivation, primary TB or IRIS has occurred. In those on first-line therapy, i.e. stavudine (4dT), lamivudine (3TC), and efavirenz/nevirapine (EFV/NVP), a possible change to a triple nucleoside reverse transcriptase inhibitor regimen could be considered, although the efficacy of this regimen is just 79% and abacavir has been associated with acute pneumonitis. A second option includes the changing of NVP to EFV, or increasing the dose of NVP by 25 - 33% to accommodate the faster metabolism of NVP in the presence of anti-TB therapy. This option carries an increased risk of hepatotoxicity, making monitoring for adverse effects essential. In patients on second-line agents, i.e. zidovudine (AZT), ddI and Kaletra, a 33% increase in the dose of ritonavir is required to combat drug interaction between rifampicin and protease inhibitors (PI). The PI dose should be slowly increased over a week.

Anti-TB drugs and HAART have similar toxicity effects. These include nausea (ddI, AZT, ritonavir, PZA), peripheral neuropathy (d4T, ddI, INH), rash (NVP, abacavir, INH) and hepatitis (rifampicin, NVP, PI).

Drug resistance to both HAART and anti-TB therapy is a third major issue. The criteria for resistance testing of children on HAART include clinical failure on a second-line regimen, virological failure (increased HIV viral load on two samples taken 1 month apart) and children who are adherent (pill count or diary entries). Innate resistance to antiretroviral agents has been seen. Acquired resistance commonly K184V mutations to 3TC and K103N to NVP is seen after structured drug interruption, use of inefficient regimens or poor adherence. Single- or multiple-drug mutations with class effects have been recorded.

Resistance to anti-TB drugs is common and increasing. Initial (*ab initio*) drug resistance is seen in 1 - 4%, secondary (post drug utilisation) resistance in 10 - 15%, and multidrug (rifampicin and INH) resistance in 2 - 6% of cases. Extensively drug-resistant TB (XDR TB) (resistance to a flouroquinolone and any of the other second-line anti-TB agents) is predominantly seen in HIV-infected adults. Transmission of these resistance strains is increasing, causing severe disease in a proportion of cases.

It is recommended that HIV-infected children receive standard regimens as suggested by the National Tuberculosis Programme. However, some modifications should be considered. Firstly, an additional 5 mg/kg dose of INH should be added to the recommended fixed-drug combination during the intensive stage of therapy because of fast acetylating of INH in childhood. Secondly, the high end of the dosing range for all drugs should be used in HIV-infected children. Thirdly, a reactivation or reinfection TB regimen must be considered for children on their second or third courses of anti-TB therapy. Fourthly, at the end of 6 months' treatment the children must be carefully evaluated as prolonged use of anti-TB therapy may be needed. It should be remembered that radiological changes may persist at this time, even if the patient is cured.

The role of chemoprophylaxis in children in many high-burden countries has been very controversial. The current recommendation for use of chemoprophylaxis in HIV-infected children includes all children with a positive TST or those in contact with an infectious case of TB after active disease was excluded. A recent placebo-controlled randomised trial from Cape Town showed HIV-infected children on INH prophylaxis had lower all-cause mortality than children on placebo although the deaths in the placebo group did not have TB. Further studies are required. The current regimens for TB prophylaxis include INH 5 mg/kg for 6 months or INH and rifampicin 10 mg/kg each for 3 months

The directly observed therapeutic strategy (DOTS) has been advocated by the WHO as a major advance in the control of the epidemic. In parts of South East Asia, this strategy has revealed significant benefit in the control of the TB epidemic while in most parts of Africa, a poor yield in the control of the epidemic has been realised. This difference is attributed to the resources utilised in the programmes in the two regions. DOTS for HIV and TB could be combined as a joint public private health initiative.

The use of BCG in HIV-infected children has recently been shown to be associated with an increased incidence of between 400 and 800 per 100 000 cases of disseminated BCGosis. The safety committee of WHO have therefore recommended that BCG vaccine should not be used in children who are known to be HIV infected. BCG should be continued to be administered at birth where the HIV status cannot be determined during early infancy. Careful monitoring for disseminated disease should be instituted where BCG vaccine is administered.

Congenital tuberculosis

The incidence of congenital TB has increased 5-fold since the onset of the HIV epidemic. This is parallel to an increase in the incidence of TB in HIV-infected women during pregnancy (774/100 000) as compared with the TB incidence of 74/100 000 in HIV-uninfected pregnant women. Perinatal transmission of TB occurs at a rate of 10 - 15% and increases by 5 - 6-fold if appropriate care is not provided for the mother. Certain anti-TB therapy such as quinolones, ethionamide, cycloserine, terizidone, PAS and potentially aminoglycosides are toxic in pregnancy and should not be used. EFV has been shown to be teratogenic while NVP has been associated with hepatotoxicity in pregnancy. Congenital TB could be acquired

in utero, during delivery or post partum. A case of congenital TB could be identified either from exposure to the TB-infected mother or as an index case in a sick newborn. Diagnosis of congenital TB is made according to the criteria of Cantwell. Features of early presentation include prematurity, growth retardation, pneumonia and hepatic disease in the first week. The diagnosis is confirmed when genital tract TB disease in the mother is diagnosed. Late presentation at 3 - 4 weeks includes hepatosplenomegaly, lymphadenopathy, chronic pneumonia, disseminated infection, seizures, skin TB and jaundice. Management of HIV and TB in the neonatal period is complex and these cases should be referred.

Conclusion

HIV infection has altered the incidence and presentation of childhood TB. The incidence of congenital TB, extrapulmonary TB and reactivation/reinfection disease is increasing. The diagnosis of TB in HIV-infected children is difficult. Treatment of HIV and TB co-infected children is challenging with adverse drug reactions and drug interactions being common. Chemoprophylaxis and immunisation require further evaluation.

Recommended reading

Gray A, Karim SSA, Gengiah TN. Ritonavir/saquinavir safety concerns curtail antiretroviral therapy options for tuberculosis-HIV coninfected patients in resource-constrained settings. *AIDS* 2006; 20: 302-303.

La Porte CJL, Colbers EPH, Bertz R, *et al*. Pharmacokinectics of adjusted-dose lopanavir-ritonavir combined with rifampicin in healthy volunteers. *Antimicrob Agents Chemother* 2004; 48: 1553-1560.

Michailidis C, Poznaik A, Mandalia S. Clinical characteristics of IRIS syndrome in patients with HIV and TB. *Antivir Ther* 2005; 10: 417-422.

World Health Organization. Guidelines on antiretroviral therapy in children. http://www.who.int.pub.guideline who paed pdf (last accessed 23 February 2007).

World Health Organization. Safety of BCG vaccine in HIV-infected children. *Wkly Epidemiol Rec* 2007; 82: 17-24. http://www.who.int/wer (last accessed 23 February 2007).