

British HIV Association guidelines for the treatment of TB/HIV coinfection 2011

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Keywords: directly observed therapy, drug interactions, drug resistance, highly active antiretroviral therapy, HIV, immune reconstitution inflammatory syndrome, interferon- γ release assay, latent tuberculosis, multi-drug resistant, treatment, tuberculosis

The guidelines have been extensively revised since the last edition in 2005. Most sections have been amended and tables updated and added. Areas where there is a need for clinical trials or data have been highlighted.

The major changes/amendments are:

- a more detailed discussion of gamma-interferon tests;
- new guidance on chemopreventative therapy;
- a complete update of the drug interactions section and tables;
- an updated section on choice of nonnucleoside reverse transcriptase inhibitor (NNRTI);
- a revised section on when to start highly active antiretroviral therapy (HAART);
- a new section on isoniazid resistance and extensively drug-resistant tuberculosis (XDR-TB);
- guidance on the diagnosis of immune reconstitution inflammatory syndrome (IRIS);
- new tables for management of adverse reactions.

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1.0 Summary of guidelines

These guidelines have been drawn up to help physicians manage adults with tuberculosis (TB)/HIV coinfection. Recommendations for the treatment of TB in HIV-infected adults are similar to those in HIV-negative adults. However, there are important exceptions which are discussed in this summary. We recommend that coinfecting patients are managed by a multidisciplinary team which includes physicians with expertise in the treatment of both TB and HIV infection.

We recommend using the optimal anti-tuberculosis regimen. In the majority of cases this will include rifampicin and isoniazid.

In the treatment of HIV infection, patients starting HAART have an ever-greater choice of drugs. We recommend that if patients on anti-tuberculosis therapy are starting HAART then antiretrovirals should be chosen to minimize interactions with TB therapy. There will be cases in which the choice of antiretrovirals is limited by intolerance, severe toxicity or genotypic resistance. TB treatment should only be modified when drug interactions with these antiretrovirals do not allow the optimal TB regimen. In some of these cases a longer duration of TB treatment may be necessary.

1.1 Diagnosis of active TB

The gold standard for diagnosing TB is microscopy followed by culture and drug sensitivity testing. Molecular diagnostics may be valuable when acid-fast bacilli are seen on smears. Rapid confirmation, by molecular diagnostics, that acid-fast bacilli are not *Mycobacterium tuberculosis* may avoid unnecessary treatment and infection-control measures.

We recommend rapid detection of rifampicin resistance using molecular techniques in patients whose initial assessment (e.g. recent immigrant from an area with a high prevalence of rifampicin-resistant disease) or clinical course suggests multi-drug-resistant TB (MDR-TB). These molecular tests should be used as an adjunct to standard laboratory techniques.

1.2 Detection of latent TB infection: tuberculin skin test (TST)/interferon- γ assays

HIV-infected individuals with latent TB infection are much more likely to progress to active TB than HIV-uninfected people. Detection and treatment of latent TB infection is therefore important, although diagnosis can be difficult.

TSTs/interferon- γ release assays (IGRAs) are used to detect latent infection. They are not recommended as a diagnostic tool in suspected active TB as they only reflect previous mycobacterial exposure. Tuberculin skin testing is

less useful in patients with HIV infection compared with HIV-uninfected patients, especially at low CD4 cell counts. IGRAs are newer blood assays derived from essentially *M. tuberculosis*-specific T cells, which are generally more sensitive than tuberculin tests for detecting both active and latent disease in HIV-negative subjects. They are also more specific in Bacillus Calmette-Guérin (BCG)-vaccinated individuals. Although there are few data regarding their performance in HIV-infected patients, especially at low blood CD4 cell counts, we believe that IGRAs may have value in detecting latent TB infection and we recommend the use of IGRAs rather than TSTs as a screening tool for latent TB. However, their precise role remains unclear and draft National Institute for Health and Clinical Excellence (NICE) guidance suggests using IGRA testing in those patients with a CD4 count >200 cells/ μ L, and both an IGRA and a tuberculin test in those with CD4 counts below this threshold. Although physicians can perform both tests in severely immunosuppressed patients, we believe that there are few data to support this strategy and doing this would add complexity, cost and difficulties in interpretation. The majority of the Committee believe that an IGRA test alone would be sufficient. New data would be welcome in guiding physicians in this difficult area.

We recommend screening for latent infection in HIV-infected patients dependent on a risk assessment based on country of origin, blood CD4 cell count and length of time on antiretroviral therapy. In addition, all HIV-positive close contacts of people who have infectious TB should be followed up and offered chemo-preventative therapy according to NICE guidelines [1].

1.3 Treatment of latent TB infection

Active TB needs to be excluded before considering treatment of latent infection, which is usually with isoniazid monotherapy for 6 months or isoniazid/rifampicin for 3 months.

Starting HAART reduces the risk of reactivation of latent TB infection and is effective at reducing the incidence of new TB. We recommend that all HIV-positive patients should be offered HAART in line with the British HIV Association (BHIVA) treatment guidelines [2].

1.4 Treatment of active TB

We recommend daily TB treatment whenever possible. Treatment may be given 5 days per week, but should be intensively supervised. This option may be useful in hospital or other highly supervised settings. Three-times-per-week directly observed therapy (DOT) should only be given to

patients who are stable and clinically well and where local logistics enable this to be undertaken successfully.

We do not recommend twice-weekly DOT for treatment of HIV/TB coinfecting patients, especially in those with CD4 counts <100 cells/ μ L, as it has been associated with unacceptably high rates of rifampicin resistance.

In cases where multiple drug resistance is not suspected, treatment should be started with four drugs (typically rifampicin, isoniazid, pyrazinamide and ethambutol) until sensitivities are known.

We recommend a 6-month treatment regimen for drug-sensitive TB outside of the central nervous system (CNS). This is usually four drugs for 2 months, followed by isoniazid and rifampicin for a further 4 months (at least 182 doses of isoniazid and rifampicin and 56 doses of pyrazinamide and ethambutol in total).

In drug-sensitive TB affecting the CNS we recommend 9 months of treatment. This usually consists of four drugs for 2 months, followed by 7 months of isoniazid and rifampicin [3].

Drug-resistant disease should be treated only by specialists with experience in such cases, in line with NICE guidelines [1].

1.5 Drug interactions and toxicities

Careful attention should be paid to drug interactions between TB drugs, HAART and other therapy. Rifampicin is a powerful inducer of cytochrome 450 (CYP450) and has effects on several metabolic pathways and P-glycoprotein (PgP). Rifampicin interacts with protease inhibitors (PIs), NNRTIs, chemokine (C-C motif) receptor 5 (CCR5) antagonists, and antimicrobials such as fluconazole. Rifabutin is a less potent inducer of CYP450 and may be used as an alternative to overcome some of these difficulties (for up-to-date drug interaction data go to www.hiv-druginteractions.org).

Toxicity profiles of antiretrovirals and anti-tuberculosis drugs overlap and make it difficult to determine the causative drug. For example, rashes occur with NNRTIs, rifampicin and isoniazid. Isoniazid and stavudine both cause peripheral neuropathy. All patients on isoniazid should take pyridoxine to try and prevent this complication. Patients with chronic liver disease have higher rates of toxicity and need more frequent monitoring of liver function tests. Drug absorption may be affected by advanced HIV disease.

1.6 Antiretroviral treatment

Rifampicin-based TB regimens should be used whenever possible. Coadministration guidance for first-line antiretrovirals is given below. There are few long-term clinical outcome data to support use of these TB/HIV drug combinations.

1.6.1 Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

There are no major interactions between rifampicin or rifabutin and lamivudine, emtricitabine, tenofovir, abacavir, zidovudine or didanosine.

Stavudine should not be given because of the increased risk of peripheral neuropathy with concomitant TB therapy.

1.6.2 NNRTIs

The preferred regimen for patients who have no contra-indication is:

Rifampicin + efavirenz	Use efavirenz 800 mg/day in patients weighing >60 kg and standard dose 600 mg/day in patients weighing <60 kg
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If side effects occur, efavirenz therapeutic drug monitoring (TDM) may be useful

Other regimens include

Rifampicin + nevirapine*	Not recommended but if given then use standard doses and perform nevirapine TDM
Rifabutin + efavirenz	Increase rifabutin to 450 mg daily
Rifabutin + nevirapine*	Not recommended but if given then use standard doses

1.6.3 PIs

Rifampicin + unboosted PI	Do not use
Rifampicin + boosted PI	Not recommended because of poor pharmacokinetics and high rates of hepatotoxicity seen in healthy volunteers
Rifabutin + unboosted PI	Reduce rifabutin to 150 mg daily; increase unboosted PI
Rifabutin + boosted PI	Reduce rifabutin to 150 mg three times per week

1.6.4 Integrase inhibitors

Rifampicin + elvitegravir	Do not use
Rifampicin + raltegravir*	Studies ongoing; use with caution double-dose raltegravir
Rifabutin + elvitegravir	No data; not recommended
Rifabutin + raltegravir	Normal doses of both drugs

1.6.5 Entry inhibitors

Rifampicin + maraviroc*	Not recommended, but if given use double-dose maraviroc
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Rifabutin + maraviroc	Use standard doses
Rifampicin + enfuvirtide	No interaction; use standard doses
Rifabutin + enfuvirtide	No interaction; use standard doses

*Where combinations are not recommended, specialist HIV treatment advice should be sought.

We recommend that therapeutic drug monitoring (TDM) of NNRTIs and PIs should be performed when drug regimens are complex. Drug levels of anti-tuberculosis drugs should be measured when there is clinical concern regarding absorption or response to TB therapy.

1.7 Starting HAART

Starting HAART during TB treatment is complicated by overlapping toxicities, drug interactions and immune reconstitution disease (IRD), and high pill burdens may reduce adherence. Delaying HAART may lead to prolonged or worsening immune suppression. Physicians have to balance these risks when deciding when to initiate HAART. Recent data suggest early treatment reduces morbidity and mortality.

We recommend, where possible: CD4 consistently >350 cells/ μ L: at physician discretion; CD4 100–350 cells/ μ L: as soon as practicable, but can wait until after completion of 2 months of TB treatment, especially when there are difficulties with drug interactions, adherence and toxicities; CD4 <100 cells/ μ L: start HAART as soon as practicable after starting TB therapy.

See BHIVA HIV treatment guidelines for details on starting HAART [2].

1.8 DOT strategies

DOT is regarded as the gold standard for delivering TB treatment, but it may not be possible to deliver all elements of the DOT package. Witnessed supervision of treatment may be impracticable and it is important to remember that patient-centred management is the cornerstone of treatment success. We recommend that DOT be used in all cases of MDR-TB.

1.9 Relapse and treatment failure

Patients with TB, with or without HIV infection, who are failing treatment or who relapse despite therapy pose particular management problems and should be referred to clinical colleagues who have expertise in the management of relapse and treatment failure, especially if taking HAART concomitantly.

1.10 Control and prevention of TB

Every hospital/trust should have a policy for the control and prevention of TB. Specific consideration should be given to prevention of transmission of TB to and from immunosuppressed patients. Further guidance is contained in [4].

2.0 Introduction

Worldwide, it is estimated that 14.8% of all new TB cases in adults are attributable to HIV infection. This proportion is much greater in Africa, where 79% of all TB/HIV coinfections are found. In 2007, 456 000 people globally died of HIV-associated TB [5].

All patients with TB, regardless of their perceived risk of HIV infection, should be offered an HIV test. In the United Kingdom, an increasing number of patients with TB are coinfecting with HIV. In 2003, 8.3% of adults with TB were HIV coinfecting [6]. The proportion is higher in London, with coinfection rates of 17–25% [7].

In HIV coinfection the clinical and radiographic presentation of TB may be atypical. Compared with the immune-competent population, TB/HIV-infected patients with active pulmonary TB are more likely to have normal chest radiographs or to have sputum that is smear negative but culture positive [8–10]. The clinician caring for HIV-infected patients therefore needs to have a high index of suspicion for TB in symptomatic individuals, especially those born abroad. As the investigation and treatment of both TB and HIV infection require specialist knowledge, it is mandatory to involve specialists in HIV, respiratory and/or infectious diseases.

These guidelines update the BHIVA guidelines from 2005 and are designed to provide a clinical framework applicable to adults in the UK coinfecting with HIV and TB. These guidelines do not cover children. They do not provide advice on HIV testing in adults with newly diagnosed TB. They are based on the evidence available, but some recommendations have to rely on expert opinion until further data are published.

These guidelines should be used in conjunction with:

- NICE: Tuberculosis: Clinical diagnosis and management of TB, and measures for its prevention and control, 2006 [1].
- BHIVA guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008 [2].
- Department of Health, The Interdepartmental Working Group on Tuberculosis: The Prevention and Control of Tuberculosis in the United Kingdom, 1998 [4].
- NICE: Tuberculosis Clinical diagnosis and management of TB, and measures for its prevention and control, update 2010 [11].

3.0 Aims of TB treatment

Treatment of TB benefits the individual and also the community.

The aim of treatment is:

- to cure the patient of TB;
- to minimize the transmission of *M. tuberculosis* to other individuals;
- to eliminate *M. tuberculosis* infection.

4.0 Diagnostic tests

The quality of any investigation is related to the quality of the specimen and the clinical detail provided within the request. There must therefore be close liaison with the mycobacterial laboratory.

4.1 Microscopic smears

Microscopic smears of body fluids remain an essential part of TB diagnosis. Results should be available within 1 working day.

4.2 Cultures and drug susceptibility tests

Identification of mycobacteria is performed at reference centres, and is based on morphology, growth and biochemical characteristics. *M. tuberculosis* needs to be distinguished from other mycobacteria, for which treatment may be different and there are no infection-control concerns.

Cultures are central to the confirmation and identification of the mycobacterium, and for drug susceptibility testing. More rapid results are obtained from liquid media, which usually grow *M. tuberculosis* in 7–28 days. Drug susceptibility tests are usually available within 10–21 days of the laboratory receipt of isolates and are performed using standard assays.

4.3 Molecular methods

When it is important to differentiate rapidly, gene probes are increasingly used in some laboratories, but are less sensitive than culture and are used mainly on respiratory specimens. Most nucleic acid amplification methods to detect *M. tuberculosis* are complex, labour-intensive, and technically challenging. The sensitivity and specificity estimates of commercial nucleic acid amplification tests (NAATs) are highly variable, compared with culture [12,13].

All specimens, even those negative for *M. tuberculosis* on polymerase chain reaction (PCR), still require culture because a negative PCR does not exclude TB and a positive PCR does not indicate the drug susceptibility profile [14,15]. However,

recently a fully automated molecular test for TB identification and drug resistance testing has been evaluated on sputum samples from adult patients with TB or MDR-TB [16].

The Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), an automated molecular test for *M. tuberculosis* identification and resistance to rifampin, uses a hemi-nested real-time PCR assay. This assay identifies >97% of all patients with culture-confirmed TB, including >90% of patients with smear-negative disease. The result can be available in hours.

The assay has been developed as a laboratory-based and point-of-care test for developing countries, but may be useful in rapid diagnosis of TB in the United Kingdom. Currently there are no data derived from children or using nonrespiratory specimens in HIV-infected persons.

Molecular tests for rifampicin resistance are useful especially when MDR-TB is suspected, as about 95% of isolates that are rifampicin resistant will also be isoniazid resistant. As MDR-TB is defined as TB resistant to at least rifampicin and isoniazid, patients with positive molecular-based rifampicin resistance should be treated as having MDR-TB until the full resistance profile from cultures is available.

4.4 Tuberculin skin testing

Tuberculin testing can identify patients with latent infection but there are high false-negative rates in HIV-positive patients, especially in those with low CD4 cell counts [17–23]. In patients with AIDS or CD4 counts <200 cells/ μ L, the sensitivity of the test is only 0–20%. False positives occur after BCG immunization. Some data suggest that combining IGRAs and tuberculin testing improves sensitivity [1,24]. We do not recommend the routine use of TSTs. [CII]

4.5 Interferon- γ tests

HIV-infected individuals with latent TB infection are much more likely to progress to active TB than HIV-uninfected people [25]. Detection and treatment of latent TB infection are therefore important.

Blood tests are available that measure interferon- γ release from T cells after stimulation with antigens largely specific to *M. tuberculosis* [such as early secreted antigen target (ESAT-6) and culture filtrate protein (CFP-10)] [26]. The current commercially available tests are T-Spot.TB (Oxford Immunotec, Abingdon, Oxfordshire, UK) [which uses enzyme-linked immunosorbent spot (ELISPOT) technology to detect the antigen-specific T cells] and QuantiFERON[®] Gold In-Tube (Cellestis International Pty Ltd., Chadstone, Victoria, Australia) (an enzyme-linked immunosorbent assay). Both tests are approved for the diagnosis of latent TB infection in HIV-negative individuals. There are some differences between the two tests,

although in general they are unaffected by previous BCG and/or infection with most other mycobacteria (an important exception in the United Kingdom being *Mycobacterium kansasii*). They are not licensed for the diagnosis of active TB, though the tests may be positive here too (as they detect the host immune response to mycobacterial infection).

Limited data exist regarding their performance in HIV infection, but studies suggest that interferon- γ assays are more specific than TSTs, especially in BCG-vaccinated subjects [27–31]. This is an area of ongoing research.

They also appear to retain sensitivity more reliably at lower CD4 cell counts, although the lower threshold has not yet been defined [32,33]. Their advantages also include being a single blood test with no need for patient recall to 'read' the result and no requirement for cold-chain storage. However, the blood samples need processing within a limited time, and 'indeterminate' (i.e. uninterpretable) IGRA results are more common in HIV-infected subjects. They are also more costly than tuberculin tests, although this may be offset by the savings in, for instance, healthcare worker time [34]. The T-spot TB test may have an advantage over the QuantiFERON[®] Gold In-Tube test as the number of lymphocytes used in the test is standardized.

This is a rapidly developing area but, based on current data, we suggest that IGRAs rather than TSTs are used when screening HIV-positive individuals for latent TB infection. [BIII]

Where a patient is considered to have active TB, IGRA tests should not be used as the means by which the diagnosis is confirmed or refuted. If a test is performed, the result must be interpreted in light of the clinical picture, microbiological data and an understanding of the assay's limitations in this population.

5.0 Type and duration of TB treatment

5.1 Treatment regimens

Most adults with previously untreated TB are given a regimen in two phases: [AII]

- **Initial phase**

Two months of isoniazid, rifampicin, pyrazinamide and ethambutol.

These four drugs are necessary because of the relatively high rate of isoniazid resistance in the United Kingdom, which is 7.7% overall (HPA 2007), and higher in non-White ethnic groups and those with previous treatment.

If drug sensitivity testing shows *M. tuberculosis* sensitive to first-line agents, ethambutol can be omitted.

- **Continuation phase**

Four months of isoniazid and rifampicin in most patients with drug-sensitive TB, prolonged to 7 months in some circumstances (see 'Longer continuation phase' [AIII]).

All patients taking isoniazid should be prescribed pyridoxine (vitamin B6) 10–25 mg daily.

TB therapy can be given five times per week with standard doses. Although there are no formal clinical trial data, considerable clinical experience suggests that five-times-weekly DOT is equivalent to seven-times-weekly treatment, and can thus be considered as 'daily'. [AIII]

5.1.1 TB or other mycobacterial infection?

In many cases the treatment conundrum is whether the patient has *Mycobacterium avium* complex or *M. tuberculosis* and often the physician will give the standard four-drug regimen until identification. In this situation, some physicians prefer to replace rifampicin with rifabutin and add azithromycin/clarithromycin. When nontuberculous mycobacteria are identified the regimen can be modified appropriately.

5.2 Longer continuation phase [AII]

The continuation phase should be extended to 7 months in:

- patients with drug-sensitive TB whose initial phase did not include pyrazinamide;
- patients with cavitating pulmonary disease and who remain sputum culture positive after 2 months of treatment [35].

The total treatment duration would thus be 9 months.

The continuation phase should be extended to 7–10 months in cases of CNS involvement, for instance meningitis or tuberculoma. The total treatment duration would thus be at least 9 months.

5.3 Intermittent therapy [AII]

It is recommended that patients receive daily therapy [36]. However, in some circumstances intermittent therapy can be given three times per week with dose modification [37,38] but must be by DOT, as one study showed a risk of acquired rifamycin resistance in patients given thrice-weekly regimens ([DII]). However, DOT was used for all doses during the intensive phase but only for one dose of three per week during the continuation phase [39].

Two strategies used in HIV-negative patients have been associated with unacceptably high relapse rates and acquired rifampicin resistance in HIV-infected patients and are *not appropriate* for use in this population [40–44]. [EII]

These are:

- once-weekly isoniazid-rifapentine in the continuation phase;
- twice-weekly isoniazid-rifampicin or isoniazid-rifabutin in patients with CD4 counts < 100 cells/ μ L.

5.4 Use of rifabutin [BII] [45]

Rifabutin has been successfully used instead of rifampicin in treating TB in HIV-negative patients [46,47]. It can be regarded as an alternative in HIV-positive patients, especially to avoid drug interactions with rifampicin, for example with PIs (see 'Drug-drug interactions'). Rifabutin showed similar efficacy to rifampicin in a single-blind randomized study of 50 HIV-positive patients in Uganda [48] and a cohort of 25 patients in the United States [49].

However, there is a paucity of long-term data for rifabutin in HIV-positive adults. Rifabutin is also expensive and toxicities include bone marrow suppression, uveitis and arthralgia.

We therefore recommend that rifampicin remains the drug of choice whenever possible. In circumstances where rifampicin cannot be used (most commonly when boosted PIs are needed to treat HIV infection), rifabutin should be substituted.

5.5 Use of rifapentine [EII]

Rifapentine has a long serum half-life which theoretically allows once-weekly dosing. However if used in the initial phase of treatment of TB in HIV-negative patients, rifapentine has unacceptable 2-year microbiological relapse rates and is not recommended. Development of rifapentine resistance appears to be more frequent in TB/HIV coinfecting patients [42] and at present rifapentine cannot be recommended and should not be used. [EII] There are few data regarding the interactions of rifapentine with HAART.

5.6 Duration and effectiveness of TB treatment

The optimal length of TB treatment in patients coinfecting with HIV is unknown. Some trials suggest that short-course therapy need not be prolonged in HIV-infected individuals [37,50,51]. A review of six studies of patients with HIV infection and three studies of patients without HIV infection given treatment for 6 months (or longer) demonstrated considerable variability in published study design, eligibility criteria, site of disease, frequency and method of dosing, and outcome definitions [52]. In the reported studies, HIV-infected patients had cure rates of 59–97%, successful treatment rates of 34–100% and relapse rates of 0–10%. In patients without HIV infection, cure rates were 62–88%, successful treatment occurred in 91–99% of patients and relapse rates were 0–3%.

Although the relapse rates appeared to be higher in some studies of coinfecting patients, other outcomes were comparable when 6-month regimens were used.

A study from Brazil showed that TB recurrence rates were high in the HIV-infected population but that, if there was completion of initial TB therapy, use of antiretroviral therapy, and subsequent increases in CD4 cell counts, then recurrence rates were low [53].

A recent retrospective review from the United States suggested that, although there were no failures in the 6-month regimen, relapse rates were four-times higher in HIV-infected patients treated with standard rifampicin-based regimens for 6 months than in those treated for longer [36]. However, the data were generated from a relatively small subset of patients as only 17% of the HIV-positive patients and 37% of the HIV-uninfected/unknown group were given just 6 months of rifampicin-based therapy. DOT was given to 57% of patients. It may be the case that, where adherence is suboptimal, 6 months of therapy is insufficient. The other important fact is that in this study reinfection could not be distinguished from relapse.

A recent meta analysis suggests that 8 months of a rifamycin-based treatment be given, but the studies examined included those in which only 2 months of rifamycin were given and in the few studies of treatment longer than 6 months the reinfection issue was not addressed [54].

Long-term randomized trials are needed to address optimal treatment duration.

We recommend that, for drug-sensitive TB not involving the CNS, regimens of 6 months should be given [41,50,51,55,56]. These should include at least 182 doses of isoniazid and rifampicin, and 56 doses of pyrazinamide (see 'Definition of completion of TB therapy'). [AII] See also 'Intermittent therapy' [AII] and 'Use of rifabutin' [BII].

5.7 Use of corticosteroids

In HIV-infected adults with pulmonary or pleural TB, corticosteroids do not improve survival or reduce TB recurrence [57,58] and are not generally recommended [59].

In the general population, NICE guidelines recommend steroids in cases of active meningeal or spinal cord TB [1]. At present there is insufficient evidence regarding their use in HIV-infected people. A randomized controlled trial in Vietnam showed no difference in mortality or a combined outcome of death and disability in HIV-infected people with a clinical diagnosis of TB meningitis, whether they were given dexamethasone or placebo with standard TB treatment [60]. However, there were few HIV-infected people in this study and the diagnosis of TB was confirmed microbiologically in fewer than 50% of cases. This study may therefore have missed a clinically important difference.

Until more data are available we recommend that HIV-infected adults with meningeal or spinal cord TB should be given corticosteroids. [BII]

NICE guidelines recommend steroids for active pericardial TB. There are limited data to support this in HIV coinfection. A small randomized controlled trial of HIV-infected adults with presumed tuberculous pericarditis treated with standard TB therapy found that prednisolone resulted in better outcomes than placebo [61]. Mortality was reduced with prednisolone compared with placebo, and improvement in raised venous pressure, hepatomegaly, ascites and physical activity occurred more rapidly. Interestingly there was no faster resolution of pericardial fluid on chest radiography or echocardiogram, and as only 38% had positive *M. tuberculosis* cultures, some of the subjects may not have had pericardial TB. These results should therefore be interpreted with caution.

Until more data are available in HIV-positive patients, we recommend that adults with pericardial TB should be given corticosteroids. [AII]

Other uses of steroids have included their use in preventing ureteric stenosis in renal TB or enlargement of, for example, a mediastinal lymph node causing collapse of a lung lobe and in management of TB-related IRIS (see 'IRIS').

The optimal dose of adjunctive corticosteroids is not known. Rifampicin induces the liver metabolism of corticosteroids, thus increasing their plasma clearance [62].

The corticosteroid and dose used in most adult trials of TB meningitis are dexamethasone 12–16 mg/day given intravenously until the patient starts taking medicines orally; then tablets can be used. Prednisolone 60 mg/day for 3 weeks and tapered over the next 3 weeks is an alternative [63].

The British Infection Society guidelines on TB meningitis [3] suggest that adults (> 14 years old) should start treatment with dexamethasone 0.4 mg/kg/24 h with a reducing course over 6–8 weeks. This works out to be a higher dose for most patients seen in the United Kingdom.

Studies have shown that corticosteroids increase the risks of high blood pressure and raised blood glucose, and can cause fluid retention [57,58]. The risk of infectious complications does not seem to be increased [57,58,61], although the data for an increase in the occurrence of Kaposi's sarcoma was found in some studies but not others.

5.8 Definition of completion of TB therapy

Treatment for a defined number of days without accounting for the number of doses taken may result in under-treatment. Determination of whether or not treatment has been completed should therefore be based on total number of doses taken as well as duration of therapy. For example: a 6-month daily regimen (given 7 days/week) should

consist of at least 182 doses of isoniazid and rifampicin, and 56 doses of pyrazinamide.

It is recommended that all of the doses for the initial phase be taken within 3 months and those for the 4-month continuation phase be taken within 6 months. The 6-month regimen should therefore be completed by 9 months.

5.9 Interruptions of therapy [AIII]

Treatment interruptions are common in HIV-associated TB. Data to support recommendations are scant. Regardless of the timing and duration of the interruption, if the patient was on self-supervised therapy, then DOT should subsequently be used. If the patient was already being managed with DOT, additional measures may be necessary to ensure adherence, for instance provision of transport, food and social services. The CDC suggest the following [64]:

Initial phase:

- If the interruption occurs during the initial phase and is 14 days or more in duration, treatment should be restarted from the beginning.
- If the interruption is < 14 days, the treatment regimen should be continued. The total number of doses for the initial phase should be given.
- If the interruption in treatment occurs in the continuation phase and the patient's interruption is 3 months or more in duration, treatment should be restarted from the beginning. If the interruption is less than 3 months in duration, treatment should be continued to complete a full course.

5.10 Investigations during TB treatment [AIII]

Baseline investigations:

- CD4 cell count and percentage;
- serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT), bilirubin and alkaline phosphatase;
- serum creatinine and estimated glomerular filtration rate;
- platelet count;
- hepatitis B and C serology;
- prior to ethambutol: testing of visual acuity with Snellen chart and colour vision with Ishihara plates.

HIV-infected patients have more drug reactions, especially those with low CD4 cell counts. Further, they may be starting concomitant antiretroviral and other therapies, all of which may cause hepatotoxicity [65].

We recommend that liver function tests should be rechecked at 1–2 weeks even if asymptomatic. Patients with pre-existing liver disease need close monitoring, for instance every 2 weeks for the first 2 months.

Most physicians will see the patient 2 weeks after starting anti-tuberculosis therapy and then monthly until

stable and 1–2-monthly until therapy has been completed. The role of a TB specialist nurse and multidisciplinary team is essential in the management of coinfecting patients.

Patients with pulmonary TB who still have a productive cough after 2 months of therapy should have a repeat sputum smear and culture. The initial phase of treatment should be continued until results are available.

6.0 Drug–drug interactions (see Tables 4–7)

Most interactions between HIV and TB therapy are through induction or inhibition of metabolic enzymes in the liver and intestine. The most important family of enzymes is CYP450. The CYP3A4 isoform metabolizes many drugs, including PIs and NNRTIs. Rifamycins are potent inducers of CYP3A4 [66,67] and have clinically important interactions with PIs and NNRTIs. Of all medicines, rifampicin is the most powerful inducer of CYP3A4. Rifapentine is a less potent inducer; and rifabutin much less so. To a smaller extent, rifampicin also induces the activity of CYP2C19 and CYP2D6. Rifampicin also increases activity of the intestinal drug transporter P-gP which contributes to the absorption, distribution and elimination of PIs [67,68].

The enzyme-inducing effect of rifampicin takes at least 2 weeks to become maximal and persists for at least 2 weeks after rifampicin has been stopped. If antiretrovirals are started or changed at the end of TB treatment, this persistent effect on enzyme induction should be taken into consideration.

Rifabutin is a less potent inducer of CYP3A4 than rifampicin [69]. Unlike rifampicin, it is also a substrate of the enzyme [66]. Any CYP3A4 inhibitors will therefore increase the concentration of rifabutin, although they have no effect on rifampicin metabolism. Most PIs are inhibitors of CYP3A4 and, when used with rifabutin, plasma concentrations of rifabutin and its metabolites may increase and cause toxicity [70].

NNRTIs are mostly known to be free of clinically significant interactions with rifampicin. In theory they should not have significant interactions with other first-line anti-tuberculosis therapies. Few data are available for the newer antiretroviral agents. The CCR5 inhibitor maraviroc interacts with rifamycins, as do the integrase inhibitors raltegravir and elvitegravir.

Individual drug–drug interactions between rifamycins and antiretroviral agents are shown in Tables 4–7. The complexity of drug–drug interactions requires expertise in the use of both antiretroviral and anti-TB drugs. One particular interaction should be noted: the metabolism of corticosteroids (e.g. prednisolone) is accelerated by rifamycins and higher doses are needed. The dose of steroid should be increased by around 50% with rifampicin and 33% with rifabutin. [AII]

6.1 Rifamycins and NNRTIs (Table 4)

6.1.1 Rifampicin and efavirenz

Several studies have found a 20–30% reduction in efavirenz levels when administered with rifampicin [71,72]. There is a lack of consensus regarding the appropriate dose of efavirenz with rifampicin, largely because some of the clinical trial data are conflicting. No randomized clinical trial has correlated patient weight, pharmacokinetics and clinical outcome.

We believe that the primary concern is to achieve adequate efavirenz levels in all patients and avoid the development of drug resistance. Using increased levels of efavirenz risks side effects, especially in those with CYP2B6 polymorphisms. However, efavirenz TDM can identify those with high levels and allow dose adjustments.

One observational cohort study examined weight, pharmacokinetics and outcomes and proposed that in patients over 60 kg the dose of efavirenz should be increased from 600 mg daily to 800 mg [73]. Other studies have also shown 800 mg to be effective and safe [71,74].

In contrast, other data support using standard-dose efavirenz. In some cohort studies (in which most participants had a low body weight), 600 mg efavirenz has been given with rifampicin without lower drug exposure or compromised clinical efficacy [75,76]. In one study, efavirenz levels were not predicted by weight or gender and were not associated with HIV clinical outcomes, even though half the cohort had concentrations below the expected therapeutic range (1000–4000 ng/mL). This, as well as other studies, confirms the large interpatient variability in efavirenz levels [77].

In one study of Black South Africans taking rifampicin, no difference was seen in mid-dose efavirenz levels between patients on efavirenz 800 mg ($n=31$) and those on efavirenz 600 mg ($n=29$) [78]. This finding may be the result of a high frequency of polymorphisms in CYP450 2B6, which occur with a rate of 20% in the Black population compared with 3% in the White population [79,80]. The frequency of polymorphisms in CYP2B6 may also explain high rates of clinical toxicity in some studies [81].

Recommendation [AII]:

- Patient under 60 kg: Use efavirenz 600 mg once daily (od).
- Patient over 60 kg: Use efavirenz 800 mg od; perform efavirenz TDM at 2 weeks.

It should be made clear to patients that they may need an extra 200 mg efavirenz in addition to Atripla.

6.1.2 Rifampicin and nevirapine

Rifampicin and nevirapine are both used widely in resource-poor countries because they are cheap and readily

available. There are data indicating that nevirapine levels are reduced by 20–55% by rifampicin [82–87]. The World Health Organization (WHO) suggest that no ‘lead-in’ period for nevirapine is needed if the patient is already on rifampicin – but they give no recommendation rating for this strategy.

To overcome the problem of low nevirapine levels with rifampicin, one trial administered 400 mg nevirapine as lead-in dose, increasing to 600 mg [88]. The pharmacokinetics were satisfactory but there was a high incidence of nevirapine hypersensitivity during the dose escalation period.

Two cohort studies have shown high rates of HIV viral suppression with standard-dose nevirapine and rifampicin [83,89]. However, in a recent study of 1283 patients starting HAART while on rifampicin, 209 people on nevirapine and 1074 on efavirenz, virological failure rates were higher, with an odds ratio of 2.9 [95% confidence interval (CI) 1.8–4.7] in the nevirapine arm *vs.* the efavirenz or not-on-TB-treatment arm [90].

We recommend that, where alternatives exist, rifampicin should not be used with nevirapine. [DII] If there are no alternatives to using nevirapine with rifampicin, then normal doses should be used and TDM performed.

6.1.3 Rifampicin and etravirine

No data are available and no studies are planned. It is thought that they should not be coadministered.

6.1.4 Rifampicin and rilpivirine

Rifampicin reduces plasma concentrations of rilpivirine by up to 90% so these drugs should not be used together [91].

6.2 Rifabutin and NNRTIs

6.2.1 Rifabutin and efavirenz

If rifabutin is used with efavirenz, the rifabutin dose should be increased to 450 mg daily because of the induction effect of efavirenz, which reduced the area under the curve (AUC) of rifabutin by 38% in one small study.

6.2.2 Rifabutin and nevirapine

Concomitant administration of nevirapine resulted in an increased rifabutin AUC (17%) and maximum concentration (C_{max}) (28%) with no change in the minimum concentration (C_{min}). The effect on nevirapine pharmacokinetics was not significant [Viramune Summary of Product Characteristics (SPC) from 2007]. Because of high intersubject variability, some patients may be at risk of rifabutin toxicity. Rifabutin and nevirapine can probably be given together with no adjustment in either of their dosages, but more data are needed before this strategy can be recommended.

6.2.3 Rifabutin and newer NNRTIs

Rifabutin can be given with etravirine with no dose adjustments.

Rifabutin decreases plasma levels of rilpivirine by 50%, so if used together the dose of rilpivirine should be doubled [91].

6.3 Rifampicin and PIs (Table 6)

In general, PIs, whether boosted or unboosted, should not be given with rifampicin and rifabutin should be considered instead.

6.3.1 Unboosted PIs

Rifampicin causes a 75–95% reduction in plasma concentrations of PIs other than ritonavir [92]. Such reductions lead to loss of antiretroviral activity of PI-containing regimens and can result in the emergence of antiretroviral resistance.

Since ritonavir is itself an inhibitor of CYP3A4 it can be used in combination with rifampicin when given at the full dose of 600 mg twice daily [93]. However, such high-dose ritonavir is very poorly tolerated and seldom used [94].

6.3.2 Boosted PIs

Most patients are given PIs with low-dose ritonavir (100 or 200 mg daily) to take advantage of its enzyme-inhibiting properties. Ritonavir boosts the concentration of the other PI, allowing more tolerable dosing.

6.3.3 Saquinavir/ritonavir

A dose of twice-daily 400 mg ritonavir with 400 mg saquinavir has been used with rifampicin with acceptable PI pharmacokinetics [95]. Saquinavir 1600 mg with ritonavir 200 mg once daily was tested in HIV-positive patients on rifampicin-based TB therapy, and saquinavir levels were inadequate [96,97].

A pharmacokinetic study performed in healthy volunteers given saquinavir/ritonavir and rifampicin then demonstrated severe hepatotoxicity [98]. Transaminases were elevated to more than 20 times the upper limit of normal.

Saquinavir/ritonavir is therefore not recommended in combination with rifampicin.

6.3.4 Lopinavir/ritonavir

Data regarding the interaction of rifampicin with standard-dose lopinavir/ritonavir suggest that ritonavir at a low dose does not compensate for the inducing effect of rifampicin on lopinavir metabolism [99]. A popular strategy in the developing world for patients with NNRTI failure who develop TB is to give lopinavir/ritonavir with increased-dose

ritonavir. If the ritonavir dose was increased to 400 mg twice daily then lopinavir trough concentrations were adequate in nine of 10 subjects, but there were high rates of elevated transaminases and lipids, and gastrointestinal toxicity [100]. A pharmacokinetic study in healthy volunteers was reminiscent of the saquinavir study, and was terminated early because of high rates of severe transaminitis [101].

6.3.5 Atazanavir/ritonavir

Recent data suggest that atazanavir with or without ritonavir boosting had unfavourable pharmacokinetics when administered with rifampicin [102–104]. Trough atazanavir concentrations were reduced by >80% [103].

6.3.6 Tipranavir/ritonavir

Tipranavir concentrations were reduced by 80% by rifampicin [105].

6.3.7 Darunavir/ritonavir

The interaction between darunavir and rifampicin has not yet been investigated. In line with other PIs, it is currently recommended that darunavir should not be coadministered with rifampicin.

6.4 Rifabutin and PIs (Table 6)

6.4.1 Unboosted PIs

The use of rifabutin in treating TB in HIV-positive patients is discussed above (see 'Use of rifapentine' [EII]). Rifabutin can be administered with unboosted PIs except saquinavir [106], although they will rarely be used in practice. The balance between rifabutin induction and PI inhibition of CYP3A4 means that the dose of rifabutin should be decreased from 300 to 150 mg daily to avoid toxicity [48,70].

6.4.2 Boosted PIs

If PIs are used with low-dose ritonavir boosting then the dose of rifabutin should be reduced to 150 mg three times per week [49,105]. This recommendation is derived from pharmacokinetic studies and modelling. There are no clinical outcome data for either HIV or TB using this strategy. Adherence should be monitored closely as the dose of rifabutin would become inadequate if the boosted PI is not taken concomitantly. Where available, drug levels of the PI should be measured. There have been reports of acquired rifabutin resistance occurring even in patients taking rifabutin 150 mg three times a week with boosted PIs. No rifabutin drug levels were available in those patients and, although there may have been other reasons for these failures, physicians may consider measuring the levels of rifabutin and its active metabolite 25-O-desacetyl rifabutin if results are available in a timely manner [107].

Complex interactions may occur when a rifamycin is given with salvage regimens such as an integrase, boosted PI and an NNRTI. Rifabutin is safer than rifampicin, but there are few data to guide the clinician regarding dose modification. TDM is recommended.

6.4.3 Recommendation for rifamycins and boosted PIs

We recommend that PI/ritonavir combinations should not be given with rifampicin. [EII] If possible, the HAART regimen should be changed to avoid PIs. If effective HAART necessitates the use of PIs then rifabutin should be used instead of rifampicin. [AII]

6.5 Rifamycins and integrase inhibitors (Table 7)

Raltegravir is metabolized by UGT1A1 glucuronidation. Rifampicin is an inducer of UGT1A1, and reduces trough levels of raltegravir by approximately 60% [108]. Because the antiviral activity of raltegravir 200 mg twice daily was very similar to that of the licensed dose (400 mg twice daily), an earlier recommendation was that standard doses of raltegravir should be used with rifampicin. There is at least one report of raltegravir failure when given like this with rifampicin (S. Taylor, personal communication; Birmingham Heartlands Hospital, Birmingham, UK).

Further pharmacokinetic studies show that even with double-dose raltegravir at 800 mg twice a day (bid) the trough concentration (C_{trough}) of raltegravir is at the lower end of the range of C_{trough} values that have been observed in clinical studies of raltegravir without rifampicin [109]. It appears for raltegravir that the important pharmacokinetic parameter is the area under the drug concentration curve at 24 hours (AUC_{24}) rather than C_{trough} in pharmacokinetic/pharmacodynamic studies and thus 800 mg bid may be adequate.

As there is little clinical experience with this dose in combination, coadministration should probably be avoided if alternatives exist.

Elvitegravir is metabolized by CYP3A4 and should not be given with rifampicin.

The data regarding interactions with rifabutin suggest normal doses of raltegravir and rifabutin can be used [110].

6.6 Rifamycins and CCR5 antagonists (Table 7)

Maraviroc is metabolized by CYP3A4 and its levels are reduced by rifampicin. Use of maraviroc with rifampicin is not recommended, especially if a second enzyme inducer such as efavirenz is used. If they are used together then they should be used with caution and the dose of maraviroc should be doubled to 600 mg bd [111]. There are no data concerning interactions with rifabutin, but maraviroc

concentrations are predicted to be adequate, and maraviroc can therefore be given at standard doses with rifabutin.

6.7 Rifamycins and enfuvirtide (Table 7)

There are no significant interactions between rifamycins and enfuvirtide [112].

6.8 Isoniazid

Pharmacokinetic or clinical interactions between isoniazid and antiretroviral agents have not been extensively investigated. *In vitro* studies have shown that isoniazid is a weak inhibitor of CYP3A4 [113,114]. When given together with rifampicin (inducer), the inhibition effect of isoniazid is masked.

6.9 Non-rifamycin regimens

HIV-related TB may be treated with non-rifamycin-containing regimens, but these are inferior in efficacy, with high relapse rates [115,116]. They should only be contemplated in patients with serious toxicity to rifamycins, where desensitization or reintroduction has failed, or in those with rifamycin-resistant isolates. There has been a review published of drug–drug interactions between drugs used in non-rifamycin regimens and antiretrovirals [117].

7.0 Overlapping toxicity profiles of antiretrovirals and TB therapy

Adverse reactions to drugs are common among patients with HIV-related TB, especially if taking HAART concomitantly.

Rash, fever and hepatitis are common side effects of anti-tuberculosis drugs, especially rifampicin, isoniazid and pyrazinamide. NNRTIs and cotrimoxazole cause similar adverse reactions. The coadministration of these drugs can lead to difficult clinical management decisions if these side effects occur, especially if HAART and TB drugs are started concurrently. A total of 167 adverse events were recorded in 99 (54%) of the 183 patients for whom data on therapy were available in a study from the southeast of England [118]. Adverse events led to cessation or interruption of either TB or HIV therapy in 63 (34%) of the 183 patients. Side effects usually occurred in the first 2 months of treatment and were peripheral neuropathy (38 patients; 21%), rash (31 patients; 17%), gastrointestinal intolerance (18 patients; 10%), hepatitis (11 patients; 6%) and neurological events (12 patients; 7%). Rifampicin was frequently implicated by the treating physicians, and was considered responsible for almost two-thirds of adverse events.

When compared with HIV-negative patients with TB, a higher rate of serious (grade III/IV) toxicities was found in

TB/HIV coinfecting patients, but there was no difference in the discontinuation rate of TB medication between the groups [65].

7.1 Hepatotoxicity [119]

Hepatotoxicity is a common and potentially serious adverse event. It is defined as:

- serum AST or ALT $>3 \times$ upper limit of normal in the presence of symptoms, or
- serum AST or ALT $>5 \times$ upper limit of normal in the absence of symptoms.

Other causes of hepatitis, such as concomitant drugs and viral hepatitis, should be investigated.

Hepatotoxicity may be caused by many drugs used in the treatment of HIV-positive patients, for instance azoles and macrolides, and not all hepatotoxic reactions are always caused by anti-tuberculosis therapy.

Hepatotoxicity caused by isoniazid in the general population increases with age, occurring in $<0.3\%$ of those under 35 years old and in 2.3% of those >50 years old. It is also more likely in those with heavy alcohol intake or hepatitis C virus coinfection and in those also on rifampicin. High rates of adverse reactions requiring changes in therapy have been reported in HIV-infected patients who are likely to have some or all of the other risk factors mentioned above. The rates of adverse reaction were 26% in one HIV-infected cohort compared with 3% in the HIV-uninfected group, and other studies have shown similar results [120,121].

Another study showed little increase in hepatotoxicity in HIV-positive patients with TB although only 16.3% were receiving antiretrovirals and the study included children [122].

Management of hepatitis:

- I. Stop all potentially hepatotoxic drugs immediately, including isoniazid, rifampicin, pyrazinamide, antiretrovirals and cotrimoxazole.
- II. Check serology for hepatitis A, B and C.
- III. Enquire about exposure to other hepatotoxins, including alcohol.
- IV. As resolution of the hepatitis may be prolonged, until the cause of the hepatitis is identified it may be necessary to treat with two or more anti-tuberculosis medications without significant risk of hepatotoxicity, such as ethambutol, streptomycin, amikacin/kanamycin, capreomycin or a fluoroquinolone (N.B. moxifloxacin can cause a severe hepatitis).
- V. Monitor serum AST (or ALT), bilirubin and symptoms frequently. Once AST drops to less than twice the upper

limit of normal and symptoms have significantly improved, first-line medications can be restarted using a reintroduction regimen (Table 8). These are based on common practice and have not been formally validated in clinical trials. Recent data in HIV-negative/unknown patients suggest that once the AST/ALT is < 100 IU/L then full-dose treatment may be reintroduced [123] – whether this also applies to HIV coinfecting subjects remains unclear.

- VI. If the drugs cannot be restarted or the initial reaction was life-threatening then an alternative regimen should be used (see ‘Pre-existing liver disease’).

7.2 Pre-existing liver disease

All patients should be screened for active hepatitis B and C. The risk of hepatotoxicity with pre-existing liver disease is greatest with pyrazinamide, then isoniazid, and then rifampicin. Isoniazid and rifampicin are essential drugs in short-course TB treatment regimens and should be used whenever possible, even in the presence of pre-existing liver disease.

In patients with baseline abnormal hepatic transaminases, a rise of two-to-three times this abnormal baseline should be used as the threshold for hepatotoxicity [119].

If hepatotoxicity occurs then other regimens can be used, for instance:

- I. Avoid pyrazinamide and treat with isoniazid and rifampicin for 9 months, adding ethambutol for the first 8 weeks or until isoniazid and rifampicin susceptibility is demonstrated. [AIII]
- II. Avoid isoniazid and treat with rifampicin, ethambutol and pyrazinamide for 2 months, followed by 10 months of rifampicin and ethambutol. [BIII]
- III. Use only one potentially hepatotoxic agent in patients with severe liver disease and treat with rifampicin plus ethambutol for 12–18 months, preferably with another agent such as a fluoroquinolone for the first 2 months. There are no data to support this recommendation. [CIII]

In patients with pre-existing liver disease, frequent clinical and laboratory monitoring should be performed to detect drug-induced hepatic injury. This should include AST (or ALT), platelet count and prothrombin time at least 2-weekly initially. Patients should be told to report symptoms such as anorexia, nausea, vomiting, abdominal pain or jaundice immediately [124,125].

7.3 Gastrointestinal side effects

Epigastric pain, nausea and vomiting are common especially in the first 2–3 weeks after starting anti-

tuberculosis therapy. If the patient has no evidence of hepatic disease and is unresponsive to symptomatic treatment, for instance with anti-emetics, then they can:

- take medications with meals (except with doses under 600 mg rifampicin daily); food delays or decreases the absorption of isoniazid and rifampicin but the effect is moderate and of little clinical significance;
- change the time of dosing;
- switch to a regimen that does not have food restrictions such as rifabutin, ethambutol, pyrazinamide and a fluoroquinolone.

Patients should avoid dividing doses or changing to alternative drugs if at all possible, although dividing the dose, for instance of pyrazinamide, can improve tolerability.

7.4 Peripheral neuropathy

The NRTIs ddI and d4T cause peripheral neuropathy and there is an additive toxicity of isoniazid when used with d4T [118,126]. In individuals already taking these anti-retrovirals, alternatives should be found if possible.

Pyridoxine 10 mg daily should be used in all patients receiving isoniazid. If peripheral neuropathy occurs the dose of pyridoxine can be increased up to 50 mg three times a day.

7.4.1 Recommendation [DII]

d4T should not be used as part of a HAART regimen if concomitant isoniazid is being administered. In patients on HAART coming from resource-poor countries where d4T is used widely in initial therapy, switching to an alternate nucleoside should be performed.

7.5 Rash

Rashes are often mild/moderate and usually occur in the first 2 months of treatment. They should be managed in a similar way to the management of nevirapine hypersensitivity rashes. Mild rashes without mucosal involvement can be treated symptomatically. More widespread worsening rashes or those with systemic symptoms require all drug cessation, and on recovery careful drug reintroduction as per protocol (see Table 8).

One compounding issue is that patients may have also recently started cotrimoxazole or antivirals and so the offending drug can be difficult to track down.

8.0 Drug absorption

8.1 Malabsorption of drugs

In HIV infection, malabsorption has been reported with all first-line anti-tuberculosis drugs, as well as ethionamide

and cycloserine. Absorption may be decreased in patients with a low CD4 cell count because of HIV enteropathy or other HIV-related gut disease. Subtherapeutic plasma drug concentrations may cause treatment failure and drug resistance [127,128]. Although some studies show lower peak concentrations of rifampicin and ethambutol as well as a lower AUC compared with controls [129–133], there are other data suggesting that rifampicin is well absorbed in HIV-infected patients, including those with AIDS or diarrhoea [134]. There are few data showing a correlation of treatment failure with poor absorption [106].

8.2 TDM

8.2.1 TDM of TB drugs [CII]

There are few data showing that TDM results in improved outcomes, and the use of TDM in TB has been reviewed [135]. However, it may be considered in patient populations who are:

- at high risk of malabsorption of TB drugs;
- responding inadequately to DOT with first-line drugs;
- being treated for MDR-TB;
- on nonstandard TB regimens or taking nonstandard doses;
- on boosted PIs with rifabutin three times a week.

One of the problems with monitoring anti-TB drugs is that the kinetics of absorption are not predictable. It is therefore difficult to know when to measure a peak plasma level, and it is probably best to check levels at more than one time-point post dose if possible. If rifabutin levels are being measured, ensure that the level of 25-O-desacetyl rifabutin, the active metabolite, is also measured.

Decisions about dosing may be difficult as there can be long delays in results being returned to the physician.

8.2.2 TDM of HIV drugs [BII]

TDM may be relevant for PIs and NNRTIs, especially when regimens are complex, when no formal pharmacokinetic data are available, and when virological failure occurs.

9.0 When to start HAART

The optimal time to start HAART in TB/HIV coinfecting patients is becoming clearer. Data from prospective trials in developing countries are helping to answer this question [136]. Given the importance of this area, we have sought to provide some pragmatic guidance.

Physicians have to balance the risk of HIV disease progression against the hazards of starting HAART, which include toxicities, side effects, IRIS and drug interactions. Antiretroviral and anti-tuberculosis drugs share similar

routes of metabolism and elimination, and extensive drug interactions may result in subtherapeutic plasma levels of either or both (see 'Drug-drug interactions'). Overlapping toxicity profiles may result in the interruption of TB or HIV regimens with subsequent microbiological or virological failure (see 'Overlapping toxicity profiles of antiretrovirals and TB therapy'). Deaths in the first month of TB treatment may be due to TB, while late deaths in coinfecting persons are attributable to HIV disease progression [137–139].

Patients with HIV infection and a CD4 cell count >350 cells/ μ L have a low risk of HIV disease progression or death during the subsequent 6 months of TB treatment, depending on age and viral load [2]. They should have their CD4 cell count monitored regularly and antiretroviral therapy can be withheld during the short-course TB treatment.

Most patients with TB in the United Kingdom present with a low CD4 count, often <100 cells/ μ L. In such patients HAART improves survival, but can be complicated by IRIS and drug toxicity. Data show that at CD4 counts <100 cells/ μ L the short-term risk of developing further AIDS-defining events and death is high, and HAART should be started as soon as practicable [118,140–143]. Some physicians prefer to wait for up to 2 weeks before starting HAART after commencing patients on TB treatment, to allow diagnosis and management of any early toxicity and adherence problems.

- A randomized trial (the SAPIT study) [144] compared two groups starting HAART during TB therapy (one group started within 4 weeks of starting TB treatment; the other started within 4 weeks of completing the TB treatment intensive phase) with a control group who did not start HAART until after completing their TB treatment. The data showed that deferring HAART until after TB treatment was completed was associated with a significant increase in mortality, even in patients with CD4 counts of >200 cells/ μ L, although there were few clinical events. We do not know if the six patients in this SAPIT study who died, out of the 86 who had TB, still had CD4 counts >200 cells/ μ L at the time of death.
- Further unpublished analyses of this important data set [145] showed that patients with CD4 counts <50 cells/ μ L at enrolment who started within 4 weeks of commencing TB treatment had a 68% lower risk of developing further AIDS-related clinical events and death compared with those with CD4 counts <50 cells/ μ L who did not start HAART.

A recent study from Cambodia suggested that treatment with HAART in the first 2 weeks of TB treatment resulted in a lower mortality rate than in the group delaying HAART to 8 weeks. The majority of these patients had a CD4 count of <100 cells/ μ L at enrolment [146].

The STRIDE (ACTG 5221) Study [147] also showed that starting HAART within 2 weeks resulted in a lower mortality rate than in the group delaying HAART until 8–12 weeks in patients who had a blood CD4 count of < 50 cells/ μ L at enrolment [146].

In these trials the disadvantage of starting early was an increased risk of IRIS.

Until we have further analyses of all data, we believe it is safer and more practicable to set a blood CD4 count of < 100 cells/ μ L as the point below which HAART should be started within 2 weeks of commencing TB treatment.

Other data sets suggest that starting HAART early, independent of CD4 cell count, improves long-term outcome [148,149]. Some physicians believe that starting HAART irrespective of CD4 cell count, including > 350 cells/ μ L, is beneficial in patients with active TB. Although the SAPIT study suggested HAART started during the course of TB therapy, even in those with CD4 counts > 350 cells/ μ L, was beneficial, almost all the patients within this arm had a CD4 count below that threshold.

A study of the risks and benefits of starting HAART early *vs.* late in patients with HIV-associated TB meningitis in the developing world, where 90% of patients were male, the majority were drug users, many had advanced disease and the diagnosis was made clinically in 40% of patients, showed no difference in mortality if HAART were started early, although there was a greater incidence of severe adverse events in the early arm [150]. How this translates to UK clinical practice remains unclear.

9.1 Suggested timing of HAART in TB/HIV coinfection [All]

Taking into account all the limited data available, we recommend:

CD4 count (cells/ μ L)	When to start HAART
< 100	As soon as practicable
100–350	As soon as practicable, but can wait until after completing 2 months of TB treatment, especially when there are difficulties with drug interactions, adherence and toxicities
> 350	At physician's discretion

10.0 IRIS

After starting anti-tuberculosis treatment, some patients develop an exacerbation of symptoms, signs or radiological manifestations of TB. This has been well described in

patients without HIV infection, but appears to occur more commonly in HIV-positive patients [151–169]. The phenomenon is known as IRIS, IRD or paradoxical reaction.

The aetiology of these reactions is unknown, but they are presumed in HIV disease to occur at least in part as a consequence of HAART-related reconstitution of immunity, which leads to an abnormal immune response to tubercle antigens released by dead or dying bacilli [170–175].

10.1 Definition

IRIS does not have a widely accepted definition, although an international attempt has been made. A definition for resource-poor countries has been developed and cases need to meet three criteria (see Table 10) [176]. IRIS is characterized by the worsening or appearance of new signs, symptoms or radiographic abnormalities, occurring after the initiation of HAART, and not the result of TB treatment failure or another disease process. It is therefore a diagnosis of exclusion. It is often defined as transient but can last many months. It is usually seen when the TB is microbiologically controlled, but cases can occur with viable organisms isolated on culture.

The features of IRIS are:

- apparent worsening/progression of TB;
- may occur at original site of disease or at remote site;
- may occur at any time after initiation of TB treatment;
- associated with commencing or continuing HAART;
- no evidence of TB relapse or recurrence (positive acid and alcohol fast bacilli smear does not exclude diagnosis of IRIS);
- appropriate investigations have excluded disease attributable to other pathogens;
- drug hypersensitivity is excluded;
- a response to corticosteroids does not confirm diagnosis of IRIS.

10.2 Epidemiology of IRIS

In the era of HAART, IRIS has been reported widely and occurred in 36% (12 of 33) and 32% (six of 19) of patients in two studies [161,162]. In another study, IRIS was not significantly more common in patients receiving HAART [three of 28 cases (11%)] compared with patients not on antiretroviral treatment [three of 44 cases (7%)] [167]. The majority of reactions occur within 60 days of initiating HAART, with a median of 15 days [168]. IRIS does not appear to be associated with any particular antiretroviral regimen or drug class [177]. Most patients with IRIS have advanced HIV infection (in one study the median baseline CD4 count was 35 cells/ μ L, and median HIV viral load > 500 000 HIV-1 RNA copies/mL). In the recent CAMELIA trial, the risk of IRIS was

increased around fourfold if HAART were started in the first 2 weeks compared with delaying HAART until beyond week 8 of TB treatment [146].

With limited data it is difficult to predict the risk of IRIS, but the following appear to be relevant [145,177–180]:

- low baseline CD4 cell count;
- rapid recovery in CD4 numbers;
- rapid decline in HIV viral load;
- dissemination of TB outside the lung (may be attributable to high burden of bacilli);
- HAART started within first 2 months of TB treatment.

10.3 Clinical features of IRIS

IRIS most often presents with fever and increased or new lymphadenopathy [151–181]. The skin overlying lymph nodes is often inflamed and dusky red, and the nodes can spontaneously rupture. New or worsening pulmonary lesions, pleural and pericardial effusions, ascites, psoas abscess, cutaneous lesions and new or expanding CNS tuberculomata, for example, have also been described.

10.4 Management of IRIS [AIII]

TB treatment failure, drug hypersensitivity and other opportunistic infections and malignancies need to be excluded.

10.4.1 Corticosteroids [AII]

The management of IRIS may require moderate-to-high-dose corticosteroids, sometimes for prolonged periods, in order to control symptoms. Prednisone or methylprednisolone has been used at a dose of 1–1.5 mg/kg, which was gradually reduced after 1–2 weeks. Patients who have been on rifampicin for 2 weeks or more will have increased liver metabolism of corticosteroids, such that the corticosteroid is effectively reduced by 33–50%. Patients may require steroids for prolonged periods of time and IRIS may recur when the dose is reduced, necessitating higher doses. Physicians should be aware of the metabolic side effects and potential for serious infections, for instance cytomegalovirus retinitis with high-dose corticosteroids.

A placebo-controlled study comparing the effect of steroids with that of placebo in early IRIS showed a benefit of steroids, but the data have to be interpreted with caution as a substantive proportion of the placebo arm were treated with open-label prednisolone [182].

10.4.2 Other treatment options

Recurrent needle aspiration of nodes or abscesses is appropriate if they become tense and/or inflamed. This

can prevent spontaneous rupture which may lead to long-term sinus formation and scarring.

Other treatments have as yet little evidence supporting their use. Nonsteroidal anti-inflammatory agents are generally not helpful. Temporary discontinuation of antiretroviral therapy has also been advocated but can cause precipitous falls in CD4 cell counts. Leukotriene overactivity has been implicated in IRIS, and montelukast can be considered as an alternative to steroids, but may need to be continued for a long period [183]. [DII]

The efficacies of other therapies such as interleukin-2, granulocyte-macrophage colony-stimulating factor and hydroxychloroquine are as yet unproven. There is one case report of the resolution of IRIS in an HIV-negative patient with the use of infliximab [184]. [DIII]

11.0 DOT

There have been no randomized controlled trials or systematic reviews examining the use of DOT in TB/HIV coinfection. However, the use of DOT is seen as the gold standard by WHO and CDC for the treatment of HIV-related TB, especially when using intermittent dosing. It is recommended by NICE for those deemed likely to have poor adherence, including those who are street- or shelter-dwelling homeless [1].

To help prevent the emergence of resistance, combination tablets (e.g. Rifater, which includes rifampicin, isoniazid and pyrazinamide) should be used whenever practicable.

It is recommended that all patients with MDR-TB have DOT. [AII]

Patient-centred care should be at the core of multi-disciplinary management and should always include an adherence strategy. This may include DOT/supervised therapy for HAART [185]. [BIII] However, there are no published data on the utility and efficacy of combined HAART/TB DOT in treating HIV/TB coinfection.

DOT usually requires that patients be observed to ingest each dose of anti-tuberculosis medication. Any treatment plan should be individualized to incorporate measures that facilitate adherence. These may include social service support, treatment incentives, housing assistance, referral for treatment of substance misuse, and co-ordination of TB services with those of other providers. There are many patients taking both HIV and TB therapies concomitantly. A maximum adherence model which is patient-centred, and utilizes family and friends and other social support as well as healthcare workers to ensure adherence, is an approach being examined more closely.

12.0 Management of relapse, treatment failure and drug resistance

12.1 Relapse

TB relapse is defined to occur in a patient who has become (and remained) culture-negative while receiving therapy but after completion of therapy:

- is culture-positive again;
- or shows clinical or radiographic deterioration consistent with active TB.

Every effort should be made to establish a diagnosis and obtain microbiological confirmation of the relapse to enable testing for drug resistance. IRIS events can mimic treatment relapse (see 'IRIS'). Strong consideration should be given to obtaining a rapid molecular rifampicin resistance test for all HIV-positive patients with relapse or treatment failure. These are available in TB reference laboratories and advice should be sought from them as soon as the diagnosis is contemplated.

Most relapses occur within 6–12 months of completing therapy. In patients with initially drug-susceptible TB, who were treated with rifamycin-containing regimens using DOT, relapse is with susceptible organisms in nearly all cases. In patients who self-administered therapy or received a nonrifamycin regimen, relapse incurs a substantial risk of acquired drug resistance.

The selection of empirical treatment for patients with relapse should be based on the prior treatment regimen and severity of disease:

- I. For patients with prior TB caused by drug-susceptible organisms, who received DOT with a rifamycin-based regimen, initiation of the standard four-drug regimen is appropriate until the results of drug susceptibility tests are available. [AII]
- II. For patients with life-threatening TB, at least three additional agents to which the organisms are likely to be susceptible should be included, even if the criteria in (I) are fulfilled. [AIII]
- III. For patients with relapse, who did not receive DOT, who had treatment interruptions, or who were not treated with a rifamycin-based regimen, then it should be assumed that drug resistance is present. Treatment is initially with isoniazid, rifampicin and pyrazinamide plus an additional three agents. Such agents could include a fluoroquinolone, an injectable agent such as amikacin, with or without additional oral drugs such as para-aminosalicylic acid (PAS), cycloserine, prothionamide and clarithromycin. [AIII]

12.2 Treatment failure

Treatment failure is defined as continued or recurrently positive cultures during the course of anti-tuberculosis therapy. After 3 months of multi-drug therapy for pulmonary TB caused by drug-susceptible organisms, up to 98% of patients will have negative cultures and show clinical improvement. All patients with positive cultures after 3 months of appropriate treatment must be evaluated carefully to identify the cause of the delayed conversion. Patients whose sputum cultures remain positive after 4 months of treatment should be classified treatment failures.

There are many reasons for treatment failure in patients receiving appropriate regimens. These include:

- nonadherence;
- drug resistance;
- malabsorption of drugs;
- laboratory error;
- extreme biological variation resulting in a prolonged time to respond;
- reinfection with a drug-resistant strain.

If treatment failure occurs, the case should be referred to a regional centre [1]. *M. tuberculosis* isolates should be sent to a reference laboratory for drug susceptibility testing to both first- and second-line agents. One of the fundamental principles in managing patients with treatment failure is never to add a single drug to a failing regimen, as this leads to acquired resistance to the new drug. Instead, at least two, and preferably three, new drugs should be added, to which the patient has not been exposed and to which susceptibility is thought likely. Empirical regimens usually include a fluoroquinolone, an injectable agent such as amikacin, and an oral agent such as cycloserine, prothionamide, clarithromycin or PAS. Once drug susceptibility test results are available, the regimen should be adjusted accordingly.

12.3 Management of isoniazid (INH) resistance without rifampicin or other significant drug resistance

The American Thoracic Society (ATS) and British Thoracic Society (BTS) have recommended several treatment regimens for the treatment of INH-resistant TB, which include: (a) 12 months of rifampicin and ethambutol (12RE); (b) 6 months of rifampicin, ethambutol and pyrazinamide (6REZ); (c) 2 months of rifampicin, ethambutol and pyrazinamide and then 10 months of rifampicin and ethambutol (2REZ/10RE); and (d) 2 months of rifampicin, ethambutol and pyrazinamide or streptomycin and then 7 months of rifampicin and ethambutol (2REZ or S/7RE).

The efficacies of these regimens have not been fully evaluated in prospective trials in HIV-positive subjects and we recommend 12 months of rifampicin and ethambutol with pyrazinamide also given in the first 2 months (2REZ/10RE).

If INH resistance is only discovered at 2 months of initial four-drug treatment then one can either continue with rifampicin and ethambutol for 10 months or continue rifampicin, ethambutol and pyrazinamide for a total of 6 months. In patients with extensive disease, one might continue both ethambutol and pyrazinamide with rifampicin for 9–12 months or even use rifampicin and ethambutol with a quinolone.

12.4 MDR-TB/extensively XDR-TB [186]

TB resistance to at least isoniazid and rifampicin is known as MDR-TB and isolates are at high risk of further acquired drug resistance. Risk factors for MDR-TB include:

- previous TB treatment;
- birth, travel or work in an area endemic for MDR-TB;
- history of poor adherence;
- sputum smear positive after 2 months of TB therapy or culture positive at 3 months;
- homelessness/hostel living.

All such patients should be referred to regional treatment centres, regardless of HIV infection status. There is a web-based discussion forum that can be used by the physician managing such cases. Further details are available on the BTS website at www.brit-thoracic.org.uk/tuberculosis.aspx

Although patients with strains resistant to rifampicin alone have a better prognosis than those with MDR-TB, they are also at increased risk of treatment failure and further resistance and should be managed in consultation with an expert. There are no definitive randomized or controlled studies to define the best regimens for MDR-TB. In principle, patients should be given four drugs to which the organism is susceptible. Recommendations are therefore based on the resistance profile and expert opinion. The optimum duration of treatment of MDR-TB in HIV-infected patients has also not been established, but many patients are treated for at least 18 months to 2 years after cultures revert to negative.

The drugs used to treat MDR-TB include the second-line and other drugs that are listed in Table 3. There are no formal data regarding interactions between these drugs and antiretrovirals but a review of the subject has been published [117]. Ethionamide has significant interactions because it is metabolized by the CYP450 system, although by which isoenzyme is unknown. There is no guidance about dose adjustment but TDM may be useful. There is a potential for renal toxicity with aminoglycosides and tenofovir but there are few data on drug interactions

between antiretrovirals and second-line anti-tuberculous treatment except for clarithromycin. Expert advice should be sought through the expert physicians network (www.brit-thoracic.org.uk/tuberculosis.aspx).

Novel drugs are being developed for treatment of MDR-TB, for example TMC-207, available in the United Kingdom on a named patient basis.

Surgical resection in the management of pulmonary MDR-TB can be used but results of randomized trials are awaited.

12.5 XDR-TB

XDR-TB is defined as TB that is resistant to at least isoniazid plus rifampicin, and to fluoroquinolones, and at least one of three injectable drugs (capreomycin, kanamycin or amikacin). XDR-TB has a high mortality [187] but is fortunately still rare in the United Kingdom. As for MDR-TB, all patients with XDR-TB should be referred to consultants with expertise in its management.

12.6 Chemo-preventative therapy in MDR/XDR-TB

In HIV-infected individuals exposed to MDR-TB, chemo-preventative therapy may be considered. If given at all it should be based on the drug sensitivity of the index case's isolate. Despite the lack of evidence, the CDC, the American Thoracic Society and the Infectious Diseases Society of America have suggested that, for the treatment of latent infection in people exposed to MDR-TB, a two-drug regimen of pyrazinamide and ethambutol *or* pyrazinamide and a quinolone (levofloxacin, moxifloxacin or ofloxacin) can be offered [188]. Further guidance is contained in references [4,189].

As with MDR-TB, in XDR-TB any chemo-preventative therapy should be based on the drug sensitivity of the index case.

The balance of benefits *vs.* detriments associated with treatment for latent TB infection in people exposed to MDR-TB or XDR-TB is not clear. The drugs have potential serious adverse effects and any decision to start or not needs careful consideration and expert advice.

13.0 Pregnancy and breast-feeding

Although TB in pregnancy carries a risk of TB in the foetus, the main problem of TB in pregnancy is a poor foetal outcome [190]. Treatment should be initiated whenever the probability of maternal disease is moderate to high. The initial phase should consist of isoniazid, rifampicin and ethambutol. Pyrazinamide is probably safe in pregnancy and is recommended by the WHO and the International Union against Tuberculosis and Lung Disease. These first-line drugs cross the placenta but do not appear to be teratogenic.

Streptomycin can cause congenital deafness [191] and prothionamide is teratogenic, so both should be avoided. Ethionamide causes birth defects at high doses in animals [192].

If pyrazinamide is not included in the initial phase, the minimum duration of therapy is 9 months. As in the general population, pyridoxine 10 mg/day is recommended for all women taking isoniazid. In pregnancy, antiretroviral pharmacokinetics are variable and TDM is recommended.

Women who are breast-feeding should be given standard TB treatment regimens. [AIII]

Pregnant women are usually on a PI-boosted HAART regimen and therefore should receive rifabutin as part of their anti-tuberculosis regimen. There are no adequate and well-controlled studies of rifabutin use in pregnant women. No teratogenic effects were observed in reproduction studies carried out in rats and rabbits.

14.0 Treatment of latent TB infection – HAART, anti-tuberculosis drugs or both?

14.1 Prophylaxis in those at risk of TB – risks and benefits

Persons from resource-poor countries, especially sub-Saharan Africa, often present with TB as their first manifestation of immunosuppression. Others who are diagnosed with HIV have high rates of latent TB infection. Low CD4 cell counts and not being on antiretroviral therapy are also associated with an increased risk of reactivation of latent TB [193,194].

Widespread use of HAART has reduced the risk of developing clinical TB among persons infected with HIV. In several studies, the risk of TB was up to 80% lower in those prescribed HAART. The protective effect was greatest in symptomatic patients and those with advanced immune suppression and was not apparent in those with CD4 counts >350 cells/ μ L [195–197]. The effect is almost certainly related to improvements in systemic immunity (reflected by increasing CD4 cell count) to a point where the risk of new infection or reactivation is greatly diminished.

There have been many short-term controlled trials in HIV-positive persons showing the protective effect of chemo-preventative therapy [198–204]. A significant protective effect of isoniazid is found only in those who are TST-positive, and appears to last only 2–4 years as compared with at least 19 years (suggesting protection is lifelong) in TB control programmes in non-HIV populations where active cases were also treated, limiting the risk of any reinfection occurring. This is an important point, as the HIV-infected populations studied have mainly been in areas of high TB prevalence, where most TB arises from new infection rather than reactivation [53]. Apart from recognized outbreaks, there is little evidence to suggest that

reinfection (as opposed to reactivation) is a major factor in the United Kingdom. Chemo-preventative therapy might therefore have a longer duration of effect in the United Kingdom, but there are no data to support this hypothesis.

There are some data from Brazil to suggest that a combination of HAART and isoniazid may be more effective than either alone in controlling TB [196]. The epidemiological situation in the United Kingdom is different, however.

Chemo-preventative therapy without HAART seemed to have little effect on HIV progression and mortality in the long term [202]. There are also theoretical concerns that widespread isoniazid monotherapy might speed the emergence of drug-resistant TB [205]. However, in a recent meta-analysis of 13 studies investigating the risk of developing isoniazid resistance as a result of chemo-preventative therapy, the relative risk for resistance was 1.45 (95% CI 0.85–2.47). Results were similar when studies of HIV-uninfected and HIV-infected persons were considered separately. Analyses were limited by small numbers and incomplete testing of isolates, and their findings did not exclude an increased risk for isoniazid-resistant TB after isoniazid preventative therapy [206].

The other risk of isoniazid preventative therapy is hepatotoxicity. The BTS Joint Tuberculosis Committee used a rate of 278/100 000 for serious hepatotoxicity. It may be more frequent in HIV-positive patients and those with active viral hepatitis (see 'Hepatotoxicity'), although the data are conflicting.

14.2 Chemo-preventative therapy for latent TB in HIV-positive patients in the United Kingdom

As there are no definitive data from developed countries on whether giving chemo-preventative therapy to patients with a positive IGRA will reduce the risk of developing TB, the available large cohort data from Europe were examined to provide a basis for a pragmatic clinical approach to this problem and to calculate the risk of developing active TB [193,194]. The risk of developing active TB *vs.* the risk of developing hepatitis on isoniazid prophylaxis was then used as the counterpoint to decide whether chemo-preventative therapy should be offered or not. A similar exercise has been performed to help decide whether to give chemo-preventative therapy to patients starting anti-tumor necrosis factor therapy, where the risk of developing TB is balanced against the risk of isoniazid-induced hepatitis.

In an HIV-infected individual with a positive IGRA, the risk of developing active TB, and therefore the need for chemo-preventative therapy, are based on (see Table 9 and Flow Chart 1):

- region of origin;
- current blood CD4 cell count;
- duration of time on HAART.

HIV-positive patients at increased risk fall into the following groups for countries of origin:

- sub-Saharan Africa – if duration of current antiretroviral therapy is <2 years, whatever the current blood CD4 cell count;
- medium TB incidence countries – if duration of current antiretroviral therapy is <2 years and current CD4 count is <500 cells/ μ L;
- low-incidence countries, for example the United Kingdom (for Caucasians) – if not on antiretrovirals, or if duration of current antiretroviral therapy is <6 months and current CD4 count is <350 cells/ μ L.

Patients should be offered screening with IGRA if (and only if) they are in one of these groups and would benefit from chemoprophylaxis [BII].

If the IGRA result is positive then we recommend the patient is given chemoprophylaxis.

If the IGRA result is negative then no chemoprophylaxis is needed.

If a patient is tested with an IGRA outside of these guidelines (not in one of the risk groups above), then no chemoprophylaxis is needed, even if the result is positive.

These recommendations are based on extrapolation from available data and further analyses are under way to refine this approach. If an IGRA test is indeterminate then we suggest repeating it and if still indeterminate the clinician should use clinical judgment regarding whether to give chemopreventative therapy or not. This Committee is aware that this new guidance will need local interpretation with regard to available resource, and that it should be subject to early audit. 2010 NICE guidance on IGRA testing suggests using IGRA testing in those patients with a CD4 count >200 cells/ μ L and both an IGRA and a tuberculin test in those with CD4 counts below this threshold. Although physicians can perform both tests in the severely immunosuppressed patients we believe that, as there are few data to support this strategy, doing this would add complexity, cost and difficulties in interpretation and we believe that an IGRA test alone would be sufficient at every CD4 cell count stratum. New data would be welcome in guiding physicians in this difficult area.

It is important to note that HIV-positive patients who are in close and prolonged contact with patients with proven or assumed active TB should be screened for TB and if no active disease is found chemo-preventative therapy recommended.

Although few data are available for patients receiving cancer chemotherapy or prolonged high-dose corticosteroids (>20 mg od prednisolone for more than 2 months) where the prognosis is >1 year, it may be reasonable to give isoniazid prophylaxis to all those with a positive IGRA who do not have active TB.

14.3 Drug regimens for chemo-preventative therapy

Individuals with a positive interferon- γ assay but no clinical or radiological evidence of active TB are assumed to have latent infection. Active TB should be excluded with a detailed history and examination and at least a chest radiograph. Other investigations might be necessary, for example lymph node biopsy (if lymphadenopathy), or colonoscopy and biopsy (if diarrhoea). It is especially important to consider subclinical TB prior to starting HAART because of the risk of IRIS [207] (see also 'IRIS').

Alternatives for treating latent TB:

- isoniazid for 6 months [201]; [A11]
- rifampicin with isoniazid for 3 months given daily in standard doses or twice a week using 900 mg isoniazid; [BI]
- rifampicin for 4 months. [BIII]

Shorter courses using other drugs have been tried to help overcome poor adherence. Rifampicin plus pyrazinamide given daily or twice weekly for 2 months has been used successfully in HIV-positive patients [200,203,204] but is not recommended [DII] because in largely non-HIV-infected patients it has been associated with severe or fatal hepatic reactions in at least 50 cases in the United States [208].

14.4 Post-treatment prophylaxis

Studies in areas of high TB prevalence have shown that isoniazid prophylaxis post-treatment achieves short-term reductions in rates of TB [209,210]. Such a strategy may in fact prevent reinfection, which is more common than true reactivation in such settings [211]. For maximum benefit the isoniazid would need to be continued long-term, or at least until CD4 cell count had substantially risen on HAART, and there are no data to support such an approach. It is clear that relapse rates are lower in patients on HAART, associated with both improved CD4 cell counts and achieving an undetectable viral load [212].

Post-treatment TB prophylaxis is therefore not recommended, but HAART should be continued. [DII]

15.0 Prevention and control of transmission

Guidelines for prevention and control of transmission of TB include:

- NICE: Tuberculosis, clinical diagnosis and management of TB, and measures for its prevention and control, 2006.
- Department of Health: Stopping tuberculosis in England, an action plan from the Chief Medical Officer, 2004.
- Department of Health: Tuberculosis prevention and treatment, a toolkit for planning, commissioning and delivering high-quality services in England, 2007.

- The Interdepartmental Working Group on Tuberculosis: The Prevention and Control of Tuberculosis in the United Kingdom, 1998 [4].

These are available at: www.dh.gov.uk/en/Publichealth/Communicablediseases/Tuberculosis/index.htm

In summary, for good control of TB there should be:

- recognition that TB is a potential diagnosis;
- prompt confirmation of diagnosis;
- no delay in starting treatment;
- an appropriate drug regimen;
- supervised therapy;
- early consideration of drug resistance in nonresponding patients.

Hospital care of patients with potential or known TB requires:

- appropriate isolation of patients;
- risk assessment for drug resistance;
- adequate negative pressure rooms which are properly monitored [4];
- aerosol-generating procedures (bronchoscopy, sputum induction or nebulizer treatment) should only take place in negative pressure rooms;
- consider all patients potentially infectious until proven otherwise;
- no mixing of HIV-infected or other immunosuppressed patients with TB patients;
- hospital TB control plan based on risk assessment;
- adequate protection of healthcare workers and other contacts.

15.1 Notification

TB is a notifiable disease in the United Kingdom, as it is in many other countries.

If the patient is concerned about disclosure of HIV status following notification by an HIV physician, then the notification can be done by any physician involved in clinical care.

Contact tracing should follow the NICE guidelines [1] but requires considerable sensitivity.

16.0 Death and clinico-pathological audit

Despite diagnosis and treatment, patients with HIV and TB infection still die. It is important that as many such patients as feasible are examined by autopsy. This categorizes the pathology and enables audit of medical practice. The significant categories of causes of death include:

- active, progressive TB;

- secondary effects of TB (e.g. lung haemorrhage and meningovascular obstruction);
- IRIS affecting one or more critical organs (e.g. lung and brain);
- anti-tuberculosis drug toxicity;
- other HIV- or non-HIV-related disease in a person effectively treated for TB;
- other disease in a person diagnosed with and treated for TB, without laboratory confirmation, who shows at autopsy no evidence of having had TB.

Culture of tuberculous autopsy tissue should be performed routinely, to evaluate drug sensitivity and bacterial viability.

Autopsies are either requested by clinicians or commanded by a Coroner (in UK) or Procurator Fiscal (in Scotland). If the autopsy is coronial, every endeavour should be made to obtain the autopsy report for clinical audit. Before any autopsy, discussion about the clinico-pathological issues with the pathologist is recommended.

17.0 Tables

Table 1 Abbreviations

AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
BHIVA	British HIV Association
BTS	British Thoracic Society
CDC	Centers for Disease Control and Prevention, USA
CNS	Central nervous system
CYP450	Cytochrome 450
d4T	Stavudine
ddC	Zalcitabine
ddl	Didanosine
DOT	Directly observed therapy
E	Ethambutol
H	Isoniazid
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
INH	Isoniazid
IGRA	Interferon-gamma release assay
IRD	Immune reconstitution disease
IRIS	Immune reconstitution inflammatory syndrome
MDR-TB	Multi-drug-resistant tuberculosis
NICE	National Institute for Health and Clinical Excellence
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
NNRTI	Nonnucleoside reverse transcriptase inhibitor
PAS	Para-aminosalicylic acid
PCR	Polymerase chain reaction
PgP	P-glycoprotein
PI	Protease inhibitor
R	Rifampicin
TB	Tuberculosis
TDM	Therapeutic drug monitoring
TST	Tuberculin skin test
WHO	World Health Organization
XDR-TB	Extensively drug-resistant TB
Z	Pyrazinamide

Table 2 Strength of treatment recommendations based on quality of evidence*

Strength of the recommendation	
A	Preferred; should generally be offered
B	Alternative; acceptable to offer
C	Offer when preferred or alternative regimens cannot be given
D	Should generally not be offered
E	Should never be offered
Quality of evidence supporting the recommendation	
I.	At least one properly randomized trial with clinical endpoints
II.	Clinical trials either not randomized or conducted in other populations
III.	Expert opinion

Table 3 Drugs used in the treatment of tuberculosis (TB)

First-line drugs	Second-line drugs
Isoniazid	Sparfloxacin, ofloxacin, levofloxacin, moxifloxacin
Rifampicin	Rifabutin*
Pyrazinamide	Streptomycin, amikacin, kanamycin
Ethambutol	Cycloserine
	Protonamide, ethionamide, capreomycin, para-aminosalicylic acid
Other drugs used in the treatment of MDR-TB but with few or no clinical outcome data:	
	clarithromycin, azithromycin, amoxicillin with clavulanic acid, linezolid [†]

See British National Formulary (BMJ Publishing Group, London, UK) for standard doses of individual drugs and fixed dose formulations.

Only physicians skilled in the treatment of TB should prescribe TB regimens. *Rifabutin may be substituted for rifampicin as a first-line drug in some situations, for example drug interactions. It is used in second-line treatment when there is rifampicin resistance but rifabutin sensitivity remains.

[†]The maximum recommended duration of linezolid is usually 28 days. All patients on linezolid should have their complete blood counts monitored weekly and be advised to report any new signs and symptoms. There have been reports of optic and peripheral neuropathy, especially after 28 days of therapy.

Tables 4–7: Drug interactions

More information at University of Liverpool website: www.hiv-druginteractions.org

Dose adjustments are described below for antiretrovirals given with rifampicin, rifabutin and clarithromycin.

No dosage adjustments are advised with isoniazid, pyrazinamide, streptomycin, amikacin, kanamycin, ethionamide, azithromycin, ofloxacin or ciprofloxacin.

Key for interaction tables

No interaction - use standard doses	◆
Potential interaction - see advice	■
Definite interaction - do not combine	●

Table 4 Nucleoside reverse transcriptase inhibitors (NRTIs)

	Rifampicin	Rifabutin
Abacavir	◆	◆
Didanosine EC	◆	◆
Emtricitabine	◆	◆
Lamivudine	◆	◆
Stavudine	◆	◆
Tenofovir	◆	◆
Zidovudine	◆	◆

Table 5 Nonnucleoside reverse transcriptase inhibitors (NNRTIs)

	Rifampicin	Rifabutin
Efavirenz	■ Efavirenz levels decreased by 20–30% Efavirenz increased to 800 mg daily if weight > 60 kg Efavirenz at 600 mg daily if weight < 60 kg Rifampicin at standard dose	■ Rifabutin levels decreased by 38% Rifabutin increased to 450 mg daily Efavirenz at standard dose
Nevirapine	● Nevirapine levels decreased 20–55% No change in rifampicin Not recommended	◆ Use standard doses but few data so not recommended
Etravirine	No data available	◆ Use standard doses but few data so use with caution
Rilpivirine	● Rilpivirine levels decreased 90% Do not use	■ Rilpivirine levels decreased 50% Double dose rilpivirine

Table 6 Protease inhibitors (PIs)

PI	Rifampicin	Rifabutin
Atazanavir	<ul style="list-style-type: none"> 80% decrease in atazanavir level Do not use 	<ul style="list-style-type: none"> Reduce rifabutin to 150 mg daily
Atazanavir/ritonavir	<ul style="list-style-type: none"> Decrease in atazanavir level Do not use 	<ul style="list-style-type: none"> Reduce rifabutin to 150 mg 3 times per week
Darunavir/ritonavir	<ul style="list-style-type: none"> No data Do not use 	<ul style="list-style-type: none"> Reduce rifabutin to 150 mg 3 times per week
Fosamprenavir/ritonavir	<ul style="list-style-type: none"> Decrease in amprenavir level Do not use 	<ul style="list-style-type: none"> Reduce rifabutin to 150 mg 3 times per week
Lopinavir/ritonavir	<ul style="list-style-type: none"> 75% decrease in lopinavir level Higher doses cause hepatotoxicity Do not use 	<ul style="list-style-type: none"> Reduce rifabutin to 150 mg 3 times per week
Ritonavir as single agent	<ul style="list-style-type: none"> 35% decrease in ritonavir level Can be used at 600 mg twice daily but very poorly tolerated 	
Saquinavir/ritonavir	<ul style="list-style-type: none"> Decrease in saquinavir level Higher doses cause hepatotoxicity Do not use 	<ul style="list-style-type: none"> Reduce rifabutin to 150 mg 3 times per week
Tipranavir/ritonavir	<ul style="list-style-type: none"> 80% decrease in tipranavir level Do not use 	<ul style="list-style-type: none"> Reduce rifabutin to 150 mg 3 times per week

Table 7 Integrase inhibitors and entry inhibitors

	Rifampicin	Rifabutin
Elvitegravir	<ul style="list-style-type: none"> Elvitegravir levels decreased 	<ul style="list-style-type: none"> If elvitegravir is given with ritonavir then reduce rifabutin to 150 mg 3 times a week
Raltegravir	<ul style="list-style-type: none"> Do not use Raltegravir levels decreased 60% Even at 800 mg bid use with caution as % C_{min} decrease 	<ul style="list-style-type: none"> Use standard doses
Maraviroc	<ul style="list-style-type: none"> Use with caution Maraviroc levels decreased Double maraviroc dose to 600 mg bid 	<ul style="list-style-type: none"> Use standard doses
Enfuvirtide (T-20)	<ul style="list-style-type: none"> No interaction Use standard doses 	<ul style="list-style-type: none"> No interaction Use standard doses

bid, twice a day; C_{min} , minimum concentration.

Table 8 Guidelines for the reintroduction of anti-tuberculosis chemotherapy following elevation of liver function tests or cutaneous reaction grade 1–3

Day	Isoniazid	Rifampicin	Pyrazinamide
1	50 mg		
2	150 mg		
3	300 mg		
4	300 mg	75 mg	
5	300 mg	150 mg	
6	300 mg	300 mg	
7	300 mg	450 mg <50 kg or 600 mg >50 kg	
8	300 mg	450 mg/600 mg	250 mg
9	300 mg	450 mg/600 mg	500 mg
10	300 mg	450 mg/600 mg	1 g
11	300 mg	450 mg/600 mg	1.5 g <50 kg or 2 g >50 kg
12	300 mg	450 mg/600 mg	1.5g/2g
13	300 mg	450 mg/600 mg	1.5g/2g

If the reaction is severe, start with one-tenth of the first-day dose for each drug.

Adapted from a reintroduction protocol for cutaneous reactions (Girling DJ. Adverse effects of antituberculous drugs. *Drugs* 1982; **23**: 56–74).

Patients who are infectious should be treated with two active drugs while standard therapy is reintroduced. Suitable agents would be ethambutol and streptomycin or ethambutol and ofloxacin/moxifloxacin (note reports of severe hepatotoxicity with moxifloxacin). In patients who are noninfectious, ethambutol should be started once the other three drugs are at full dose.

An alternative reintroduction regimen was described in 1996 for patients with hepatotoxic adverse reactions [213] and adopted by the Joint Tuberculosis Committee in 1998 [55]:

Once liver function is normal, the original drugs can be reintroduced sequentially in the order isoniazid, rifampicin and pyrazinamide, with daily monitoring of the patient's condition and liver function. Isoniazid should be introduced initially at 50 mg/day, increasing sequentially to 300 mg/day after 2–3 days if no reaction occurs, and then continued. After a further 2–3 days without reaction, rifampicin at a dose of 75 mg/day can be added, increasing to 300 mg/day after 2–3 days, and then after a further 2–3 days without reaction to 450 mg (<50 kg) or 600 mg (>50 kg) per day as appropriate for the patient's weight, and then continued. Finally, pyrazinamide can be added at 250 mg/day, increasing to 1 g/day after 2–3 days and then 1.5g/day (<50 kg) or 2.0g/day (>50 kg).

Example of alternative schedule

Day	Isoniazid	Rifampicin	Pyrazinamide
1	50 mg		
2	50 mg		
3	150 mg		
4	300 mg		
5	300 mg		
6	300 mg	75 mg	
7	300 mg	75 mg	
8	300 mg	150 mg	
9	300 mg	300 mg	
10	300 mg	300 mg	
11	300 mg	450 mg <50 kg or 600 mg >50 kg	
12	300 mg	450 mg/600 mg	
13	300 mg	450 mg/600 mg	
14	300 mg	450 mg/600 mg	250 mg
15	300 mg	450 mg/600 mg	250 mg
16	300 mg	450 mg/600 mg	500 mg
17	300 mg	450 mg/600 mg	1g
18	300 mg	450 mg/600 mg	1.5g <50 kg or 2.0g >50 kg
19	300 mg	450 mg/600 mg	1.5g/2g

Table 9 Recommendations for chemo-preventative therapy in HIV-infected persons by interferon- γ release assay (IGRA) status and epidemiological risk factors [193,194]

IGRA positive	
Sub-Saharan Africans	→ Whatever blood CD4 cell count and duration of HAART <2 years
Medium incidence	→ Blood CD4 count <500 cells/ μ L and duration of HAART <2 years
Low incidence	→ Blood CD4 count <350 cells/ μ L and not on treatment or on treatment less than 6 months
IGRA negative	
No chemo-preventative therapy	

Regions of origin (1), sub-Saharan Africa; (2), medium-risk regions, including Eastern Europe, Central Asia, North Africa and the Middle East, South Asia, East Asia, and the Caribbean; and (3), low-risk regions, including UK, Western Europe, Australia, USA, Canada and New Zealand.

Table 10 Case definition of immune reconstitution inflammatory syndrome (IRIS) [176]

Although this was developed for a resource-poor setting it is comprehensive and is a useful checklist.

There are three components to this case definition:

(A) Antecedent requirements

Both of the two following requirements must be met:

- Diagnosis of tuberculosis: the tuberculosis diagnosis was made before starting antiretroviral therapy and this should fulfil WHO criteria for diagnosis of smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis or extrapulmonary tuberculosis [55].
- Initial response to tuberculosis treatment: the patient's condition should have stabilized or improved on appropriate tuberculosis treatment before antiretroviral therapy initiation – e.g. cessation of night sweats, fevers, cough and weight loss. (Note: this does not apply to patients starting antiretroviral therapy within 2 weeks of starting tuberculosis treatment as insufficient time may have elapsed for a clinical response to be reported.)

(B) Clinical criteria

The onset of tuberculosis-associated IRIS manifestations should be within 3 months of antiretroviral therapy initiation, reinitiation, or regimen change because of treatment failure.

Of the following, at least one major criterion or two minor clinical criteria are required:

Major criteria

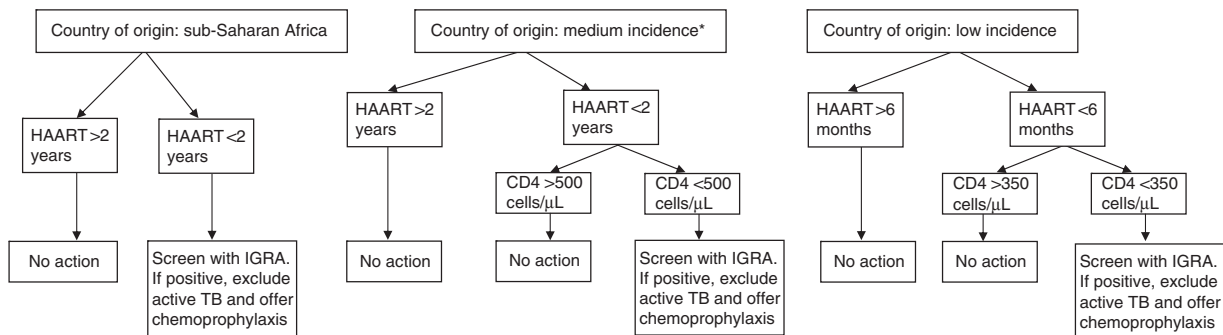
- New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement – e.g. tuberculous arthritis.
- New or worsening radiological features of tuberculosis [found by chest radiography, abdominal ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI)].
- New or worsening CNS tuberculosis (meningitis or focal neurological deficit – e.g. caused by tuberculoma).
- New or worsening serositis (pleural effusion, ascites, or pericardial effusion).

Minor criteria

- New or worsening constitutional symptoms such as fever, night sweats or weight loss.
- New or worsening respiratory symptoms such as cough, dyspnoea or stridor.
- New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly or abdominal adenopathy.

(C) Alternative explanations for clinical deterioration must be excluded if possible*

- Failure of tuberculosis treatment because of tuberculosis drug resistance.
- Poor adherence to tuberculosis treatment.
- Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis where the initial tuberculosis diagnosis has not been microbiologically confirmed).

**Flow Chart 1** Algorithm for screening for latent tuberculosis (TB)

*Medium incidence regions include Eastern Europe, Central Asia, North Africa and the Middle East, South Asia, East Asia, and the Caribbean. HAART, highly active antiretroviral therapy; IGRA, interferon- γ release assay.

18.0 Key points

18.1 Treatment of uncomplicated non-CNS TB

A four-drug regimen of rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months; followed by rifampicin and isoniazid for 4 months.

18.2 Treatment of CNS or MDR-TB

A prolonged treatment duration is recommended.

TB meningitis is treated for at least 9 months.

In MDR-TB, treatment for up to 2 years may be indicated.

18.3 Treatment schedule

Daily therapy is recommended.

If therapy is given three or five times per week it should be supervised, preferably as DOT.

18.4 Liver disease

Patients with pre-existing liver disease need their liver function tests monitored closely.

They need to be advised to present immediately if they develop vomiting, abdominal pain or jaundice.

18.5 Molecular diagnostic techniques

Molecular diagnostic tests can give rapid identification of mycobacterial species.

PCR probes can rapidly detect resistance to rifampicin.

These results can help decisions about treatment and infection control measures.

18.6 Notification of TB

All patients with TB, regardless of HIV status, must be notified.

18.7 Infection control

All potentially infectious patients should be managed in appropriate isolation facilities, such as negative pressure rooms, with staff and visitors wearing high-efficiency particulate filtration masks.

18.8 Drug interactions

Complex drug interactions occur between rifamycins and antiretroviral drugs and other drugs that may affect dosages and dosing frequencies.

18.9 Starting HAART

The decision on whether to commence HAART in patients on anti-tuberculosis medication or not should take into consideration primarily the CD4 cell count; HAART should be strongly considered if the CD4 count is < 100 cells/ μ L. Other factors such as adherence, potential toxicities and drug-drug interactions are also important.

18.10 Chemo-preventative therapy

IGRA tests are preferred to TSTs (e.g. Mantoux). Chemo-preventative therapy should be considered for all IGRA-positive HIV-infected patients dependent on a risk assessment based on country of origin, blood CD4 cell count and length of time on HAART.

Appendix: BHIVA Guidelines Writing Group on TB Coinfection

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