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Contents

Summary 1

Introduction 3

1 Epidemiology 4
   1.1 The world 4
   1.2 New Zealand 4
   1.3 Surveillance of tuberculosis–HIV co-infection 5

2 HIV-associated Tuberculosis: Immunopathology 6

3 HIV-associated Tuberculosis: Clinical Aspects 7
   3.1 HIV testing in tuberculosis 7
   3.2 Susceptibility 7
   3.3 Clinical presentation 7
   3.4 Infectivity 9

4 Treatment of Tuberculosis in HIV-infected Patients 10
   4.1 Drug treatment: general principles 10
   4.2 Anti-retroviral therapy and tuberculosis treatment 11
   4.3 Paradoxical reactions during therapy 14
   4.4 Tuberculosis-related immune reconstitution syndrome 14
   4.5 Drug-resistant tuberculosis in HIV-infected patients 15
   4.6 Cotrimoxazole preventive therapy 15

5 Prevention of Tuberculosis in HIV-infected Patients 16
   5.1 Co-ordination of control measures 16
   5.2 Screening for latent tuberculosis infection in HIV-infected patients 16
   5.3 Investigation of inactive pulmonary tuberculosis 17
   5.4 Treatment of latent tuberculosis infection in HIV infection 17

References 19

List of Tables
Table 1.1: Number of patients with HIV-associated TB in New Zealand, 2004–2008 4
Table 4.1: Recommendations for using non-nucleoside reverse transcriptase inhibitor (NNRTI) anti-retrovirals with rifampicin, and protease inhibitor (PI) and NNRTI anti-retrovirals with rifabutin 13

List of Figures
Figure 3.1: HIV-associated tuberculosis clinical features related to degree of immune-suppression 8
Summary

Epidemiology

Human immunodeficiency virus (HIV) is the single greatest risk factor for the development of tuberculosis (TB) disease and TB is the most common opportunistic infection of people infected with HIV. People with HIV infection are at high risk of TB if they are latently infected with \textit{M. tuberculosis} or are contacts of infectious cases.

In New Zealand, from 2004 until 2009, 2\% of the patients notified with TB disease had HIV infection.

HIV-associated tuberculosis: immunopathology

With progression of HIV infection, CD4+ lymphocytes are depleted resulting in a weakened response to \textit{M. tuberculosis}. The natural history of HIV infection is also altered by TB. People with active TB experience increased viral replication and an accelerated course of HIV infection.

HIV-associated tuberculosis: clinical aspects

It is recommended that all patients diagnosed or suspected to have TB should be offered HIV testing.

There should be a high index of suspicion for TB in patients with HIV infection. TB may present in HIV infection at any CD4+ lymphocyte count. The clinical presentation of TB in HIV infection is influenced by the degree of immune-suppression. With increasing immunosuppression, particularly when the CD4+ count falls below 200 cells/mm$^3$, the clinical presentation becomes less typical. Pulmonary manifestations are often atypical and extra-pulmonary TB becomes more common, either alone or concurrently with pulmonary disease.

Efforts should always be made to prove the diagnosis unequivocally with culture and drug susceptibility.

Infectious patients should be appropriately isolated. The same guidelines apply as for HIV-negative infectious cases (see Chapter 12). Infection control processes must be rigorously applied in settings where HIV-infected people may come into contact with infectious TB cases.

Treatment of tuberculosis in HIV-infected patients

Of paramount importance in the co-infected patient is appropriate and adequate treatment of TB. Six-month regimens are considered appropriate only for patients with fully sensitive TB who have limited disease. Treatment should be extended to a minimum of nine months for patients with more extensive disease, including cavitary disease or where there is a slow response to treatment. A six- to nine-month regimen is recommended for fully sensitive extra-pulmonary TB unless there is central nervous system disease or bone and joint TB, which may require 12 months of treatment.
Intermittent dosing regimens of TB drugs less than three times weekly may result in poor outcomes in some HIV-infected groups. All patients with HIV-associated TB should receive daily therapy for the first eight weeks of treatment. For the continuation phase, the optimal dosing frequency is also daily. If daily continuation phase treatment is not possible, three times weekly dosing during the continuation phase may be used in selected cases.

Adverse events are common in TB patients with HIV infection. Directly observed therapy (DOT) is recommended for HIV-infected patients with TB disease. It is paramount that patients do not miss doses of TB treatment.

The optimal time to start Anti-retroviral Therapy (ART) in relation to the start of TB treatment is not yet clear. One randomized controlled trial provides some evidence for early initiation of ART in terms of reduced all-cause mortality, improved TB outcomes and reduced incidence of immune reconstitution inflammatory syndrome (IRIS). In 2009, the recommendations of World Health Organisation and Centre for Disease Control are that TB treatment should be commenced first and ART subsequently commenced as soon as possible and **within the first eight weeks** of starting TB treatment.

The treatment of HIV-associated TB is complex and requires expertise in the management of both HIV disease and TB. There are significant drug–drug interactions between the rifamycin drugs (rifampicin and rifabutin) and both the protease inhibitors (PIs) and the non-nucleoside reverse transcriptase inhibitors (NNRTIs).

**Drug-resistant tuberculosis in HIV infection**

In patients with advanced HIV and CD4+ counts below 100, there is an increased risk of acquired rifamycin resistance if these drugs are given once or twice weekly and these regimens should not be used. Multi-drug–resistant TB is a serious threat to patients with HIV infection and outcomes may be improved by ART and immune recovery.

**Prevention of tuberculosis in HIV-infected patients**

HIV is the single greatest risk factor for the reactivation of TB and therefore screening for latent TB infection (LTBI) should form part of the regular evaluation of all HIV-infected individuals. A Mantoux test or IGRA should be performed in all HIV-positive people.

Preventive treatment for LTBI should be given to HIV-infected patients with a Mantoux ≥ 5 mm or positive IGRA, previously documented positive Mantoux and no prior LTBI treatment, minor or slight chest X-ray (CXR) abnormalities consistent with old TB (but consider the need for full preventive treatment) or a documented recent exposure to a smear-positive case.

The efficacy of treatment of LTBI in HIV-infected people has been proven in placebo-controlled trials. The preferred regimen for LTBI in a patient with HIV infection is nine months of daily isoniazid (9H).
Introduction

The management of human immunodeficiency virus (HIV) and tuberculosis (TB) co-infection is complex, so this chapter provides a broad overview of the field. The information elsewhere in these guidelines is largely applicable to the HIV-infected patient, but certain issues are unique to this population and warrant special attention.

The chapter provides a brief epidemiological overview of the global and local situation with respect to co-infection, highlighting those areas where clinical features may differ from those found in the HIV-negative patient. A review of the treatment of TB in HIV infection is presented, with particular emphasis on the issues and decisions required with the concurrent use of anti-retroviral therapy and anti-TB therapy.

Co-infected patients should be managed by clinicians experienced in the management of both HIV and TB or in close liaison with an infectious diseases physician.

Several review articles and guidelines have been published on this topic, and the reader’s attention is drawn to these for additional detail.1–10
1 Epidemiology

1.1 The world

HIV is the single greatest risk factor for the development of TB disease. The HIV epidemic has compounded the worldwide problem of TB, which is the most common opportunistic infection of people infected with HIV.

Despite significant public health advances in some of the countries hardest-hit by the HIV epidemic, new infections continue at an alarming rate. The United Nations Joint Programme on HIV/AIDS and the World Health Organization (WHO) estimated there were 2.7 million new infections in 2008, with 33 million people living with HIV worldwide. It is estimated that one-third of these are also infected with *Mycobacterium tuberculosis*.

1.2 New Zealand

New Zealand has relatively low rates of HIV infection compared with most of the world, but infected people here remain at high risk of TB if they are latently infected with *M. tuberculosis* or are contacts of infectious cases. From the beginning of the HIV epidemic until the end of December 2009, 2,248 people in New Zealand were known to have been infected with the HIV virus.

In New Zealand, from 2004 until 2009, 2% of the patients notified with TB disease had HIV infection (Table 1.1).

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of TB disease notifications*</th>
<th>Number (%) of patients with HIV-associated TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>376</td>
<td>10 (2.7)</td>
</tr>
<tr>
<td>2005</td>
<td>344</td>
<td>8 (2.3)</td>
</tr>
<tr>
<td>2006</td>
<td>355</td>
<td>10 (2.8)</td>
</tr>
<tr>
<td>2007</td>
<td>288</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>2008</td>
<td>297</td>
<td>8 (2.7)</td>
</tr>
</tbody>
</table>

* TB disease notifications in EpiSurv at time of data downloaded to send to AIDS Epidemiology Group to identify HIV co-infected cases.

Source: ESR

The majority of patients with HIV-associated TB were born outside New Zealand, mostly in parts of the world with high rates of TB.
1.3 Surveillance of tuberculosis–HIV co-infection

1.3.1 HIV-infection rates in people with tuberculosis

Surveillance of HIV-associated TB is important because of the significant interactions in pathology and treatment between the two infections. From 1995 to 2004, 45 out of 3772 (1.2%) notified TB cases in New Zealand were diagnosed with HIV infection,14 and from 2004 until 2009, 40 out of 1660 (2.4%) of notified TB cases had HIV infection. These data were obtained by comparing anonymised HIV surveillance data and anonymised TB surveillance data. The TB case report form does not collect information on HIV status and so this rate of co-infection may underestimate the proportion of people with TB disease who have HIV infection. This rate also does not capture the proportion of people with latent TB and HIV infection.

1.3.2 Tuberculosis infection rates in HIV-positive people

The proportion of HIV-infected people in New Zealand who have also been infected with *M. tuberculosis* is not known. Although clinical awareness of the possibility of co-infection and a low threshold for testing for both infections have been encouraged, the extent of dual testing is not known.13
2 HIV-associated Tuberculosis: Immunopathology

One of the components of host immunity critical to defence from TB is the CD4+ lymphocyte. Antigen-specific type 1 CD4+ T helper lymphocytes provide stimulatory signals (eg, the cytokine gamma-interferon) that activate TB-infected macrophages to limit intra-cellular replication of \textit{M. tuberculosis}. HIV also targets these cells, which become infected and are ultimately destroyed by the virus.

With progression of HIV infection CD4+ lymphocytes are depleted, which results in a weakened response to \textit{M. tuberculosis}. The range of clinical manifestations of TB in HIV-infected people reflects the variability of the impaired host response to the infecting organism. The CD4+ lymphocyte count is a useful marker of the degree of immune-deficiency in HIV-positive patients, and clinical features of TB in HIV infection correlate to a degree with CD4+ count.

Conversely, the natural history of HIV infection is also altered by TB. In studies of HIV-associated TB in environments without effective anti-viral therapy, higher rates of death were seen in those with co-infection. This occurred during treatment for TB, but also after successful treatment. Death was seldom attributable to TB but rather to other complications of HIV infection, suggesting an accelerated course of HIV infection in those with active TB.

The concentration of HIV in the blood (the HIV viral load) is elevated in TB disease, and it has been demonstrated in vitro that HIV replication is increased in alveolar macrophages and peripheral lymphocytes on exposure to \textit{M. tuberculosis} antigens. The inflammatory cytokines tumour necrosis factor alpha (TNF-\(\alpha\)) and interleukin-1 (IL-1) are implicated as mediators of this enhanced viral replication, and both are released during the host response to mycobacterial infection. It is suggested that these pro-inflammatory cytokines lead to an increase in viral replication with a subsequent decline in the CD4+ lymphocyte count.
3 HIV-associated Tuberculosis: Clinical Aspects

3.1 HIV testing in tuberculosis

TB is an important indicator illness for HIV infection. An HIV test should be offered to every patient diagnosed or suspected to have TB because classical risk factors may not be apparent.\(^3\)

3.2 Susceptibility

It is clear from reports of nosocomial outbreaks of TB among HIV-positive patients that HIV infection leads to much greater susceptibility to TB infection progressing to disease.\(^22–25\) HIV can radically alter the natural history of primary TB infection with a high proportion of infections resulting in disease and potentially a very short time between exposure and the development of symptoms.\(^23\)

**Practice point**

Infection control processes must be rigorously applied in settings where HIV-infected people may come into contact with people with infectious TB.

3.3 Clinical presentation

*There should be a high index of suspicion for TB in the context of HIV infection.* TB may present in HIV infection at any CD4+ lymphocyte count, including those within the normal range. The clinical presentation of TB in HIV is influenced by the degree of immune-suppression (see Figure 3.1).\(^1,5,15\)

With normal or moderately reduced CD4+ counts (ie, more than 200 cells/mm\(^3\)) the presentation is more ‘typical’, with pulmonary disease likely and radiological findings including an upper lobe distribution and cavity formation. With increasing immune-suppression, especially when the CD4+ lymphocyte count falls below 200 cells/mm\(^3\), the clinical presentation becomes less typical. Pulmonary manifestations alter and extra-pulmonary TB becomes more common, either alone or concurrently with pulmonary disease.\(^1,5,15,26,27\) A chest X-ray (CXR) may show lower zone infiltrates and unilateral or diffuse bilateral shadowing, and may even be normal despite culture-positive or even smear-positive sputum.\(^27\)

Mediastinal and hilar lymphadenopathy and disseminated disease are seen with increasing frequency at low CD4+ lymphocyte counts, a situation similar to primary disease in the HIV-negative population.\(^1,15\) Pleural effusions occur at a range of CD4+ counts and seem to be more common than in HIV-negative cases.\(^26\)
A variety of CXR findings have been found in TB with advanced HIV infection, including:

- hilar and mediastinal adenopathy with localised parenchymal shadowing
- diffuse opacities, usually bilateral
- localised coarse nodular opacities
- miliary pattern
- pleural effusion
- a normal CXR.

In advanced HIV infection cavities are not usually seen on chest X-ray. Rapid progression may occur and radiological deterioration can occur on treatment.

These types of presentation in the severely immune-compromised are explained by both the high rates of progression to disease following primary infection and reactivation of latent TB infection (LTBI) in the context of impaired immunity, leading to a weak delayed-type hypersensitivity response.

Tuberculin reactivity is lost as immunodeficiency progresses, also due to the loss of an effective delayed-type hypersensitivity response to mycobacterial antigens. A negative Mantoux should not discourage active investigation for possible TB, especially when the CD4+ lymphocyte count is low (see also section 5.2).

**Figure 3.1:** HIV-associated tuberculosis clinical features related to degree of immune-suppression

<table>
<thead>
<tr>
<th>Pattern of disease</th>
<th>TST reactivity</th>
<th>Sputum</th>
<th>Smear</th>
<th>Chest X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary +ve</td>
<td>+ve</td>
<td>+ve</td>
<td></td>
<td>Upper lobe infiltrates cavities</td>
</tr>
<tr>
<td>Higher infectivity</td>
<td></td>
<td></td>
<td></td>
<td>Pleural effusion</td>
</tr>
<tr>
<td>Declining CD4+ count</td>
<td>-ve</td>
<td>-ve</td>
<td></td>
<td>Atypical infiltrates lymphadenopathy normal</td>
</tr>
<tr>
<td>Lower infectivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary – concurrent pulmonary</td>
<td>-ve</td>
<td>-ve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– multifocal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TB should be considered in any HIV-infected person with respiratory symptoms. Sputum smears should be examined for acid-fast bacilli and sent for mycobacterial culture.

In a patient with unexplained fever, occult sites of extra-pulmonary TB infection should be sought, particularly when the CD4+ count is low. Abdominal TB can be difficult to diagnose and, at low CD4+ counts, tends to present with visceral involvement and adenopathy rather than the peritoneal TB typically seen in HIV-negative patients.²⁸

As with all TB, it is important to confirm the diagnosis with culture of the organism so that the identity can be confirmed and drug susceptibility testing undertaken.

### 3.4 Infectivity

Infectious patients should be appropriately isolated, and the same guidelines apply as for HIV-negative infectious cases (see Chapter 12).

A meta-analysis concluded there is no evidence that HIV-positive cases are intrinsically more infectious to their contacts than HIV-negative cases.²⁹
4 Treatment of Tuberculosis in HIV-infected Patients

4.1 Drug treatment: general principles

4.1.1 Drug regimens
The drug treatment of TB in the context of HIV infection follows the same approach as in HIV-negative individuals. However, the approach may need to be modified, depending on concurrent anti-retroviral medication (see below for information on TB treatment while on anti-retroviral therapy (ART)).

4.1.2 Duration of therapy
The American Thoracic Society and Centers for Disease Control and Prevention’s most recent guidelines on the treatment of TB recommend that six-month regimens are appropriate for fully sensitive pulmonary disease in patients co-infected with HIV and TB. However, controversy remains about short-course rifampicin-containing regimens in HIV-infected people due to concerns about relapse. A recent meta-analysis of randomised controlled trials and cohort studies to evaluate the impact of duration of rifamycin showed a trend toward higher relapse rates if rifamycins were used for only six months compared with ≥ 8 months.

Before completion of therapy, careful evaluation is required to ensure TB has been completely resolved. If there has been inadequate response, treatment should be continued. Six-month regimens are considered appropriate only for patients with fully sensitive TB with minimal disease. However, treatment should be extended to a minimum of nine months for patients with extensive disease, including cavitary disease or where the response to treatment has been slow. In most cases, a six- to nine-month regimen is recommended for extra-pulmonary TB unless there is CNS disease or bone and joint TB where 12 months of treatment may be required.

4.1.3 Daily compared with intermittent dosing; self-administration compared with directly observed therapy
Intermittent dosing regimens of TB drugs less than three times weekly may result in poor outcomes in some HIV-infected groups. Acquired resistance has been observed in patients on both twice-weekly rifampicin and rifabutin-based regimens.

All patients with co-infection should receive daily therapy for the first eight weeks of treatment. For the continuation phase, the optimal dosing frequency is also daily. If daily continuation phase treatment is not possible, three times weekly dosing during the continuation phase may be used in selected cases.
Directly observed therapy (DOT) is strongly recommended for HIV-infected patients with TB disease. Adverse events are common in HIV infected patients treated for TB disease. Anti-retroviral therapy regimens may be complex and DOT reduces the number of medications the patient must assume direct responsibility for administering. Study of ART regimens has confirmed the relationship between pill burden and missed doses, and avoiding missed doses of anti-TB drugs is paramount. DOT is appropriate for a large proportion of patients and should be used in the majority of cases, including all children. However, if self-administration is chosen, patients should be monitored closely with regular community supervision.

4.2 Anti-retroviral therapy and tuberculosis treatment

Anti-retroviral therapy (ART), which uses highly active combinations of drugs, consists of combination therapy with at least three anti-retroviral agents, usually with a ‘backbone’ of two nucleoside analogue reverse transcriptase inhibitor (NRTI) drugs combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI).

4.2.1 Efficacy of combination anti-retroviral therapy

The development of ART has dramatically altered the natural history of HIV infection, with a reduction in the frequency of opportunistic infections and a decline in the rate of death from AIDS.37,38 ART aims to suppress HIV replication with a subsequent recovery in CD4+ lymphocyte count. This is achieved, at least initially, in the majority of recipients of this treatment.

The natural history of TB–HIV co-infection in the ART era has not been studied in the same detail as in untreated HIV infection, but evidence suggests that effective viral suppression and immune reconstitution will impact favourably and reduce the incidence of reactivation disease and new infection.39–41

4.2.2 Issues with anti-retroviral therapy and tuberculosis treatment

The treatment of HIV-related TB is complex and requires expertise in the management of both HIV disease and TB. The key issue with respect to treatment of HIV and TB is that there are significant drug–drug interactions between the rifamycin drugs (rifampicin and rifabutin) and the PI and NNRTI anti-retrovirals. Both the PIs and NNRTIs act as substrates for cytochrome P-450 (CYP450) isoenzymes, and, depending on the drug, may induce or inhibit CYP450. The rifamycins are inducers of CYP450 (rifampicin more so than rifabutin). The net result of co-administration is a reduction in the serum level of the anti-viral agent, the extent of reduction varying between agents. HIV resistance develops in an environment of sub-therapeutic anti-viral drug concentrations, and this situation must be avoided whenever possible.
ART regimens that include an NNRTI have fewer interactions with rifampicin-based TB treatment than regimens that include a PI. For patients on treatment for TB disease, starting ART with an efavirenz containing regimen is preferred due to fewer interactions and evidence to support the use of this drug with rifampicin based TB treatment. Some authors recommend increasing the dose of efavirenz to 800mg daily in patients over 60 kilograms but other experts suggest that no dose adjustment is necessary. Inferior virological outcomes have been observed when nevirapine based antiretroviral therapy is commenced while taking anti-tuberculosis treatment. It has been suggested that this relates to sub-therapeutic nevirapine levels in the initial two week lead in period as the cytochrome P450 enzyme system has already been induced by rifampicin. Despite these concerns one study has shown 80% virological suppression at 18 months in patients receiving TB treatment and subsequent nevirapine. If nevirapine is used with rifampicin the lead-in phase is not required and full-dose nevirapine may be used from the start.

Use of protease inhibitors with rifabutin results in reduced metabolism of rifabutin, resulting in significantly increased serum rifabutin levels with a potential increase in toxicity (eg, uveitis). Hence, the dose of rifabutin should be reduced, especially if the PI is boosted with ritonavir.

Rifampicin is not recommended for patients on PIs due to its induction of PI metabolism. The use of saquinavir–ritonavir or lopinavir–ritonavir with rifampicin has been associated with high incidence of hepatotoxicity in healthy volunteers, so these combinations should be avoided.

There are no significant drug–drug interactions between the NRTIs and the rifamycins. However, several clinical studies of triple-NRTI regimens have shown suboptimal anti-HIV activity, so this combination is generally not recommended.

Table 6.3 summarises current recommendations about the concurrent use of rifamycins and PI and NNRTI drugs. Rifabutin levels are increased by all PIs and dose reduction is required, as indicated, to avoid toxicity. Careful clinical monitoring of the patient is also mandatory. Careful follow-up is required with attention to both TB response and HIV suppression.

Rifabutin 150 mg three times weekly in combination with LPV/r has resulted in inadequate rifabutin levels and has led to acquired rifamycin resistance in patients with HIV-associated TB. Therapeutic drug monitoring for rifabutin is recommended.
Data on the drug-drug interactions with the new antiretroviral drugs are limited and further studies are awaited. Etravirine should not be used together with rifampicin because of rapid metabolism. Limited pharmacodynamic studies predict that the combination of rifampicin, and possibly rifabutin, will result in decreased levels of maraviroc and raltegravir. Recent guidelines, however, suggest raltegravir does not require dose adjustment when given with either rifampicin or rifabutin and that maraviroc should be increased to 600 mg twice daily when given with rifampicin but no dose adjustment is required when given with rifabutin. However, until further data are available these drugs should be avoided or used with extreme caution in combination with rifamycins.

Table 4.1: Recommendations for using non-nucleoside reverse transcriptase inhibitor (NNRTI) anti-retrovirals with rifampicin, and protease inhibitor (PI) and NNRTI anti-retrovirals with rifabutin

<table>
<thead>
<tr>
<th>Anti-retroviral drug</th>
<th>Recommended change in dose of anti-retroviral drug</th>
<th>Recommended change in dose of rifamycin</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendations with rifampicin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>600 mg daily (consider 800 mg daily if weight over 60 kg)</td>
<td>None</td>
<td>May use 600 mg daily if higher dose not tolerated</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>200 mg twice a day</td>
<td>None</td>
<td>Use when no other option available</td>
</tr>
<tr>
<td><strong>Recommendations with rifabutin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protease inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>None</td>
<td>150 mg every other day or thrice weekly</td>
<td>Rifabutin AUC increased 430%</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>None</td>
<td>150 mg every other day or thrice weekly</td>
<td>Rifabutin AUC increased 250%</td>
</tr>
<tr>
<td>Lopinavir–ritonavir</td>
<td>None</td>
<td>150 mg every other day or thrice weekly</td>
<td>Rifabutin AUC increased 303%</td>
</tr>
<tr>
<td><strong>NNRTI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>None</td>
<td>450–600 mg daily or 600 mg thrice weekly</td>
<td>Rifabutin AUC decreased 38%</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>None</td>
<td>300 mg daily or 300 mg thrice weekly</td>
<td>Rifabutin and nevirapine AUC not significantly changed</td>
</tr>
</tbody>
</table>

Notes: The table applies to combination anti-retroviral therapy regimens that consist of a 2NRTI 'backbone' plus one of the above. No relevant data pertain to PI–NNRTI combinations. AUC = area under the curve (a measure of drug concentration).

* Rifabutin 150 mg three times weekly in combination with LPV/r has resulted in inadequate rifabutin levels and has led to acquired rifamycin resistance in patients with HIV-associated TB. Therapeutic drug monitoring for rifabutin is recommended.

Source: Adapted from Centers for Disease Control and Prevention (2007).
4.2.3 Ensuring adequate tuberculosis treatment and adequate anti-viral treatment in co-infection

The optimal time to start ART in relation to the start of TB treatment is not yet clear but there is increasing evidence to support early treatment.\(^{53,54,76,77}\) One randomised controlled trial provides some evidence for early initiation of ART in terms of reduced all-cause mortality, improved TB outcomes and reduced incidence of immune reconstitution inflammatory syndrome (IRIS).\(^{54}\) In 2009, the recommendations of World Health Organization and Centre for Disease Control are that TB treatment should be commenced first and ART subsequently commenced as soon as possible and within the first eight weeks of starting TB treatment.\(^{1,2,3}\)

4.3 Paradoxical reactions during therapy

Paradoxical reactions are the worsening of signs or symptoms of TB or the development of new manifestations of TB in people on appropriate anti-TB chemotherapy.\(^{1,5,42,55}\) This phenomenon is observed in the HIV-negative population (about 2%), but it has been noted to be more common in HIV-infected TB patients. Estimates of frequency range from 7% to 36%, and the highest incidence has been seen in patients receiving anti-retroviral therapy.\(^{55}\)

Clinically, in patients with HIV infection, paradoxical reactions most commonly involve lymph nodes, with progressive lymphadenopathy. Fever and worsening or development of pulmonary infiltrates may be seen, and the reaction usually occurs within a month of starting anti-retroviral therapy.\(^{55,56}\)

In general, paradoxical reactions are self-limited and last 10–40 days. They are not an indication to stop either anti-TB or anti-retroviral therapy, but if severe may require investigation to exclude other causes of deterioration, and even symptomatic treatment with corticosteroids.\(^{42,55,56}\)

4.4 Tuberculosis-related immune reconstitution syndrome

Reconstitution syndromes are a group of disorders that can occur during ART treatment of HIV. In many respects the phenomenon is analogous to the process described above and is thought to reflect restoration of competent CD4+ and CD8+ responses directed against latent infection with a variety of pathogens. Reconstitution syndromes have been most commonly described secondary to *Mycobacterium avium intracellulare* complex and cytomegalovirus, but can also occur with TB.\(^{42}\) In patients with HIV, who are treated with ART within six weeks of starting anti-TB treatment 11–45% develop immune reconstitution inflammatory syndrome (IRIS). The risks of IRIS developing are low baseline CD4+ count, high baseline viral load, good CD4+ and HIV response to ART and extra-pulmonary disease.\(^{57,79}\)

TB-related IRIS may manifest as lymphadenitis or pneumonitis, typically with low bacillary numbers. Most patients can be managed conservatively however anti-inflammatory agents or corticosteroids may be required to control troublesome inflammatory symptoms.\(^{42}\)
4.5 Drug-resistant tuberculosis in HIV-infected patients

Treatment of drug-resistant TB in HIV-infected patients applies the same principles as in non-HIV-infected people (see Chapter 6). Well-documented outbreaks of multi-drug–resistant disease among HIV-infected people have highlighted the difficulties of treating this group with drug-resistant isolates.24

A higher-than-expected rate of rifampicin mono-resistance has been noted by some investigators in HIV-infected individuals. Different studies have noted both primary and acquired rifampicin resistance and risk factors for acquired resistance, included diarrhoea, advanced immune-suppression and non-compliance.58,59

4.6 Cotrimoxazole preventive therapy

Cotrimoxazole preventive therapy (CPT) has been shown to improve survival in TB patients with HIV infection in several studies from sub-Saharan Africa. In that setting, the benefit of CPT has been ascribed to decreasing the incidence of malaria, Pneumocystis pneumonia and a variety of bacterial infections.60–64

WHO guidelines recommend CPT for all people with both TB and HIV regardless of CD4 count.65 The epidemiology of opportunistic infection in New Zealand differs from that in developing countries and local experts do not recommend CPT in TB and HIV co-infected patients with CD4 counts greater than 200 cells/mm3.
5 Prevention of Tuberculosis in HIV-infected Patients

5.1 Co-ordination of control measures

TB prevention should be a key component of the care of HIV-infected patients. Identification and treatment of LTBI and prevention of severe immunodeficiency by the appropriate use of ART are all strategies that might be expected to reduce the mortality and morbidity of HIV-associated TB.

5.2 Screening for latent tuberculosis infection in HIV-infected patients

HIV is the single greatest risk factor for the reactivation of TB, so screening for LTBI should be part of the evaluation of all patients with HIV-infection and a Mantoux test or interferon gamma release assay (IGRA) obtained in all HIV-positive people.

Induration of 5 mm or greater in response to a standard 5 TU purified protein derivative test, (or positive IGRA – see Chapter 2), irrespective of prior Bacillus Calmette-Guérin (BCG) vaccination, should be regarded as positive in this population. In view of the high risk of developing disease, treatment of LTBI should be offered. A previously documented positive Mantoux with no record of preventive therapy is also an indication for treatment.

With increasing immune-deficiency the likelihood of a negative Mantoux increases due to impaired delayed-type hypersensitivity response, but anergy testing is no longer recommended as an adjunct to Mantoux testing. There is no evidence for benefit of treatment for LTBI in anergic HIV-positive people solely on the basis that they are at high risk for TB infection.

Practice points

Preventive treatment for LTBI should be given to HIV-positive patients with:
- Mantoux ≥ 5 mm or positive IGRA
- previously documented positive Mantoux and no prior LTBI treatment
- minor or slight CXR abnormalities consistent with old TB (but consider full preventive treatment)
- documented recent exposure to a smear-positive case.
5.3 Investigation of inactive pulmonary tuberculosis

A CXR should be completed for all patients with:
- with respiratory symptoms
- with a positive Mantoux or IGRA
- with a history of pulmonary disease or tuberculosis
- at risk of exposure to tuberculosis.

This is especially important in people from countries with a high incidence of TB. A CXR may show changes consistent with prior, inactive TB (see Chapter 2). These people should be investigated to exclude active disease, including induced sputum or bronchoscopy if they have little or no spontaneous sputum. If microbiological tests show no evidence of active disease, they should be considered for preventive treatment of inactive TB disease (see Chapter 8).

5.4 Treatment of latent tuberculosis infection in HIV infection

The efficacy of treatment of LTBI in HIV-infected people has been shown in placebo-controlled trials. A systematic review has confirmed the benefits of treating LTBI in the context of HIV infection. A recent Cochrane review showed an odds ratio for active TB of 0.38 in people with a positive Mantoux, based on 12 trials and 8578 patients. Regimens include 6H, 12H, 3RH and 3RHZ. 

The current preferred regimen for the treatment of LTBI with HIV infection is 9H, but the following should be noted.

- The 9H regimen has no relevant interactions and can be introduced after ART is established.
- To overcome adherence issues shorter courses of treatment have been used. 2RZ was recommended as an alternative in 2000 based on data from patients with HIV infection. Despite reports that the combination of rifampicin and pyrazinamide appeared to be safe in HIV-infected patients in contrast to those who were HIV-negative, the American Thoracic Society and Centers for Disease Control and Prevention have revised their recommendations and recommend that this regimen should generally no longer be offered to patients. Cases of hepatotoxicity in HIV-infected patients have been subsequently reported.
- Rifampicin for four months is an acceptable alternative for treatment of LTBI in HIV-negative individuals. No studies demonstrate the efficacy or safety of this regimen in individuals with HIV infection, and the use of rifampicin is often limited by the co-administration of ART.
- The dose adjustments outlined in Table 6.3 when combining rifamycins with PI–NNRTI drugs also apply in this situation.

* The number in front of the letters is the number of months of the treatment regimen, the letters stand for the drugs (R = rifampicin; H = isoniazid; Z = pyrazinamide), so 6H = six months of daily isoniazid; 12H = 12 months of daily isoniazid; 3RH = three months of daily rifampicin and isoniazid; and 3RHZ = three months of daily rifampicin, isoniazid and pyrazinamide. For more information about treatment regimens, see Chapter 3.
6.5.5 BCG vaccination in HIV-infected patients

The Global Advisory Committee on Vaccine Safety recommends that the BCG vaccination should not be used in any children who are known to have HIV infection due to studies showing an increased risk of their developing disseminated BCG disease.\textsuperscript{74,75} BCG vaccination is also not recommended for adults with HIV infection.\textsuperscript{6}
References


