Chapter 3: Management of TB in the HIV-infected child

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SUMMARY

Human immunodeficiency virus (HIV) infected children are at risk of a range of lung diseases related to HIV infection, including tuberculosis (TB). As in non-HIV-infected children, the presence of three or more of the following four features strongly suggests the diagnosis of TB: 1) chronic symptoms suggestive of TB; 2) physical changes highly suggestive of TB; 3) a positive tuberculin skin test; 4) a chest radiograph suggestive of TB. Every effort must be made to expedite the process of making the diagnosis, as TB may be rapidly progressive in HIV-infected children. As many children who present with chronic symptoms suggestive of TB may not have been tested for HIV infection, in high HIV prevalence settings (and in all settings where HIV is suspected in a child) children and their families should be offered HIV counselling and testing as part of a full TB work-up. Most current international guidelines recommend that TB in HIV-infected children, as in non-HIV-infected children, should be treated with a 6-month regimen containing rifampicin throughout. All HIV-infected children with advanced immunosuppression, including many with TB, should receive cotrimoxazole prophylaxis. Although the optimal timing for the initiation of antiretroviral treatment (ART) during TB treatment is not known, the decision to initiate ART should take into consideration the degree of immune suppression and the child's progress during TB treatment.

KEY WORDS: tuberculosis; management; treatment; HIV; children

DIAGNOSIS

Human immunodeficiency virus (HIV) infected children are at risk of tuberculosis (TB). However, these children often have other lung disease related to their HIV infection, including Pneumocystis jirovecii (PCP, formerly Pneumocystis carinii pneumonia), lymphoid interstitial pneumonitis (LIP) and viral and bacterial pneumonias. Table 1 shows the differential diagnosis of respiratory illness in HIV-infected children. The final common pathway of multiple lung infections is bronchiectasis and chronic lung disease for many HIV-infected children. Most of these diagnoses must be made clinically, often resulting in confusion about which opportunistic infections are causing a child’s illness. Children with HIV may also have multiple and concurrent opportunistic infections, so the presence of one diagnosis does not exclude other causes of illness. There is therefore a risk both that TB will be over-diagnosed in children (and they will be treated unnecessarily) and also that TB may be missed, and therefore an opportunity to treat an HIV-infected child for a curable disease will also be missed. LIP is the most difficult condition to distinguish from TB, due to radiological similarities. Bacteriologically confirmed TB can occur in children with an underlying diagnosis of LIP, bronchiectasis or any other lung infection.

The approach to diagnosing TB in HIV-infected children is essentially the same as for non-HIV-infected children, i.e., the presence of three or more of the following should strongly suggest the diagnosis of TB:

1. A positive tuberculin skin test (defined as ≥5 mm if HIV-infected)
2. Chronic symptoms suggestive of TB
3. Physical changes highly suggestive of TB
4. Chest radiograph suggestive of TB.
### Differential diagnosis of respiratory illness in HIV-infected children

<table>
<thead>
<tr>
<th>Illness</th>
<th>Causative agent(s)</th>
<th>Clinical features</th>
<th>Age ranges</th>
<th>Radiological features</th>
<th>Diagnostic technique</th>
<th>Treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>Mycobacterium tuberculosis</td>
<td>Subacute onset, persistent and unremitting cough, weight loss, fever, night sweats</td>
<td>All ages</td>
<td>Lymph node enlargement, infiltration, primary complex</td>
<td>Smear microscopy, chest radiograph, tuberculin skin test, history of contact, chest X-ray (if other tests not available)</td>
<td>TB medications</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>S. pneumoniae, M. influenzae, S. aureus, K. pneumonieae, E. coli</td>
<td>Respiratory syncytial virus, adenovirus, enterovirus, parainfluenza virus, influenza virus</td>
<td>All ages</td>
<td>Diffuse interstitial infiltrates, hyperinflation</td>
<td>Sputum culture not useful in children; blood cultures (including coverage of gram-negative organisms)</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Viral pneumonia</td>
<td>H. influenzae, RSV, rhinovirus, parainfluenza virus, influenza virus</td>
<td>Acute onset, cough, fever, respiratory distress</td>
<td>Infants</td>
<td>Diffuse interstitial infiltrates, hyperinflation</td>
<td>Serology, chest X-ray</td>
<td>Corticosteroids for moderate to severe cases</td>
</tr>
<tr>
<td>Lymphoid interstitial pneumonitis (LIP)</td>
<td>Epstein-Barr virus, adenovirus, parainfluenza virus</td>
<td>Slow onset, cough, mild hypoxia, associated with generalized lymphadenopathy, parotidomegaly, peribronchial adenopathy</td>
<td>Older children</td>
<td>Further enlargement, lymph node enlargement</td>
<td>Sputum culture, chest X-ray</td>
<td>Supportive care</td>
</tr>
<tr>
<td>PCP</td>
<td>Pneumocystis jirovecii</td>
<td>Abrupt severe pneumonia, respiratory distress, chest X-ray</td>
<td>Infants</td>
<td>Diffuse interstitial infiltrates, hyperinflation</td>
<td>Chest X-ray</td>
<td>Cotrimoxazole, sometimes bronchiectasis resection (lobectomy)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Reiter's disease</td>
<td>Recurrent respiratory infections (usually complication of LIP or TB)</td>
<td>Older children</td>
<td>Honeycombing, usually of lower lobes</td>
<td>Chest X-ray</td>
<td>Bronchodilator therapy</td>
</tr>
</tbody>
</table>

*Note that in addition, the improvement in many of these conditions with the specific treatment indicated, their severity and frequency usually improve with antiretroviral therapy.

† Onset can occasionally be acute, especially in immunocompromised infants.

### Treatment of tuberculosis

**Cotrimoxazole prophylaxis**

Daily cotrimoxazole prophylaxis (20 mg trimethoprim [TMP] + 100 mg sulfamethoxazole [SMX] if aged <6 months; 40 mg TMP + 200 mg SMX if <5 years; 80 mg TMP + 400 mg SMX if ≥5 years) prolongs survival in HIV-infected children and reduces the incidence of respiratory infections and hospitalisation. No studies have been done in HIV-infected children with TB, but a number of studies of cotrimoxazole prophylaxis in HIV-infected adults with TB have shown clear and consistent benefit. The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have recently revised provisional recommendations for HIV-infected children. All HIV-infected children with advanced immunosuppression should be started on cotrimoxazole. There is no consensus yet on whether children on antiretroviral therapy (ART) who have immune reconstitution can safely stop cotrimoxazole.

**Antiretroviral therapy**

The WHO has published standardised recommendations for managing TB in HIV-infected infants and children. HIV-infected children benefit from treatment...
Table 2 Recommendations for the timing of ART following the initiation of TB treatment with a rifampicin-containing regimen in HIV-infected infants and children

<table>
<thead>
<tr>
<th>Clinical stage of child with TB (as an event indicating need for ART)</th>
<th>Timing of ART following initiation of TB treatment (rifampicin-containing regimen)*</th>
<th>Recommended ARV regimen</th>
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</thead>
<tbody>
<tr>
<td>WHO paediatric clinical stage 4†</td>
<td>Start ART soon after TB treatment (between 2 and 8 weeks following start of TB treatment)</td>
<td>In children &lt;3 years:</td>
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<td></td>
<td>With clinical management alone:</td>
<td>• Preferred: triple NRTI first-line regimen (d4T or AZT + 3TC + ABC)</td>
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<td></td>
<td>• Start ART soon after TB treatment (between 2 and 8 weeks following start of TB treatment)</td>
<td>• Alternative: standard first-line regimen of two NRTIs + NVP§</td>
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<td></td>
<td>• If excellent clinical response to TB treatment in first 2 to 8 weeks of TB treatment, and child is stable and on cotrimoxazole preventive therapy (CPT)‡ it may be reasonable to delay initiation of ART</td>
<td></td>
</tr>
<tr>
<td>Where CD4 is available:</td>
<td>Evaluating the possibility of delaying initiation of ART depending on assessment of clinical status and CD4, and clinical and immunological response to TB treatment:</td>
<td>Following completion of TB treatment it is preferable to remain on the ART regimen as outlined above.</td>
</tr>
<tr>
<td>Severe and advanced immunodeficiency:**</td>
<td>initiate ART soon after TB treatment (between 2 and 8 weeks following start of TB treatment)</td>
<td>• Regimens as recommended above</td>
</tr>
<tr>
<td>Mild or no immunodeficiency:††</td>
<td>initiation of ART may be delayed until after the completion of TB treatment; closely monitor response to TB treatment and reassess for ART after TB treatment; if no improvement, consider starting ART</td>
<td>Where ART can be delayed until after completion of TB treatment, initiation with a standard two NRTIs + NNRTI first-line regimen is recommended</td>
</tr>
</tbody>
</table>

* Administration of CPT is important in children with TB-HIV coinfection.
† All children with clinical stage 4 (that includes extra-pulmonary TB other than lymph node TB) should be initiated on ART regardless of CD4 criteria.
‡ Pulmonary TB and lymph node TB represent clinical stage 3.
†† Careful clinical monitoring with laboratory support, if available, is recommended where NVP is administered concurrently with rifampicin.
¶ Because of lack of data the ranking of preferred or alternative ARV regimens is not a consensus recommendation.
# EFV is not currently recommended for children <3 years of age or <10 kg, and should not be given to postpubertal adolescent girls who are either in the first trimester of pregnancy or are sexually active and not using adequate contraception.
** Severe immunodeficiency: advanced immunodeficiency is assumed to be up to 5% above the age-specific CD4 threshold for severe immunodeficiency or CD4 200–349 cells/μL for children >5 years of age.
†‡ Mild or nonsignificant immunodeficiency is assumed at CD4 levels above those defining advanced immunodeficiency.
†† Mild or no immunodeficiency is assumed at CD4 levels above those defining advanced immunodeficiency.
ART = antiretroviral treatment; TB = tuberculosis; HIV = human immunodeficiency virus; WHO = World Health Organization; NRTI = nucleoside reverse transcriptase inhibitors; d4T = stavudine; AZT = zidovudine; 3TC = lamivudine; ABC = abacavir; EFV = efavirenz; NNRTI = non-nucleoside reverse transcriptase inhibitors; NVP = nevirapine.

of HIV with ART. In HIV-infected children with confirmed or presumptive TB, the initiation of TB treatment is the priority. Treatment of TB in HIV-infected children on ART or who are planned to start on ART needs careful consideration, as the rifamycins, especially rifampicin, and some of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) cause clinically significant drug interactions. Furthermore, the adverse events of antituberculosis drugs and antiretroviral drugs are similar and can cause confusion as to which drugs need to be stopped. Rifampicin reduces the serum concentrations of most PIs by 80% or more, and NNRTIs by between 20% and 60%. Because recommendations on combinations of anti-tuberculosis drugs and antiretroviral drugs are frequently revised, obtaining the most recent information from the WHO website* is advised. The CDC website† also provides useful information.

Although the optimal timing for the initiation of ART during anti-tuberculosis treatment is not known, the decision to initiate ART should take into consideration the degree of immune suppression and the child’s progress during anti-tuberculosis treatment. Table 2 shows the recommendations for the timing of

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* http://www.who.int/hiv/mediacentre
† http://www.cdc.gov/nchstp/tb/
ART following the initiation of anti-tuberculosis treatment in children who are coinfected with HIV. The clinical and immunological condition of the HIV-infected child should guide the decision as to whether to:

- start ART treatment soon (2–8 weeks) after the start of anti-tuberculosis treatment;
- delay ART until after completion of the initial phase of anti-tuberculosis treatment; or
- delay start of ART until anti-tuberculosis treatment is completed.

Where possible, the initiation of ART should be deferred for at least 2–8 weeks in children starting anti-tuberculosis treatment who have not yet started ART (i.e., antiretroviral ‘naïve’ patients). A careful review of any possible drug interactions between ART and anti-tuberculosis medications should be carried out, and any modifications should be determined with the guidance of an HIV treatment expert.

**Immune reconstitution inflammatory syndrome**

Immune reconstitution inflammatory syndrome (IRIS), characterised by clinical deterioration after initial improvement, has been observed in patients on anti-tuberculosis treatment who have started ART. The reaction may occur during the first 3–6 months of ART, is generally self-limiting and lasts 10–40 days.

Sometimes a child on ART may develop TB. Consideration of the timing of development of TB after starting ART is important in determining the likely cause of TB. TB occurring in the first 6 months of ART may be part of IRIS. TB occurring after 6 months of ART may be a sign of failure of the ART regimen. TB occurring at any time during ART may be attributable to a new TB infection, depending on exposure. Anti-tuberculosis treatment should be started without delay. The CD4 cell count or percentage is useful to guide clinical management (see Tables 2 and 3).

**PREVENTION**

**General and specific strategies**

Global efforts to control the co-epidemics of TB and HIV will benefit children. This includes the expansion of prevention of maternal-to-child transmission (PMTCT) programmes that will reduce new HIV infections in young children, and expansion of the Stop TB strategy. However, additional specific strategies are needed. At a minimum, all HIV-infected children should be screened for TB and all children with TB should be offered HIV testing and counselling in high HIV prevalence settings. Irrespective of age, all HIV-infected children who are household contacts of infectious cases should be evaluated for TB disease and treated with prophylaxis (see Chapter 4 in this series ‘Childhood contact screening and management’

Innovative approaches are needed to ensure that co-infected children are identified, and that where possible, disease is prevented.

**BCG vaccination**

The HIV pandemic has implications for BCG vaccination (see section on BCG in Chapter 5 in this series ‘Roles and responsibilities, recording and reporting, and BCG vaccination’

Although there have been a few reports of disseminated BCG infection after BCG immunisation of HIV-infected children, prospective studies comparing BCG immunisation in HIV-infected and non-infected infants have showed no difference in risk of complications. It is recommended that BCG vaccination policy should depend on the prevalence of TB in a country. In countries with a high TB prevalence, the benefits of BCG vaccination outweigh the risks, and the WHO recommends a policy of routine BCG immunisation for all neonates.

A child who has not had routine neonatal BCG immunisation and has symptoms of HIV/AIDS should not be given BCG because of the risk of disseminated BCG disease. BCG should not be given to HIV-infected children in low TB prevalence countries.

Concerning the management of BCG disease in HIV-infected children (or children with other immunodeficiencies), the diagnosis is difficult and the treatment is specialized, as *Mycobacterium bovis* is resistant to pyrazinamide and requires higher doses of other first-line TB medications. Some experts recommend 15 mg/kg/dose of isoniazid and 15–20 mg/kg/dose of rifampicin. HIV-infected children suspected of having BCG disease should be referred to an expert for management.

**References**


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**Table 3** Proposed classification of HIV-associated immunodeficiency in infants and children

<table>
<thead>
<tr>
<th>Classification of HIV-associated immunodeficiency</th>
<th>Age-related CD4 values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤11 months</td>
</tr>
<tr>
<td>Not significant</td>
<td>%</td>
</tr>
<tr>
<td>Mild</td>
<td>&gt;25</td>
</tr>
<tr>
<td>Advanced</td>
<td>&gt;25</td>
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</tbody>
</table>

HIV = human immunodeficiency virus.
Les enfants infectés par le virus de l'immunodéficience humaine (VIH) encouragent le risque de toute une série de maladies pulmonaires liées à l'infection par le VIH, y compris la tuberculose (TB). Comme chez les enfants non-infectés par le VIH, la présence de trois ou davantage des quatre signes suivants suggère vigoureusement le diagnostic de TB : 1) un test cutané tuberculinique positif ; 2) des symptômes chroniques suggestifs de TB ; 3) des signes objectifs hautement suggestifs de TB ; 4) et un cliché thoracique suggestif de TB. Il faut faire des efforts maximaux pour accélérer le processus de diagnostic car la TB peut s'étendre rapidement chez les enfants infectés par le VIH. Puisque beaucoup d'êfants qui se présentent avec des symptômes chroniques suggestifs de TB peuvent ne pas avoir été testés pour l'infection VIH, dans les contextes à prévalence élevée du VIH (ainsi que dans tous les contextes où l'on suspecte le VIH chez un enfant), les enfants et leurs familles devraient se voir offrir l'accompagnement et le test VIH au sein d'une mise au point globale de la TB. La plupart des directives internationales actuelles recommandent que, chez les enfants infectés par le VIH, y compris ceux qui ne le sont pas, la TB devrait être soignée par un régime de 6 mois comportant la rifampicine de bout en bout. Tous les enfants infectés par le VIH et dont l'état d'immunodépression est avancé, y compris ceux atteints de TB, devraient bénéficier d'une prophylaxie au cotrimoxazole. Bien que le moment optimal de mise en œuvre du traitement anti-
Los niños con infección por el virus de la inmunodeficiencia humana (VIH) son vulnerables a una variedad de enfermedades pulmonares asociadas con dicha infección, entre ellas la tuberculosis (TB). Al igual que en niños sin infección por el VIH, la presencia de tres o más de las siguientes cuatro características representa un alto grado de presunción diagnóstica de TB: 1) una prueba cutánea positiva a la tuberculina; 2) síntomas crónicos compatibles con TB; 3) cambios físicos indicativos de TB y 4) radiografía de tórax con signos de TB. Es preciso hacer todo lo posible por facilitar el diagnóstico, pues la TB puede progresar rápidamente en los niños infectados por el VIH. Puesto que muchos niños con signos crónicos indicativos de TB no han tenido la prueba serológica para el VIH, la orientación y la prueba para el VIH deben formar parte de todo estudio completo de TB en los entornos con alta prevalencia (y en cualquier medio cuando se sospecha la infección por el VIH en un niño). La mayor parte de las normas internacionales recomienda el tratamiento de la TB en niños infectados o no por el VIH con una pauta de 6 meses que contenga rifampicina durante todo el tratamiento. Todos los niños infectados por el VIH con inmunodepresión avanzada, incluidos aquellos con TB, deben recibir profilaxis con la cotrimoxazol. Aunque se desconoce el momento óptimo para la iniciación del tratamiento antirretrovírico durante el régimen antituberculoso, la decisión de comenzar los medicamentos antirretrovíricos debe tomarse considerando el grado de depresión inmunitaria y el progreso del niño durante el tratamiento antituberculoso.