10. TB and HIV Infection

The management of patients with TB and HIV infection is complex, requiring management by a multidisciplinary team which includes physicians with expertise in the treatment of both TB and HIV. This chapter provides a broad overview of the management and treatment of HIV-infected individuals with confirmed or suspected TB or LTBI. Readers are advised to refer to this document together with current international guidelines from the CDC,[342;343] WHO[344] and the British HIV Association (BHIVA).[345]

Recommendation:

Cases of TB/HIV should always be managed by physicians with expertise in treating both TB and HIV.

10.1 Epidemiology and Surveillance of TB Infection

TB can occur at any point in the course of progression of HIV infection. It is the commonest opportunistic infection in HIV-infected individuals and is reported as the cause of death for 11% of all AIDS patients.[2] HIV infection acts by lowering the host's immune response to mycobacteria, heightening susceptibility to infection and progression to active disease. HIV is recognised as the single greatest risk factor for development of active TB disease.[6;346;347] The lifetime risk of a HIV and *M. tuberculosis*-infected individual developing active TB is 50%, ten times greater than a non-infected individual. It is therefore important that a high index of suspicion for TB should be maintained in HIV-infected individuals.[344] It is notable that 63% of AIDS patients with active TB infection have positive blood cultures.[139] Blood cultures should be the first step in the routine evaluation of HIV positive patients with suspected TB.[140]

Globally, the number of HIV positive TB cases continues to grow.[1] HIV infection has had a significant impact on the incidence of TB, particularly in areas where rates are highest e.g. Sub-Saharan Africa. WHO estimates that 9% of all TB cases are co-infected with HIV. Rates are believed to range from 1.1% in the Western Pacific, to 5.9% in the Americas, and to 31% in Africa.[346] In countries with a low incidence of disease, sub-populations with both infections are recognisable. In the United States, particular ethnic groups are disproportionately affected, while injecting drug use is a factor in other countries.[348]
In Ireland, the incidence of TB in HIV-infected individuals is uncertain. This is due to a combination of factors, including the absence of routine HIV screening in TB patients, incomplete reporting of HIV as a risk factor for TB, and non-statutory notification of HIV. TB surveillance data indicate that between 2 and 19 cases were known to be infected with HIV per annum (2001-2006) (personal communication, HPSC). However, these figures are an under-estimate due to the factors outlined above.

Recommendation:

A high index of suspicion should be maintained for TB in all HIV-infected individuals.

10.2 Pathophysiology

HIV infection destroys CD4 lymphocytes and affects monocyte function, rendering them unable to destroy certain invading microorganisms. HIV produces a progressively deficient immune response and as the infection develops, CD4 lymphocytes are depleted and immunity to *M. tuberculosis* is reduced. CD4 lymphocyte counts are a useful indicator of the degree of immunodeficiency and clinical features of TB in HIV-infected individuals have been found to correlate with CD4 counts.[349]

The tubercle bacillus begins its infection in the alveolar macrophage where it multiplies in activated

macrophages and leads to cell necrosis. Bacteraemia and secondary spread occurs when the macrophage cannot contain the bacilli. A T-cell mediated delayed hypersensitivity reaction may limit further spread of bacteria by granuloma formation at initial or regional sites of infection. The destruction of mycobacteria depends on increases in metabolic and enzymatic activity which is largely dependent on inhibitory mechanisms primed by CD4 lymphocytes.

HIV viral replication increases in alveolar macrophages and peripheral lymphocytes when exposed to *M. tuberculosis* antigens,[350-352] and inflammatory cytokines tumour necrosis factor alpha (TNF-alpha) and interleukin-1 (IL-1) are mediators of this enhanced replication. HIV acts by destroying lymphocytes and inhibiting the release of lymphokines from CD4 cells which are responsible for recruiting and enhancing macrophage resistance to mycobacterial replication. The result of the progression of CD4 lymphocyte destruction and consequent effect on macrophages results in poorly formed granulomas and the inability to kill ingested mycobacteria and the spread of infection. The results are seen in clinical TB as poorly formed granuloma, large organism load and blood stream invasion.

10.3 Diagnosis of TB in HIV-infected Cases

The diagnosis of TB in a HIV-infected individual may be difficult. The clinical, radiological and histopathological presentation of HIV-related TB disease can be atypical and is influenced by the degree of immunodeficiency.[349;353] Clinical presentation may mimic or co-exist with other opportunistic infections such as *M. avium* or *Pneumocystis carinii*.

Evaluation of a suspected HIV-infected TB case should always include a chest X-ray and sputum should be obtained for smear and culture. However, results become less sensitive with increasing immunodeficiency.

Bacteriological and histological findings

As with all TB cases, obtaining appropriate specimens is important for diagnosing HIV-related TB disease. The yield from sputum smear and culture is similar to that in immunocompetent individuals when HIV-infected individuals have high CD4 counts. However, in severely immunocompromised individuals, culture positive sputum is more likely to be smear negative.[354]

The likelihood of obtaining a positive culture from infected extra-pulmonary sites is greater in patients with advanced HIV than in HIV-uninfected cases.[355-357] Smear positive specimens from those sites may have a large burden of bacilli due to an impaired immune response.

Histological findings range from typical granulomatous inflammation in individuals with CD4 counts above 200 cells/μl, to poorly formed/absent granulomas in those with decreasing immunocompetence, particularly in individuals with CD4 counts below 100/μl. In those circumstances, AFB are more likely to be observed microscopically.

Radiological findings

The spectrum of clinical features associated with TB/HIV positive persons is influenced by the degree of immunosuppression. Chest X-ray findings of cases with CD4 lymphocyte counts above 350 cells/μl,[342] appear like those of non-HIV infected cases,[343] with disease confined to the lungs with upper lobe fibronodular infiltrates and with/without cavitation. Pleural effusions are more common in persons with CD4 counts of > 200 cells/μl. During advanced stages of HIV infection, pulmonary disease may present with unilateral or diffuse shadowing in lower and middle lobes or miliary infiltrates on X-ray. Cavitation is uncommon. TB may present as a systemic disease with high fever and sepsis.

At CD4 counts lower than 50 cells/μl, extra pulmonary disease (pleuritis, pericarditis, meningitis) becomes increasingly common (with or without pulmonary involvement).[342] Extrapulmonary disease is detected with greater frequency in HIV-infected than non HIV- infected individuals, however, the clinical presentation of extrapulmonary disease does not differ according to HIV status.

In patients with severe immunodeficiency, it is not uncommon to have normal chest X-rays and culture and smear positive sputum specimens.[25]

10.4 Diagnosis of HIV in TB Cases

It is recognised that currently HIV testing may not be undertaken routinely for all TB cases in Ireland. An optimal strategy for HIV screening in TB patients would involve all TB patients, regardless of the perceived risk of HIV infection, being offered HIV testing as part of their TB assessment.[358] In countries with a low-incidence of TB, studies have shown that cases of TB/HIV infection have been missed because heterosexual transmission was not considered as an important risk factor for HIV infection.[359]

Recommendation:

All TB cases should be offered HIV testing.

10.5 Screening for LTBI

Individuals with symptoms of TB should have a chest X-ray and clinical evaluation as soon as possible, regardless of the TST result. Asymptomatic HIV-infected cases should have a TST (Mantoux test), an IGRA (if available) and chest X-ray to investigate the possibility that the patient has active disease. HIV positive individuals with an induration of >5mm and no chest X-ray findings are eligible for treatment of latent infection.

A baseline chest X-ray should be taken when a HIV diagnosis is confirmed,[360] and this committee recommends that screening by chest X-ray should be undertaken every two to three years thereafter, to determine any changes. CDC suggests annual repeat testing for those TST negative on initial testing and who belong to a population at substantial risk of exposure. Furthermore, hepatitis C screening should also be considered, particularly for HIV-infected cases with a history of injecting drug use.

Tuberculin skin testing

The prevalence of positive TSTs decreases progressively with declining CD4 count,[361] therefore the TST has limited diagnostic value among patients with severe immunodeficiency.[34] The proportion of cases reacting to PPD declines from 50-90% for cases with a CD4 count of ≥ 500 cells/μl, to 0-20% for cases with a CD4 count of ≤ 200 cells/μl.[345] Tuberculin reactivity tends to be lost because increasing immunodeficiency results in a weakened delayed-type hypersensitivity response to mycobacterial antigens. HAART (Highly Active Antiretroviral Therapy) may improve the immune response to TB but patients most likely to go from a negative to a positive TST result are those whose CD4 rises by > 200 cells/μl.[345]

In the UK, BHIVA do not recommend tuberculin skin testing in patients with CD4 counts < 400 cells/μl,[345] while CDC guidance indicates that TSTs are positive in the majority of patients with pulmonary disease and CD4+ T lymphocyte count > 200 cells/ul. The view of this committee is that a TST should be undertaken regardless of CD4+ T lymphocyte count, with the proviso that the result may be unreliable in an individual with lower CD4 counts. TST indurations of >5mm should be considered positive regardless of BCG status, and evaluation and treatment of latent infection should be considered. Previous BCG vaccination in a HIV-infected individual does not infer immunity.

Interferon gamma release assays (IGRA)

The use of interferon gamma release assay for diagnosing latent and active TB has been addressed elsewhere in these guidelines (chapter 2). Despite being an immunological assay, studies suggest it may be more useful for diagnosing LTBI in HIV-infected individuals than the tuberculin skin test.[34;362] However, further studies are required to correlate IGRA results with CD4 counts and to test the reproducibility of the test in this population.[345] The lack of evidence concerning the utility of an IGRA in this population makes it difficult to devise recommendations.

It is recommended that the TST should be used initially to detect LTBI and a person with a positive result should be considered to have LTBI.[30] False negative results are not uncommon in immunodeficient individuals; therefore if a clinician is concerned about the possibility of such a TST result, an IGRA can be conducted. LTBI can be considered if an IGRA test is positive, while indeterminate results should be

repeated. Indeterminate results may indicate laboratory error or anergy, therefore a person's history, clinical features and laboratory findings must be taken into account when diagnosing LTBI using an IGRA.

Diagnosis in children

A high index of suspicion is required for TB in HIV infected children, as those under two years of age are at risk of disseminated disease causing miliary TB or TB meningitis. It is advised therefore, that HIV infected children are screened annually for TB, beginning at age three to 12 months.[217]

Diagnosis of TB can be complicated by failure to detect *M. tuberculosis* in gastric washings, pre-existence or coincidental fever, pulmonary symptoms and chest X-ray abnormalities.[343] Cervical lymph nodes are commonly involved in extra-pulmonary cases. In children, lymphoid interstitial pneumonitis (LIP) is often associated with persistent generalised lymphadenopathy (PGL), a feature of HIV infection. It can be confused with TB as chronic symptoms are common. Lymphadenopathy due to LIP is generalised, symmetrical, mobile, non-tender, firm and non-fluctuant. Further information is available from the WHO's guidelines for clinical management of TB/HIV.[344] (www.who.int/tb/hiv/en/).

Recommendation:

In HIV-infected individuals, routine screening for TB is advisable. HIV-infected children should be screened annually for TB, beginning at age three to 12 months.

10.6 Treatment of Active Disease

The standard treatment regimen for adult TB/HIV- infected persons is the same as for non HIV- infected TB cases. It is recommended that physicians with appropriate expertise should be consulted prior to the initiation of treatment, due to the complexity of co-administration of anti-TB and antiretroviral therapies.

Treatment of TB/HIV infected children

In children aged less than five years, treatment should commence as soon as possible to avoid dissemination of disease. As with adults, the initial phase of treatment should involve a four drug treatment regimen. Ethionamide can be used instead of ethambutol where TB meningitis is indicated, as it penetrates the CNS more effectively. For HIV-infected children with active pulmonary disease, treatment duration should be nine months and 12 months for extrapulmonary TB.

10.7 Treatment of LTBI in HIV-Positive Individuals

Treatment of LTBI has been proven efficacious in HIV-infected individuals.[363-365] The optimal treatment regimen for LTBI in HIV-infected persons of all ages is isoniazid for nine months or rifampicin and isoniazid for four months, once medical evaluation has ruled out active TB disease. However, six months treatment may be realistic and easier to enforce. These recommended regimens are based on a review of the evidence and guidance in the international literature and by consensus of the National TB Advisory Committee. Pyridoxine should also be administered to those in receipt of isoniazid to reduce the risk of peripheral neuropathy (chapter 3). Antiretroviral therapy can be delayed until LTBI treatment is completed.

Recommendation:

The recommended treatment regimens for LTBI in adults who are HIV positive are:
(i) Isoniazid for an optimum duration of nine months or
(ii) Rifampicin for four months or
(iii) A combination of rifampicin and isoniazid for four months.

Treatment of LTBI in HIV-positive children

For exposed contacts with impaired immunity i.e. with HIV infection and for all contacts younger than five years of age, isoniazid therapy should be initiated, even if the TST result is negative, once TB disease is excluded.

Recommendation:

The recommended treatment regimens for LTBI in children who are HIV positive are:
(i) Isoniazid for a minimum of six months with an optimum duration of nine months or
(ii) Rifampicin for six months or
(iii) A combination of rifampicin and isoniazid for four months.

As there is significant potential for an interaction between rifampicin and antiretroviral agents it is important that treatment of LTBI in HIV positive children be undertaken by a specialist both in TB and HIV.

Directly observed therapy (DOT)

During the 1990s, the United States experienced a resurgence in TB because of immigration, a failing public health infrastructure and due to the emerging HIV epidemic. In New York, case notifications tripled and the proportion of drug-resistant isolates more than doubled between 1978 and 1992. To tackle this growing problem, the programme of supervised medication taking was expanded. Improved rates of treatment completion and decreasing case numbers were observed, giving credence to the concept of directly observed therapy (DOT).[366-368] CDC and WHO advocate the use of DOT for HIV-positive individuals in receipt of a multiple TB drug regimen, due to the severity of the disease in immunodeficient persons.[369]

It is recommended that all TB/HIV patients should receive daily TB therapy. However, TB treatment may be given five days a week by directly observed therapy.[345] Indications for intermittent therapy are the same for HIV-infected and non HIV-infected patients. Thrice-weekly administration of a modified dose of treatment can be used, particularly after daily administration during the initiation phase of treatment (first two months). However, certain alternative regimens (once weekly isoniazid-rifapentine in the continuation phase, and twice weekly isoniazid-rifampicin/rifabutin in any HIV patient with CD4 count < 100 cells/*u*l) have been associated with the acquisition of rifampicin resistance and should be avoided.[345] Guidelines for managing treatment and interruptions to treatment are provided in the BHIVA guidelines (www.bhiva.org/).

Recommendation:

Directly observed therapy (DOT) is recommended for treatment of all HIV-infected TB cases.

10.8 Evaluation of a TB/HIV Case

Baseline evaluation

The BHIVA guidelines recommend that the following baseline measurements are made:[345]

1. Absolute CD4 count and percentage
2. Measure LFTs, i.e. serum aminotransferases (AST, ALT), bilirubin and alkaline phosphatase. LFTs should be retested at one to two weeks if asymptomatic
3. Serum creatinine and a platelet count
4. Serological testing for hepatitis B and C
5. Visual acuity with Snellen charts when ethambutol is to be used
6. A repeat smear and culture should be done after two months of treatment in a pulmonary TB patient who still has a productive cough
7. Chest X-ray if progress is unsatisfactory after two months. For patients with pulmonary TB, baseline and 'completion of treatment' chest X-rays are necessary and
8. Other evaluations e.g. additional chest X-rays, ultrasound or CT scans may be indicated depending on the clinical need.

Follow up evaluation

A clinical evaluation should be performed monthly to assess medication intolerance and adherence in TB/HIV-infected individuals. Treatment effectiveness should be monitored throughout the treatment period. In pulmonary TB/HIV patients, a minimum of one sputum specimen should be examined microscopically each month, until two consecutive specimens are negative on culture. Drug susceptibility should be re-evaluated in patients with culture positive specimens after three months of treatment. The ease of monitoring treatment effectiveness will be determined by the site of infection in extrapulmonary cases. More frequent monitoring is required for patients with underlying liver disease including hepatitis C.

The risk of relapse is believed to be the same in HIV-infected and non-infected TB cases receiving rifampicin for a minimum of six months. HAART has been shown to reduce the risk of relapse.[370-372]

Commencement of HAART

The International Standards for TB Care[25] propose that all patients with TB/HIV co-infection should be evaluated to determine if antiretroviral therapy is indicated during the course of TB treatment. The use of co-trimoxazole in TB/HIV-infected individuals as prophylaxis against other infections should also be evaluated.

While initiation of TB treatment should not be delayed, there is no international agreement on the optimal time to start HAART in TB/HIV patients. Case-by-case assessments are made in an attempt to balance the risk of progression of HIV against that of having to interrupt/discontinue therapies due to toxicities, side effects, drug interactions, etc. Delaying antiretroviral therapy can simplify patient management, limit adverse events, drug interactions and immune restoration reactions. Furthermore, studies have shown deaths due to TB are more common in the first month of TB treatment, while deaths occurring later on may be due to HIV disease progression.[373-375] BHIVA recommend the following start times of antiretroviral therapy in TB/HIV-infected patients.

Table 10.1: Recommended HAART starting times (adapted from BHIVA guidelines)

CD4 cells/μL	Commencement of HAART
<100	Case-by-case assessment (possibly delay up to 2 months)
100-200	After 2 months of TB treatment
>200	After completing 6 months of TB treatment®

® CD4 count monitoring should be performed every 6-8 weeks. If CD4 count falls, patient may need to start HAART.

The initiation of HAART within two to four weeks of anti-tuberculous therapy has been associated with decreased HIV-1 progression (CDC) but a high incidence of adverse events and paradoxical reactions (see below). By delaying HAART by a minimum of four to eight weeks after initiation of TB therapy, specific causes can be assigned to drug side effects and the severity of a paradoxical reaction can be reduced. Optimal timing for starting HAART should be based on an individual's initial response to treatment, side effects and acceptance of antiretroviral treatment.[342]

TB treatment should only be modified when a patient has developed intolerance to, or severe toxicity from, HIV drugs or has evidence of genotypic resistance to specific HIV drugs thus limiting HAART therapy to agents which are likely to interact with anti-TB therapy. These factors may require the duration of TB treatment to be extended.[345]

Factors complicating the treatment of TB/HIV[344;345]

Adverse pharmacological interactions occur between rifampicin and antiretroviral drugs used in the treatment of HIV disease due to shared routes of metabolism. Due to these complexities of treatment, it is important that the use of both HAART and anti-TB treatment is managed by those with relevant expertise. Here we provide an overview of the complexities of concomitant treatment of HIV and TB.

Rifampicin induces an enzyme in the hepatic cytochrome P-450 (CYP) system which is involved in the metabolism of protease inhibitors (PIs) and non-nucleoside reverse inhibitors (NNRTI). Rifampicin can accelerate clearance of PIs and NNRTIs metabolised by the liver, resulting in sub-therapeutic levels of the

drugs. Clinically important drug interactions can become evident after two weeks of treatment when the inducing effect is maximised and can persist for two weeks after rifampicin has been withdrawn from the treatment regimen. Furthermore, rifampicin can enhance the activity that results in the elimination of PIs from the body. Despite these interactions, rifampicin should not normally be excluded from the standard treatment regimen for TB/HIV cases receiving antiretroviral therapy.

An immune reconstitution inflammation syndrome (IRIS) or a paradoxical reaction is a temporary exacerbation of TB symptoms or radiographic findings after beginning anti-TB treatment. It has been described in non HIV-infected individuals but is more common in HIV positive cases. It occurs because of reconstitution of immune responsiveness due to HIV or TB treatment which leads to an abnormal immune response to TB antigens released by dead/dying bacilli and is accompanied by a high fever, increased size and inflammation of lymph nodes, new lymphadenopathy, expanding CNS lesions, worsening of lung parenchymal infiltrations and pleural effusions. Management of a non-severe paradoxical reaction involves treatment of symptoms with non-steroidal anti-inflammatory agents. Some studies have shown that more severe reactions involving high fever, airway compromise by enlarging lymph nodes, enlarging serosal fluid collections and sepsis syndrome can be treated with prednisone or methylprednisolone. IRIS can be transient, yet last for many months. Most cases experiencing IRIS are at an advanced stage of immunodeficiency. Patients commenced on HAART within the first two months of TB treatment are at greater risk of IRIS.

Overlapping toxicity profiles also occur in individuals receiving concomitant treatment for HIV and TB. NNRTIs and co-trimoxazole, and rifampicin, isoniazid and pyrazinamide used to treat TB are all associated with side effects of fever, rash, peripheral neuropathy and other neurological events, gastrointestinal intolerance and hepatitis. Side effects are most common in the first two months of treatment.

Dispensing of HIV and anti-TB therapy

Given the complex drug interactions that can occur between HIV and anti-TB medications, and the need to be able to monitor compliance, patients receiving therapy for both HIV and TB or LTBI should receive their HIV and TB medications from the same pharmacy, from a pharmacist experienced in the use of these medications. The pharmacist should keep records of TB and HIV medications dispensed to each patient and advise patients on the importance of compliance with their treatment and on potential adverse drug reactions and interactions. Pharmacists should also be part of the multidisciplinary team looking after patients with TB/HIV infection. They have an important role in the provision of advice on dosages for anti-TB and HIV medications, on therapeutic drug monitoring for patients who are receiving treatment with drugs such as amikacin and in monitoring the patient for adverse drug reactions e.g. hepatotoxicity.

10.9 Prevention and Control

Cases of TB in HIV positive individuals should be notified and contact tracing undertaken as recommended for non-HIV infected TB cases (chapter 8).

HIV positive cases are not considered to be more infectious to their contacts than HIV negative individuals.[376;377] On the contrary, it has even been suggested that the likelihood of transmission is reduced because bacillary loads are lower and cavitary disease is less common than in non-HIV infected TB cases. However, this has not been proven on an individual case basis, and procedures for contact tracing and infection control measures should be applied in the same manner as for non-HIV infectious TB cases.

HIV infection does lead to a greater likelihood of TB infection progressing to active disease and a high proportion of infections in this population result in disease with a short time frame between exposure and the development of symptoms.

BCG

There is international agreement that BCG is contraindicated in HIV positive individuals.[26;52;369] In countries where the risk of TB is low, it is recommended that BCG should be withheld from all individuals known or suspected to be HIV positive.[26] Infants born to known HIV positive women should have BCG deferred until after the second HIV PCR proves negative (usually at/after 6 weeks of age).[332] The benefit of vaccinating HIV-infected individuals to prevent the development of TB is as yet unproven,[378] and adverse events

relating to complications from BCG e.g. ulceration, regional lymphadenopathy and dissemination have been reported.[255, 257]

Infection prevention and control (see chapter 6)

Hospital management of a HIV-TB case should include single room accommodation for a pulmonary case, preferably with negative pressure ventilation. HIV positive or other immunosuppressed individuals should not be exposed to possible or confirmed infectious cases.[379] Aerosol-producing procedures should be conducted in isolation rooms with sufficient ventilation to ensure airborne particles are removed between each patient's use. Furthermore, exposure to HCWs should be minimised by reducing the number of workers involved in direct care, e.g. using a named-nurse system/primary nursing. Individual assessments should be made with regards to risks for visitors.