HIV and TB co-infection in children

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Abstract

The epidemiology of tuberculosis is adversely impacted by the human immunodeficiency virus (HIV) co-infection. HIV-infected patients are more prone to opportunistic infections, most commonly tuberculosis, and the risk of death in co-infected patients is higher than in those without HIV due to the impaired cellular immunity and reduced immunological response in HIV-infected patients.

Introduction

The management of HIV infection has changed significantly over the last 10 years, with the development of new antiretroviral medications, including better formulations and fixed-dose combinations. Since the introduction of earlier treatment as well as pre-exposure prophylaxis, there has been both a significant reduction in HIV-related illnesses and an increase in the proportion of patients who are virally suppressed. This article aims to improve pharmacists' understanding of the particular needs of the HIV/TB co-infected child, with reference to updated treatment guidelines, and to emphasise the role that pharmacists can play in the care of these patients.

Epidemiology and pathophysiology

HIV is transmitted through contact with the blood, semen, vaginal secretions, breast milk, saliva, or exudate from wounds or skin and mucosal lesions of someone infected with the virus.[1] The main means of transfer of the virus is directly via bodily fluids.[2] However, the primary paediatric route is vertical transmission from mother to child. Vertical transmission rates in Africa vary from 25–52%. Prevention of mother-to-child transmission (pMTCT) interventions can decrease this percentage to less than 2%.[3]

Vertical transmission can occur before birth (intrauterine), during birth (intrapartum), or after delivery (usually via breastfeeding). As early as 10 weeks' post-conception, intrauterine transmission can be detected by polymerase chain reaction (PCR) testing of foetal tissue. About 30–40% of newborns are infected *in utero*, if the mother is not successfully treated with antiretrovirals (i.e. is not virally suppressed). Detection of the virus soon after birth correlates with early onset of symptoms and rapid progression to AIDS, consistent with more long-standing infection during gestation. Nonetheless, it is estimated that 60–70% of neonates do not have detectable virus before one week of age. The mechanism of transmission appears to be exposure to infected blood and/or cervico-vaginal secretions in the birth canal.[3] Transmission can occur transplacentally or perinatally.

The least common route of transmission is via breast milk. Both free as well as cell-associated viruses have been detected in breast milk from HIV-infected mothers. The risk of transmission via breast milk is 14% in children whose mothers were HIV infected before pregnancy and 29% in children whose mothers were infected postnatally, as the viraemia experienced by the newly infected mother increases the risk of transmission.[3] Other risk factors include preterm delivery (< 34 weeks), a low maternal CD4+ cell count and the use of illicit drugs. The most important variables appear to be prolonged (more than 4 hours) ruptured membranes and a birth weight less than 2 500 g. Each of these factors doubles the transmission rate of the virus. The transmission rate can be decreased by 87% by caesarean section delivery, in combination with zidovudine therapy for both the mother and infant.[3] There is an increased rate of transmission in women with advanced disease.[3] If the mother is not receiving antiretroviral treatment (either for pMTCT or as combination antiretroviral treatment [cART]), the risk of transmission is 25–35%.[1]

Access to ART varies dramatically, with only 21% of paediatric patients accessing treatment, compared with 55% of adults.[4] Without treatment, 50% of African children living with HIV will die before their second birthday. The prevalence of HIV among children infected with TB is difficult to estimate due to problems with diagnosis, under-ascertainment as well as selection of study populations. It has been estimated by the WHO that the prevalence ranges from 10–60%. This prevalence differs depending on the background rates of HIV as well as the economic status and education level of the population.[2]

The prevalence of TB in HIV infected patients differs according to whether or not the area is a TB endemic area and whether or not ART is freely accessible. Under-ascertainment as well as difficulty in diagnosing the patient also remains a problem. In a South African retrospective study, the incidence of TB in HIV infected children was estimated at 5 per 100 child-years among HIV-positive children receiving HIV care. Although more and more of the population is gaining access to ART, the prevalence of TB remains higher in HIV co-infected children than in HIV-uninfected children.[2]

The pathogenesis of TB is also affected by HIV. In people living with HIV there is a 6–30 fold increase in the chances of developing HIV. The chances of developing TB increases when the patient has a lower CD_4 count or is living in a high TB incidence area, for example.[2]

Clinical presentation

Often a child is not suspected of having HIV until they develop symptoms of the disease. This can vary according to age and each child can present differently. Symptoms may result from HIV or from opportunistic infections. Common presentations include lymphadenopathy, white plaques due to oral *Candida*, painful rash

due to *Herpes zoster*, diarrhoea, fatigue and fever with intermittent sweats.[1] Most commonly, children are detected through a failure to thrive (FTT), which is the failure to gain weight or grow according to standardised growth charts. In addition, neurological complications may be detected, such as seizures, difficulty with walking or poor performance at school. There may be frequent childhood illnesses such as ear infections, colds as well as diarrhoea. When HIV progresses further, the incidence of opportunistic infections increases. These infections include *Pneumocystis jirovecii*, cytomegalovirus, lymphocytic interstitial pneumonia (LIP), oral *Candida*, diaper rashes, tuberculosis as well as meningitis.

The first signs and symptoms may be subtle and non-specific, e.g. lymphadenopathy, hepatosplenomegaly, FTT, chronic or recurrent diarrhoea, interstitial pneumonia or oral thrush. If these are recurrent, HIV is more likely. In Africa, chronic diarrhoea, wasting, as well as severe malnutrition are the predominant signs/symptoms. In children, certain signs and symptoms are more commonly found than in adults. These include recurrent bacterial infections, chronic parotid swelling or LIP. Some children experience early onset progressive neurological deterioration.[3] In TB co-infected patients, cough for more than 1 610 days, fever for more than 2 weeks as well as weight loss and FTT may be present.

Criteria/diagnostics

As per current South African standard treatment guidelines,[5] the criteria for testing for HIV in children are as follows: all infants/children accessing care should have their HIV status determined. However, those who have tested positive or are already on ART should not be tested again. Table I explains the role of PCR and rapid antibody tests in the management of infants and children.

In addition, mothers who tested negative in pregnancy, should have their HIV status determined three-monthly whilst breastfeeding. The guidelines emphasise that breastfeeding should be encouraged in all mothers with HIV-infected children, 2 years or longer, as in HIV-unexposed children. Weaning foods can be introduced from 6 months of age. Importantly, providers are encouraged to ask about TB contacts and TB symptoms in all children and their caregivers at every visit.

If ART is initiated in a child on TB treatment, liver enzymes should be checked at initiation. In addition, TB should be excluded in all patients before starting ART. This can be done by means of a careful history of TB contacts, clinical examination, chest X-ray, tuberculin skin test (TST), or lateral flow urine lipoarabinomannan (TB-lam), *M tuberculosis* PCR test and mycobacterial culture (where TB disease is suspected on clinical or radiological grounds).

TB prophylaxis should be given to all HIV-infected children exposed to a close contact with an infectious pulmonary TB case, or who are newly found to have a positive TB-lam or TST, but in whom no evidence of TB disease is present. The standard dose is isoniazid 10 mg/kg/dose (up to a maximum of 300 mg) once daily for 6 months. Importantly, the course needs to be repeated if an HIV-infected patient, irrespective of age, is re-exposed to a TB contact at any point after completing TB treatment or prophylaxis. However, if the patient has been exposed to a known drug-resistant TB case, then expert advice is needed on the choice of prophylaxis.

Table I: HIV testing recommendations for infants and children[5]

Recommended intervals for infant and child testing	
HIV PCR test	**Rapid HIV antibody test**
At birth • All HIV-exposed neonates **At 10 weeks** • All HIV-exposed infants **At 6 months** • All HIV-exposed infants Repeat HIV PCR testing at 10 weeks and 6 months should be done on all HIV- exposed infants with a prior negative or indeterminate HIV PCR Any infant with a positive birth HIV PCR should be urgently initiated on ART as per section 9.1.2: The HIV-Infected Neonate	**At 18 months** • Universal HIV testing at 18 months (HIV rapid test for ALL infants regardless of HIV exposure, except in those who previously tested HIV-positive and are on ART) **Note:** Patients already on ART should not have a repeat HIV antibody test **Breastfed infants: (6 weeks post cessation of breastfeeding)** • All HIV-exposed infants – age appropriate: < 18 months old – do an HIV PCR ≥ 18 months old – do a rapid HIV antibody test (confirm HIV test in children between 18–24 months with an HIV PCR) **HIV testing should be offered to all children as well as their family and caregivers.**

The timing of TB and ART is critical, and depends on when each diagnosis is made. If a child is diagnosed with TB and HIV, but is not yet on ART, then the TB treatment should be commenced first, and ART initiated after 2–4 weeks. However, in children with TB meningitis, ART must only be initiated after 4 weeks regardless of CD4 count, in order to avoid immune reconstitution inflammatory syndrome (IRIS). If a child is diagnosed with TB when already on ART, TB treatment can be commenced immediately, with due regard for possible drug interactions. There may be a need for ART dosage adjustments. For example, if a child is to receive a rifampicin-containing TB regimen and is taking dolutegravir, the ARV should be dosed twice daily. No dose adjustments are needed in children receiving efavirenz, abacavir or lamivudine. Boosted ritonavir dosing is needed in children treated with lopinavir/ritonavir. However, double-dosing the lopinavir/ritonavir solution in young children is not recommended.

All children on TB treatment and ART should receive pyridoxine to prevent neurological adverse effects.

Goals of therapy

The goals of therapy in the child with TB/HIV co-infection vary. The long-term goals with ART are to prevent progression of the disease, including opportunistic infections, and to suppress viral replication. Other goals include avoiding adverse effects from the ART and interactions with other medication. The goals of TB treatment are to cure the infection, while avoiding adverse effects and drug interactions, and to prevent the development of complications. Preventing recurrent or reactivation of TB are longer-term goals.

The role of pharmacists

Pharmacists can play a vital role in optimising HIV treatment outcomes in numerous ways and in all medical settings, such as ensuring patients are taking a complete and appropriate regimen, recommending alternative therapy, dose or formulation adjustments, mitigating drug-drug interactions, and modifying drug schedules to optimise absorption. Current literature suggests a profound impact on improving safety in HIV patients through pharmacist interventions, via medication error prevention and daily monitoring. Retrospective studies have seen rates of antiretroviral stewardship interventions for medication errors related to antiretrovirals increase from 16% to 52%. Various methods of stewardship interventions have been utilised, including prescriber and pharmacist education[6-9]

Conclusion

There is still much left to be done, even with the great progress that has been achieved over the recent years. Although there are fewer HIV diagnoses and improved viral suppression, globally, the world has yet to meet the UNAIDS 90-90-90 targets. The risks of medication errors are high in children being treated for HIV/TB co-infection, due to the multiple agents having to be used simultaneously. However, this provides a great opportunity for pharmacists to optimise and improve the medication use process. Pharmacists can play a key role in the management of patients on ART and TB treatment, ensuring patient safety and optimal patient care. With a variety of methods to reduce medication errors, such as use of computerised order entry sets, provider education, and prospective feedback, pharmacists can continue to work to make an impact in advancing HIV/TB patient care and supporting the continuum of care.

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