

British HIV Association guidelines for the treatment of TB/ HIV co-infection 2009

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The guidelines have been extensively revised since the last edition in 2005; most sections have been amended and 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;
- a complete update of the drug interactions section and tables;
- an updated section on choice of NNRTI;
- a new section on isoniazid resistance and XDR;
- guidance on the diagnosis of IRIS;
- new tables for management of adverse reactions.

1.0 Summary of guidelines

These guidelines have been drawn up to help physicians manage adults with 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 tuberculosis and HIV.

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

In the treatment of HIV, patients starting highly active antiretroviral therapy (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 avoid 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 tuberculosis 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 *M. tuberculosis*, may avoid unnecessary treatment and infection-control measures.

We recommend rapid detection of rifampicin resistance using molecular techniques in patients whose clinical course or initial assessment suggest multi-drug resistant tuberculosis. These molecular tests should be used as an adjunct to standard laboratory techniques.

1.2 Tuberculin skin test/interferon- γ assays

Tuberculin skin testing is less useful in patients with HIV infection compared with HIV-uninfected patients. We do not recommend routine tuberculin skin testing in HIV patients either for diagnosis or screening. Newer blood assays for interferon- γ release from essentially MTB-specific T cells are more sensitive than tuberculin tests for detecting

both active and latent disease in HIV-negative subjects. They are also more specific in BCG-vaccinated individuals. However, there is still little information regarding their performance in HIV-infected patients, especially at low blood CD4 cell counts. Data are required to define the use of these tests in the diagnosis of latent tuberculosis in HIV-positive patients before widespread routine screening can be recommended.

1.3 Treatment of active TB

We recommend daily tuberculosis 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 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, since it has been associated with unacceptably high relapse rates.

In cases where 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 9–12 months of treatment. This usually consists of four drugs for 2 months, followed by 7–10 months of isoniazid and rifampicin. Drug resistant disease should be treated by only specialists with experience in such cases, in line with NICE guidelines [1].

1.4 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 CYP450 and has effects on several metabolic pathways and PgP. Rifampicin interacts with protease inhibitors, NNRTIs, CCR5 inhibitors, 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-TB 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. 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.

1.5 Antiretroviral treatment

Rifamycin-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.

1.5.1 Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

There are no major interactions between rifampicin or rifabutin and lamivudine (3TC), emtricitabine (FTC), tenofovir, abacavir, zidovudine (AZT) or didanosine (ddI).

Stavudine (d4T) should not be given because of the increased risk of peripheral neuropathy with concomitant TB therapy.

1.5.2 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Rifampicin + Efavirenz	Use efavirenz 800mg/day in patients weighing >50kg and standard dose 600mg/day in patients weighing <50kg If side effects occur, efavirenz TDM may be useful
Rifampicin + Nevirapine*	Not recommended but if given then use standard doses and perform nevirapine TDM
Rifabutin + Efavirenz	Increase rifabutin to 450mg daily
Rifabutin + Nevirapine*	Not recommended but if given then use standard doses

1.5.3 Protease inhibitors (PI)

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

1.5.4 integrase Inhibitors

Rifampicin + Elvitegravir	Do not use
Rifampicin + Raltegravir*	Use with caution; if given then use standard doses
Rifabutin + Elvitegravir	No data, not recommended
Rifabutin + Raltegravir	No data, not recommended

1.5.5 Entry inhibitors

Rifampicin + Maraviroc*	Not recommended, but if given double dose of maraviroc
Rifabutin + Maraviroc	Use standard doses
Rifampicin + T-20	No interaction, use standard doses
Rifabutin + T-20	No interaction, use standard doses

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

We recommend that TDM of NNRTI and PI 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.

1.6 Starting HAART

Starting HAART during TB treatment is complicated by overlapping toxicities, drug interactions and immune reconstitution disease, 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 >200 and <350 cells/ μ L: wait until TB therapy complete before starting HAART

CD4 100–200 cells/ μ L: start HAART if practical but may defer until after initial phase of TB therapy (2 months)

CD4 <100 cells/ μ L: start HAART as soon as practical after starting TB therapy

See BHIVA HIV treatment guidelines for details on starting HAART [178].

1.7 Directly Observed Therapy (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 drug resistant TB.

1.8 Treatment of latent TB infection

We do not recommend routine chemo-preventative therapy for HIV-infected patients. However, close contacts of people who have infectious TB should be followed up and offered chemo-preventative therapy according to NICE guidelines [1]. HAART is effective at reducing the incidence of new TB and we recommend that all HIV-positive patients should be offered HAART in line with the BHIVA guidelines.

1.9 Latent TB

HIV-infected individuals with latent TB are much more likely to progress to active TB than HIV-uninfected people. Detection and treatment of latent TB is therefore important, although diagnosis can be difficult. Tuberculin skin tests and blood interferon- γ assays may give contradictory results especially at low CD4 cell counts. Active TB needs to be completely excluded before considering treatment of latent disease, 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 but individuals need to be monitored for signs of immune reconstitution inflammatory syndrome (IRIS).

1.10 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.

1.11 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 [18].

2.0 Introduction

Worldwide, it is estimated that 8 per cent of all new TB cases in adults are attributable to HIV infection. This proportion is much greater in Africa, where 85% of all TB/HIV coinfections are found. In 2006 TB/HIV killed 200 000 people globally [2].

All patients with TB, regardless of their perceived risk of HIV infection, should be offered an HIV test. In the UK, an increasing number of TB cases are coinfecting with HIV. In 2003, 8.3% of adults with TB were HIV infected [3]. The proportion is higher in London, with coinfection rates of 17–25% [4].

In HIV coinfection the clinical and radiographic presentation of TB may be atypical. Compared to the immune-competent population, TB/HIV patients with active pulmonary TB are more likely to have normal chest radiographs or to have sputum which is smear negative but culture positive [5–7]. 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 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 guidelines (www.nice.org.uk/Guidance/CG33): Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control, April 2006
- BHIVA guidelines (www.bhiva.org/cms1222226.asp): Treatment of HIV-infected adults with antiretroviral therapy (2008).

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 *Mycobacterium tuberculosis* to other individuals;
- to eliminate MTB 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

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 to 28 days.

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. 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. All specimens, even those negative for *M. tuberculosis* on PCR, still require culture because a negative PCR does not exclude TB and a positive PCR does not indicate the drug susceptibility profile. In many cases the treatment conundrum is whether the patient has *M. avium* 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 azithromycin/clarithromycin. When opportunistic mycobacteria are identified the regimen can be modified appropriately.

4.3 Drug susceptibility tests

These are usually available within 10–21 days of the laboratory receipt of isolates and are performed by standard assays. Molecular detection of resistance to rifampicin is available although not 100% sensitive. This molecular test is useful when drug resistance is suspected, as about 95% of isolates which are rifampicin resistant will also be isoniazid resistant. MDR-TB is defined as TB resistant to at least rifampicin and isoniazid. Patients with gene probe positive rifampicin resistance should be treated as 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 at low CD4 cell counts [9–13,19,20]. In patients with AIDS or CD4 <200 cells/ μ L, the sensitivity of the test is only 0–20%. False positives occur after bacillus Calmette–Guèrin (BCG) immunization. Some data suggest combining Interferon- γ release assays and tuberculin testing [21]. We do not recommend the routine use of tuberculin skin tests. **[DII]**

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 [8]. Detection and treatment of latent TB is therefore important. The tuberculin skin test is not sensitive in HIV-infected individuals, especially in severe immunosuppression [9–13], and cross-reacts with antigens from BCG vaccination.

Blood tests are available that measure Interferon- γ release from T cells after stimulation with antigens largely specific to *M. tuberculosis* (ESAT-6 and CFP-10) [14]. These tests are approved for the diagnosis of latent TB in HIV-negative individuals, and will also be positive in active TB. The result is expected to be negative after BCG vaccination, after repeated tuberculin skin testing, and in infection with most other mycobacteria (an important exception in the UK being *M. kansasii*). Limited data exist regarding their performance in HIV infection, but studies suggest that Interferon- γ assays are more sensitive and specific than tuberculin skin tests, especially in BCG-vaccinated subjects [15]. They also appear to retain sensitivity more reliably at lower CD4 cell counts, although the lower threshold has not yet been defined [16–17]. 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” IGRA results are more common in HIV-infected subjects. They are also more costly than tuberculin tests, though this may be offset by the savings in, for instance, healthcare worker time ref Diel R, Wrighton-Smith P and Zellweger J-P. Cost-effectiveness of interferon- γ release assay testing for the treatment of latent tuberculosis [42].

We do not recommend routine use of these tests in screening HIV-positive individuals outside of a clinical study. Nor should IGRA be used in the diagnostic work-up of patients suspected of having active tuberculosis. If a test is performed, the result must be interpreted in light of the clinical picture and 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**

2 months of isoniazid, rifampicin, pyrazinamide and ethambutol.

These 4 drugs are necessary because of the relatively high rates of isoniazid resistance in the UK, which is 7.7% overall (HPA 2007), and higher in non-white ethnic groups and those with previous resistance.

If drug sensitivity testing shows MTB sensitive to first line agents, ethambutol can be omitted.

- **Continuation phase**

4 months of isoniazid and rifampicin in most patients with drug-sensitive TB, prolonged to 7 months in some circumstances (see 5.3).

All patients taking isoniazid should be prescribed pyridoxine (vitamin B6) 10–25mg 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 Directly Observed Therapy (DOT) is equivalent to seven-times-weekly treatment, and can thus be considered as “daily”. **[AIII]**

5.2 Use of Corticosteroids

In HIV-infected adults with pulmonary or pleural TB, corticosteroids do not improve survival or reduce TB recurrence [22–23] and are not generally recommended. However, in pleural TB, prednisolone does result in more rapid resolution of pleural effusions [23].

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 randomised 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 tuberculosis meningitis, whether they were given dexamethasone or placebo with standard TB treatment [24]. However, the number of HIV-infected people in this study was small (98) and the diagnosis of TB was confirmed microbiologically in less 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 randomised controlled trial of HIV-infected adults with presumed tuberculous pericarditis treated with standard TB therapy found that prednisolone results in better outcomes than placebo [25]. Mortality was reduced with prednisolone compared to placebo, and raised venous pressure, hepatomegaly, ascites and improvement in physical activity occurred more rapidly. However, there was no

faster resolution of pericardial fluid on chest radiography or echocardiogram, and since 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]**

Steroids should be given for approximately six weeks. An appropriate daily starting dose is prednisolone 1mg/kg or equivalent. The daily dose should be reduced by about 10mg per week, starting after 2–3 weeks.

The studies above have shown that corticosteroids increase the risk of high blood pressure, raised blood glucose and fluid retention [22,23]. The risk of infectious complications does not seem to be increased [22,23,25] although the data for Kaposi's sarcoma are contradictory.

5.3 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 who remain sputum culture positive after 2 months of treatment.

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.

5.4 Intermittent therapy [AII]

It is recommended that patients receive daily therapy [26]. However, in some circumstances intermittent therapy can be given three times per week with dose modification [27,28] but must be by DOT.

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 [29–33]. **[AII]**.

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

5.5 Use of rifabutin [BII]

Rifabutin has been successfully used instead of rifampicin in treating TB in HIV-negative patients [34,35]. It can be regarded as an alternative in HIV-positive patients, especially to avoid drug interactions with rifampicin, for example with protease inhibitors (see 6.0). Rifabutin showed similar efficacy to rifampicin in a single-blind randomised study of 50 HIV-positive patients in Uganda [36] and a cohort of 25 patients in the US [37].

However, there is a paucity of long-term data with 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), rifabutin should be substituted.

5.6 Use of rifapentine [DII]

Rifapentine has a long serum half-life which theoretically allows once-weekly dosing. However, in the initial phase of treatment of TB in HIV-negative patients, rifapentine has unacceptable 2-year microbiological relapse rates and is not recommended. Data on its use in the continuation phase are encouraging, but this is accrued from studies of HIV-negative patients. Development of rifapentine resistance appears more frequent in TB/HIV coinfecting patients [38] and at present rifapentine cannot be recommended and should not be used. **[DII]** There are few data regarding the interactions of rifapentine with HAART.

5.7 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 [27,39,40]. 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 [41]. 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% and relapse rates were 0–3%. Although the relapse rates appeared higher in some studies of coinfecting patients, other outcomes were comparable when 6-month regimens were used.

A more recent retrospective review from the US suggested that relapse rates are four-times higher in HIV patients treated with standard rifampicin-based regimens for 6 months than in those treated for longer [26]. The authors evaluated treatment outcomes in HIV-negative and HIV-positive patients, stratified by duration of rifampicin-based therapy. 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 the cases. Although there were no formal adherence assessments in those not on DOT, HIV-positive patients were significantly more likely to experience adverse drug reactions and to acquire drug resistant TB than the HIV-uninfected/unknown group. It may be the case that where adherence was suboptimal, 6 months of therapy is insufficient.

Long-term randomised 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 [30,39,40,43,44]. These should include at least 182 doses of isoniazid and rifampicin, and 56 doses of pyrazinamide (see 5.8). **[All]** See also sections 5.3 and 5.4.

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;
- a 6-month DOT regimen (given 5 days/week) should consist of at least 130 doses of isoniazid and rifampicin, and 40 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 tuberculosis. 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, social services. The CDC suggest the following [45]:

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 less than 14 days, the treatment regimen should be continued. The total number of doses for the initial phase should be given.

5.10 Investigations during TB treatment [AIII]

Baseline investigations:

- CD4 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.

Liver function tests should be rechecked at 1–2 weeks if asymptomatic [1]. Patients with pre-existing liver disease need close monitoring, for instance every 2 weeks for first 2 months.

In patients with pulmonary TB who are not improving and still have a productive cough after 2 months, 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 cytochrome P450 (CYP450). The CYP3A4 isoform metabolizes many drugs including protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Rifamycins are potent inducers of CYP3A4 [46,47] and have clinically important interactions with PIs and NNRTIs. Rifampicin is the most powerful inducer of CYP3A4 of all medicines. Rifapentine is a less potent inducer; and rifabutin much less so.

To a smaller extent, rifampicin also induces the activity of CYP2C19 and CYP6. Rifampicin also increases activity of the intestinal drug transporter P-glycoprotein (PgP) that contributes to the absorption, distribution and elimination of PIs [135,136].

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 [50]. Unlike rifampicin, it is also a substrate of the enzyme [46]. 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 [51].

Rifapentine is dosed once per week, although for reasons discussed above (see 5.6) it is not recommended in HIV infection. Few data are available regarding its interactions with HAART. Rifapentine is a CYP3A4 inducer, but not a substrate for this enzyme. It may decrease levels of antiretrovirals but its own metabolism would be unchanged.

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are mostly known to be free of clinically significant interactions. 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 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 33–50% with rifampicin and 25–33% with rifabutin. **[All]**

6.1 Rifamycins and NRTIs (Table 4)

When NRTIs are given with rifampicin either the pharmacokinetics change little, or the interactions are unknown. Rifampicin reduces the AUC and increases the clearance of zidovudine via increased glucuronidation [52]. This is not clinically significant and dose alteration is not required. Rifabutin does not affect the clearance of zidovudine [53].

Triple-NRTI regimens are theoretically attractive as HAART because they are free of interactions with TB treatment, and have been used with success in Africa [54,55]. However, they are virologically inferior to HAART containing an NNRTI [56]. Quadruple-NRTI regimens (most commonly abacavir, lamivudine, zidovudine, tenofovir) have also been used in adults taking TB treatment. There are data from a small trial to support this approach [57], but it is not recommended as standard of care in the UK.

6.2 Rifamycins and NNRTIs (Table 5)

Efavirenz, nevirapine, etravirine and TMC-278 are substrates for, and inducers of, CYP3A4. The clinical use of these drugs together with rifamycins is complex.

6.2.1 Rifampicin and NNRTIs

6.2.1.1 Rifampicin and efavirenz

There is still debate regarding the appropriate dose of efavirenz with rifampicin. Several studies have found a 20–30% reduction in efavirenz levels when administered with rifampicin [58,59]. Increasing the efavirenz dose from 600mg to 800mg is effective and safe [58,60]. However, in cohorts with low body weight standard dose efavirenz has been given with rifampicin without lower drug exposure or clinical efficacy [61,62]. None of the clinical trial data has correlated patient weight, pharmacokinetics and clinical

outcome. It is therefore difficult to make recommendations for patients in the UK where body weights are usually >50kg.

Efavirenz levels and toxicity are increased in individuals with polymorphisms in CYP2B6 which are present in 20% of the black population compared with 3% of whites [63,64]. This may explain high rates of clinical toxicity in some studies [65]. If side effects occur, TDM can identify those individuals with high efavirenz levels.

We recommend that when rifampicin is used with efavirenz in patients over 50kg, the efavirenz dose is increased to 800mg daily. Standard doses of efavirenz are recommended if the patient weighs less than 50kg. **[AII]**

6.2.1.2 Rifampicin and nevirapine

Rifampicin and nevirapine are both used widely in resource-poor countries because they are cheap and readily available. There are data that nevirapine levels are reduced by 20–55% by rifampicin [66–71]. A recent South African study found that in sixteen HIV/TB patients taking HAART with standard doses of nevirapine, nevirapine concentrations were significantly decreased when rifampicin-based TB therapy was started [70]. C_{max} was decreased by 39%, AUC by 36% and C_{min} by 32%. Nevirapine C_{min} was subtherapeutic (<3 mg/L) in 6 of the 16 patients during anti-TB therapy (one of whom developed virological failure) and in none afterwards.

In a Thai cohort nevirapine levels were significantly reduced by rifampicin but 86% maintained levels >3.1 mg/L which were adequate for HIV viral suppression [69]. The difference from the South African cohort may have been that the Thai patients had lower body weight.

To overcome the problem of low nevirapine levels with rifampicin, one trial administered 400mg nevirapine as lead-in dose, increasing to 600mg [72]. 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 [67,73]. 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 OR (CI) of 2.9 (1.8–4.7) in the nevirapine arm vs. the efavirenz or not-on-TB-treatment arms [48].

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

6.2.1.3 Rifampicin and etravirine

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

6.2.1.4 Rifampicin and TMC-278 (rilpivirine)

Rifampicin reduces plasma concentrations of TMC-278 by up to 90% so these drugs should not be used together [74].

6.2.2 Rifabutin and NNRTIs

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

Concomitant administration of nevirapine results in increased rifabutin AUC (17%) and C_{max} (28%) with no change in C_{min} . The effect on nevirapine pharmacokinetics was not significant (Viramune SPC 2007). Due to high intersubject variability, some patients may be at risk of rifabutin toxicity. In conclusion, 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.

Rifabutin can be given with etravirine with no dose adjustments.

Rifabutin decreases plasma levels of TMC-278 by 50%, so if used together the dose of TMC-278 should be doubled [74].

6.3 Rifamycins and Protease Inhibitors (PIs)

6.3.1 Rifampicin and PIs (Table 6)

6.3.1.1 Unboosted PIs

Rifampicin causes a 75–95% reduction in plasma concentrations of PIs other than ritonavir [75]. 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 full dose of 600mg twice daily [76]. However such high dose ritonavir is very poorly tolerated and seldom used [77].

6.3.1.2 Boosted PIs

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

6.3.1.3 Saquinavir/ritonavir

A dose of twice-daily 400mg ritonavir with 400mg saquinavir has been used with rifampicin with acceptable PI pharmacokinetics [78]. Saquinavir 1600mg with ritonavir 200mg once daily was tested in HIV-positive patients on rifampicin-based TB therapy, and saquinavir levels were inadequate [79,80].

A pharmacokinetic study performed in healthy volunteers given saquinavir/ritonavir and rifampicin then demonstrated severe hepatotoxicity [81]. Transaminases were elevated to more than 20-times upper limit of normal.

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

6.3.1.4 Lopinavir/ritonavir

Data regarding the interaction of rifampicin with standard-dose lopinavir/ritonavir suggest that ritonavir at low dose does not compensate for the inducing effect of rifampicin on lopinavir metabolism [82]. 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 400mg twice daily then lopinavir trough concentrations were adequate in 9/10 subjects but there were high rates of elevated transaminases and lipids, and gastrointestinal toxicity [83]. A pharmacokinetic study in healthy volunteers was reminiscent of the saquinavir study, and was terminated early because of high rates of severe transaminitis [84].

6.3.1.5 Atazanavir/ritonavir

Recent data suggest that atazanavir with or without ritonavir boosting had unfavourable pharmacokinetics when administered with rifampicin [85–87]. Trough atazanavir concentrations were reduced by >80% [86].

6.3.1.6 Tipranavir/ritonavir

Tipranavir concentrations were reduced by 80% by rifampicin [88].

6.3.1.7 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.

6.3.1.8 Recommendation

We recommend that PI/ritonavir combinations should not be given with rifampicin. 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 (5.5).

6.3.2 Rifabutin and PIs (Table 6)

6.3.2.1 Unboosted PIs

The use of rifabutin in treating TB in HIV-positive patients is discussed above (see 5.5). Rifabutin can be administered with unboosted PIs except saquinavir [89], although they will rarely be used in practice. The balance between rifabutin induction and PI inhibition of CYP3A4 means that a modification in the dose of the PI may be required, and the dose of rifabutin should be decreased from 300mg to 150mg daily to avoid toxicity [36, 51].

6.3.2.2 Boosted PIs

If PIs are used with low-dose ritonavir boosting then the dose of rifabutin should be reduced to 150mg three times per week [37, 88].

Complex interactions may occur when a rifamycin is given with salvage regimens such as two PIs plus boosted ritonavir, or with a boosted or non-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 Rifamycins and Integrase Inhibitors (Table 7)

Raltegravir is metabolized by UGT1A1 glucuronidation. Rifampicin reduces trough levels of raltegravir by approximately 60% [90]. Because the antiviral activity of raltegravir 200mg twice daily was very similar to that of the licensed dose (400mg twice daily) the current recommendation is that standard doses of raltegravir should be used with rifampicin. However, there is little clinical experience with this combination and coadministration should probably be avoided if alternatives exist. There is at least one

report of raltegravir failure when given with rifampicin (S Taylor, personal communication).

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

There are no data available regarding interactions with rifabutin.

6.5 Rifamycins and CCR5-antagonists (Table 7)

Maraviroc is metabolized by CYP3A4 and its levels are reduced by rifampicin. Doubling the dose of maraviroc may compensate for this effect [91]. There are no data about interactions with rifabutin but maraviroc concentrations are predicted to be adequate, and maraviroc can therefore be given at standard doses with rifabutin.

6.6 Rifamycins and enfuvirtide (Table 7)

There are no significant interactions between rifamycins and enfuvirtide [92].

6.7 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 [93,94]. When given together with rifampicin (inducer), the inhibition effect of isoniazid is masked. However, when used alone to treat latent TB the inhibition effect might increase plasma levels of PIs or NNRTIs and cause toxicity. This potential concern has not been reported as a major issue in clinical practice.

There is a theoretical interaction between isoniazid and abacavir since both are metabolized by cytosolic enzymes, which may result in increased isoniazid levels and decreased abacavir levels. However this is unlikely to be clinically relevant.

6.8 Non-rifamycin regimens

HIV-related tuberculosis may be treated with non-rifamycin containing regimens but these are inferior in efficacy, with high relapse rates [95,96]. 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.

7.0 Overlapping toxicity profiles of antiretrovirals and TB therapy

Adverse reactions to drugs are common among patients with HIV-related tuberculosis 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 South East of England [97]. 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 in 12 patients (7%). Rifampicin was frequently implicated by the treating physicians, and was considered responsible for almost two-thirds of adverse events.

When compared to HIV-negative TB patients, a higher rate of serious (grade III/IV) toxicities has been found in TB/HIV coinfection, but there was no difference in discontinuation rate of TB medication between the groups [98].

7.1 Hepatotoxicity

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

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

Hepatotoxicity due to isoniazid in the general population increases with age, occurring in less than 0.3% of those under 35 years and 2.3% of those over 50 years. It is also more likely with heavy alcohol intake, hepatitis C 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 above. The rates of adverse reaction were 26% in one HIV cohort compared with 3% in the HIV-uninfected group, and other studies have shown similar results [99,100]

Management of hepatitis:

- I. Stop all potentially hepatotoxic drugs immediately, including isoniazid, rifampicin, pyrazinamide, antiretrovirals and co-trimoxazole.
- 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 and until the cause of the hepatitis is identified then 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).
- VI. If the drugs cannot be restarted or the initial reaction was life-threatening then an alternative regimen should be used (see 7.2).

7.2 Pre-existing liver disease

The risk of hepatotoxicity with pre-existing liver disease is greatest with pyrazinamide, then rifampicin and then isoniazid. 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. However, if the serum AST is more than three-times normal, even before starting treatment, 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 are 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 [101,102].

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 600mg 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 nucleoside analogues ddI, ddC and d4T cause peripheral neuropathy and there is an additive toxicity of isoniazid when used with d4T [103]. In individuals already taking these antiretrovirals alternatives should be found if possible. **[All]**

Pyridoxine 10–25mg daily should be used in all patients receiving isoniazid.

7.4.1 Recommendation

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-TB 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. Sub-therapeutic plasma drug concentrations may cause treatment failure and drug resistance [104,105]. Although some studies show lower peak concentrations of rifampicin and ethambutol as well as lower AUC compared with controls [106–110], there are other data suggesting that rifampicin is well absorbed in HIV patients including those with AIDS or diarrhoea [111].

8.2 Therapeutic drug monitoring (TDM)

8.2.1 TDM of TB drugs: [BII]

Based on the limited amount of available data [112], TB drug therapeutic monitoring might be useful (but is often not very helpful) in patients:

- at high risk of malabsorption of TB drugs;
- responding inadequately to DOT with first-line drugs;
- with multi-drug resistant TB;
- on non-standard TB regimens or taking non-standard doses.

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, for instance 1, 2 and 4 hours post-dose. 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 patients is not known. Prospective trials are underway in developing countries to answer this question Blanc FX, Havlir DV, Onyebujoh PC, Thim S, Goldfeld AE, Delfraissy JF Treatment strategies for HIV-infected patients with tuberculosis: ongoing and planned clinical trials [49].

Physicians have to balance the risk of HIV progression against the hazards of starting HAART, which include toxicities, side effects, immune reconstitution inflammatory syndrome (IRIS) and drug interactions. Antiretroviral and anti-tuberculosis drugs share similar routes of metabolism and elimination, and extensive drug interactions may result in sub-therapeutic plasma levels of either or both (see 6.0). Overlapping toxicity profiles may result in the interruption of TB or HIV regimens with subsequent microbiological or virological failure (see 7.0). 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 [113–115].

Patients with HIV and a CD4 cell count >200 cells/ μ L have a low risk of HIV disease progression or death during the subsequent 6 months of tuberculosis treatment. They should have their CD4 cell count monitored regularly and antiretroviral therapy withheld if possible during the short-course tuberculosis treatment.

Most patients with tuberculosis in the UK 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. Some recommend that antiretroviral therapy be delayed until the first 2 months of tuberculosis therapy has been completed but 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 [116–120]. Starting HAART early in severely immunosuppressed HIV-positive patients presenting with TB is associated with decreased mortality and a lowering of the rates of progression [97]. A South African study of those with low CD4 cell counts starting HAART early showed rates of IRIS are high but mortality is low [121]. 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 modelling study of early (<2 months) versus deferred HAART in patients with TB and CD4 count <200 cells/ μ L found that early HAART was preferable, assuming an IRIS-related mortality of less than 4.6%, which is the case in most cohorts [122]. Further data will emerge from ongoing studies.

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

CD4 count, cells/ μ L	When to start HAART
<100	As soon as practical
100–200	As soon as practical, but can wait until after completing 2 months TB treatment
>200 and <350	After completing 6 months TB treatment

CD4 count should be checked every 6–8 weeks.

10.0 Directly observed therapy (DOT)

There have been no randomized controlled trials or systematic reviews into the use of DOT in TB/HIV coinfection. However, the use of directly observed therapy is seen as the gold standard by WHO and CDC for the treatment of HIV-related tuberculosis, 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].

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

Patient-centred care should be at the core of multidisciplinary management and should always include an adherence strategy. This may include DOT/supervised therapy for HAART [123]. [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 tuberculosis 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 health care workers to ensure adherence, is an approach being examined more closely.

11.0 Management of relapse, treatment failure and drug resistance

11.1 Relapse

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

- culture-positive again;
- or 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. 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 non-rifamycin 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 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, or 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 such as streptomycin or amikacin, with or without additional oral drugs such as para-aminosalicylic acid (PAS), cycloserine, prothionamide and clarithromycin. **[AIII]**

11.2 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 tuberculosis 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:

- non-adherence;
- drug resistance;
- malabsorption of drugs;
- laboratory error;
- extreme biological variation resulting in a prolonged time to respond.

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 streptomycin, and an oral agent such as para-aminosalicylic acid (PAS), cycloserine, prothionamide or clarithromycin. Once drug susceptibility test results are available, the regimen should be adjusted accordingly.

11.3 Management of INH resistance without rifampicin or other significant drug resistance

The ATS and BTS have recommended several treatment regimens for the treatment of INH-resistant TB, which include a). 6REZ, b). 2REZ/10RE, c). 12RE and d). 2REZ or S/7RE, but the efficacies of these regimens have not been fully evaluated in prospective trials.

If INH resistance is only discovered at 2 months of initial four drug treatment then one can either continue with RE for 10 months or continue REZ for a total of six months. In patients with extensive disease, one might continue both E and Z with R for 9–12 months or even use RE with a quinolone.

11.4 Multi-Drug resistant-TB (MDR-TB)/and extensively resistant TB XDRTB [142]

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 TB therapy or culture positive at 3 months.

All such patients should be referred to regional treatment centres, regardless of HIV status. There is a web based discussion forum that can be used by the physician managing such cases. Please contact damian.cullen@lhch.nhs.uk.

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 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 patients has also not been established, but many cases are treated for at least 18 months to 2 years after cultures revert to negative.

The drugs used to treat MDR-TB include fluoroquinolones, streptomycin, ethionamide, cycloserine, kanamycin, amikacin, capreomycin and para-aminosalicylate. There are no published data regarding interactions between these drugs and antiretrovirals. Ethionamide has significant interactions because it is metabolized by the CYP450 system, although which isoenzyme is unknown. There is no guidance about dose adjustment but therapeutic drug monitoring 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.

Surgical resection in the management of pulmonary MDR-TB has had mixed results and its role has not been established in randomized studies. Nebulised interferon has been used in some patients before surgery in order to render sputum smears negative. It has also been used to reduce spread of infection when all other treatments have failed.

11.5 XDR-TB

Extensively drug-resistant 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 [124] but is fortunately still rare in the UK. As for MDR-TB, all cases should be referred to consultants with expertise in management.

11.6 Chemo preventative therapy in MDR/XDR-TB

In HIV-infected individuals exposed to MDR-TB/XDR-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. Further guidance is contained in [183].

12.0 Pregnancy and breast-feeding

Tuberculosis in pregnancy carries a risk of tuberculosis in the fetus. 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 (IUATLD). These first-line drugs cross the placenta but do not appear to be teratogenic.

Streptomycin can cause congenital deafness [125] and prothionamide is teratogenic, so both should be avoided. Ethionamide causes birth defects at high doses in animals [126].

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 regimes. **[AIII]**

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

13.1 Prophylaxis in those at risk of TB

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 than in those not prescribed antiretroviral therapy. The protective effect of HAART was greatest in symptomatic patients and those with advanced immune suppression and was not apparent in those with CD4 counts >350 cells/ μ L [127–129]. 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 [130–138]. A protective effect of isoniazid is found only in those who are tuberculin skin test-positive, and appears to only last 2 to 4 years as compared with 19 years or more in non-HIV populations. However, the populations studied have mainly been in areas of high TB prevalence, where most TB arises from new infection rather than reactivation. Apart from recognized outbreaks, there is little evidence to suggest that reinfection (as opposed to reactivation) is a major

factor in the UK. Chemo-preventative therapy might therefore have a longer duration of effect in the UK 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. The epidemiological situation in the UK is different however.

A potential approach in HIV patients at increased risk of TB, for instance immigrants, is to give isoniazid prophylaxis until the CD4 count has risen on HAART above a reasonable threshold, for instance 200–300 cells/ μ L. Patients may need isoniazid for more than 1 year and the effects of this, including hepatotoxicity, are relatively unknown. Chemo-preventative therapy seemed to have no effect on HIV progression and mortality in the long-term [134]. There are also concerns that widespread isoniazid monotherapy might speed the emergence of drug resistant TB [139,140]. In a recent meta analysis of 13 studies investigating the risk of developing isoniazid resistance as a result of chemopreventative therapy, the relative risk for resistance was 1.45 (95% confidence interval 0.85–2.47). Results were similar when studies of HIV-uninfected and HIV-infected persons were considered separately. This suggests that the risk is not significant [140].

Chemo-preventative therapy for all HIV patients is not routinely recommended at present but can be considered in patients with a positive mantoux or IGRA test [DII], however, there are no data from developed countries on whether giving chemopreventative therapy to patients with a positive IGRA will reduce the risk of developing TB below that of the effect seen by treating patients with HAART.

It is important to note that HIV-positive patients who are in close and prolonged contact with patients with proven or assumed active tuberculosis should be screened for TB and if no active disease is found chemopreventative therapy recommended. The utility of repeat TST and IGRA tests in this situation is not known.

Though few data are available for patients receiving cancer chemotherapy where the prognosis is > 1 year it may be reasonable to give isoniazid prophylaxis to those with a positive gamma interferon test who do not have active tuberculosis.

13.2 Treatment of latent tuberculosis

Individuals with a positive Interferon- γ assay but no clinical or radiological evidence of active TB are assumed to have latent disease. 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 [141] (see also 14.0).

Alternatives for treating latent tuberculosis:

- isoniazid for 6 months;
- rifampicin with isoniazid for 3 months;
- rifampicin for 4 months.

Shorter courses using other drugs have been tried to help overcome poor adherence. Rifampicin and pyrazinamide given three times per week for 2 months has been used successfully in HIV-positive patients [136–138] but is not recommended [DII] because in

non-HIV patients it has been associated with severe or fatal hepatic reactions in at least 50 cases in the USA [144].

13.3 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 [145,146]. Such a strategy may in fact prevent reinfection, which is more common than true reactivation in such settings [147]. 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 [148].

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

14.0 Immune reconstitution inflammatory syndrome (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 [149–168]. The phenomenon is known as immune reconstitution inflammatory syndrome (IRIS), immune reconstitution disease (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 [169–174].

Definition

IRIS does not have a widely accepted definition although an international attempt is underway to standardize one [175]. A definition for resource-poor countries has been developed and cases need to meet the following three criteria:

- an initial clinical response to TB treatment, based on a combination of some of the following factors: cessation of fever, relief of pulmonary symptoms, decrease in lymph node size, termination of meningeal signs (depending on presenting symptoms);
- new persistent fevers without an identifiable source or reason (e.g., an allergic reaction, malaria) and/or worsening or emergence of dyspnoea, and/or stridor, and/or increase in lymph node size, and/or development of abscesses, and/or development of abdominal pain with ultrasound evidence of abdominal adenopathies and/or unexplained CNS symptoms;
- adequate adherence to ART and TB treatment.

It is characterised by worsening or appearance of new signs, symptoms, or radiographic abnormalities, occurring after 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 tuberculosis;
- 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 AAFB smear does not exclude diagnosis of IRIS);
- appropriate investigations have excluded disease due to other pathogens;
- drug hypersensitivity is excluded;
- a response to corticosteroids does not confirm diagnosis of IRIS.

14.1 Epidemiology of IRIS

In the era of HAART, IRIS has been reported widely and occurred in 36% (12/33) and 32% (6/19) of patients in two studies [159,165]. In another study IRIS was not significantly more common in patients receiving HAART (3 of 28 cases or 11%) compared with patients not on antiretroviral treatment (3 of 44 cases or 7%) [166]. The majority of reactions occur within 60 days of initiating HAART, with a median of 15 days [167]. IRIS does not appear to be associated with any particular antiretroviral regimen or drug class [176]. 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 copies/mL).

With limited data it is difficult to predict risk of IRIS, but the following appear to be relevant [121,176,177,179]:

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

14.2 Clinical features of IRIS

IRIS most often presents with fever and increased or new lymphadenopathy [180]. The skin overlying lymph nodes is often inflamed and dusky red, and the nodes can spontaneously rupture. Pleural and pericardial effusions, ascites, psoas abscess, cutaneous lesions and new or expanding central nervous system tuberculomata have also been described, as have worsening pulmonary lesions.

14.3 Management of IRIS [AIII]

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

14.3.1 Corticosteroids

The management of IRIS may require moderate to high-dose corticosteroids to control symptoms. Prednisone or methylprednisolone have been used at a dose of 1–1.5 mg/kg and gradually reduced after 1 to 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 relapse 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.

14.3.2 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, worsened by the use of steroids.

Non-steroidal 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 [181].

Preliminary data suggest a potential role for IL-2 and granulocyte-macrophage colony stimulating factor (GM-CSF) in improving abnormal T cell responses [182]. Other therapies such as 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 [143].

15.0 Prevention and control of transmission

Guidelines for prevention and control of transmission of TB include:

- Stopping Tuberculosis in England: An action plan from the Chief Medical Officer, published by Department of Health, 7 October 2004;
- Tuberculosis prevention and treatment: a toolkit for planning, commissioning and delivering high-quality services in England, published by Department of Health, 15 June 2007;
- The Prevention and Control of Tuberculosis in the United Kingdom published by The Interdepartmental Working Group on Tuberculosis, 1998.

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 non-responding 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 [183];
- aerosol generating procedures (bronchoscopy, sputum induction or nebuliser 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 health care workers and other contacts.

15.1 Notification

TB is a notifiable disease in the UK 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 tuberculosis still die. It is important that as many such patients as feasible are examined by autopsy. This categorises the pathology and enables audit of medical practice. The significant categories of causes of death include:

- active, progressive tuberculosis;
- secondary effects of tuberculosis (e.g. lung haemorrhage, meningovascular obstruction);
- IRIS affecting one or more critical organs (e.g. lung, 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
CYP	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
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	non-nucleoside 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 end points
- II. Clinical trials either not randomized or conducted in other populations
- III. Expert opinion

* Adapted from Gross PA, Barrett TL, Dellinger EP *et al. Clin Infect Dis* 1994; **18**: 421.

Table 3: Drugs used in the treatment of TB

First-line drugs	Second-line drugs
isoniazid	clarithromycin, azithromycin
rifampicin*	ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin
pyrazinamide	streptomycin, amikacin, kanamycin
ethambutol	cycloserine
	protionamide, ethionamide
rifabutin	para-aminosalicylic acid
	capreomycin, viomycin, enviomycin
	amoxicillin with clavulanic acid
	linezolid

* rifabutin may be substituted for rifampicin in some situations, e.g. drug interactions

Only physicians skilled in the treatment of TB should prescribe TB regimens.

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	Clarithromycin
Abacavir	◆	◆	◆
Didanosine EC	◆	◆	◆
Emtricitabine	◆	◆	◆
Lamivudine	◆	◆	◆
Stavudine	◆	◆	◆
Tenofovir	◆	◆	◆
Zidovudine	◆	◆	◆

Table 5: Non-nucleoside reverse transcription inhibitors (NNRTIs)

	Rifampicin	Rifabutin	Clarithromycin
Efavirenz	<p>■</p> <p>Efavirenz levels ↓ by 20–30%</p> <p>Efavirenz increased to 800mg daily if weight >50kg</p> <p>Efavirenz at 600mg daily if weight <50kg</p> <p>Rifampicin at standard dose</p>	<p>■</p> <p>Rifabutin levels ↓ by 38%.</p> <p>Rifabutin increased to 450mg daily</p> <p>Efavirenz at standard dose</p>	<p>◆</p> <p>No significant interaction</p> <p>Use standard doses</p> <p>Reports of ↑ rates of rash: consider Azithromycin instead (no interaction)</p>
Nevirapine	<p>●</p> <p>Nevirapine levels ↓ 20–55%</p> <p>No change in rifampicin</p> <p>Not recommended</p>	<p>◆</p> <p>Use standard doses but little data so not recommended</p>	<p>◆</p> <p>No significant interaction</p> <p>Use standard doses</p>
Etravirine	No data available	<p>◆</p> <p>Use standard doses but little data so use with caution</p>	<p>Use with caution</p> <p>Use alternative when possible</p>
TMC-278	<p>●</p> <p>TMC-278 levels ↓ 90%</p> <p>Do not use</p>	<p>■</p> <p>TMC-278 levels ↓ 50%</p> <p>Double dose TMC-278</p>	

Table 6: Protease inhibitors (PIs)

PI	Rifampicin	Rifabutin	Clarithromycin
Amprenavir	● 81% ↓ level amprenavir Do not use	■ Reduce rifabutin to 150mg daily	◆
Atazanavir	● 80% ↓ level atazanavir Do not use	■ Reduce rifabutin to 150mg daily	
Atazanavir/ Ritonavir	● ↓ level atazanavir Do not use	■ Reduce rifabutin to 150mg 3x per week	
Darunavir/ Ritonavir	● No data Do not use	■ Reduce rifabutin to 150mg 3x per week	
Fosamprenavir	● ↓ levels amprenavir Do not use	■ Reduce rifabutin to 150mg daily	◆
Fosamprenavir/ Ritonavir	● ↓ levels amprenavir Do not use	■ Reduce rifabutin to 150mg 3x per week	◆
Indinavir	● 89% ↓AUC for indinavir. Do not use	● ↓AUC for indinavir and ↑AUC 204% for rifabutin. Do not use	◆
Lopinavir/ Ritonavir	● 75% ↓ level lopinavir Higher doses cause hepatotoxicity Do not use	■ Reduce rifabutin to 150mg 3x per week	◆
Nelfinavir	● 82% ↓AUC for nelfinavir. Do not use	■ Reduce rifabutin to 150mg daily	◆
Ritonavir as single agent	■ 35% ↓ level ritonavir Can be used at 600mg twice daily but very poorly tolerated		
Saquinavir	● 80% ↓ level saquinavir Do not use	● Do not use	◆
Saquinavir/ Ritonavir	● ↓ level saquinavir Higher doses cause hepatotoxicity Do not use	■ Reduce rifabutin to 150mg 3x per week	◆
Tipranavir/ Ritonavir	● 80% ↓ level tipranavir Do not use	■ Reduce rifabutin to 150mg 3x per week	

Table 7: Integrase inhibitors and entry inhibitors

	Rifampicin	Rifabutin	Clarithromycin
Elvitegravir	● Elvitegravir levels ↓ Do not use	No data	
Raltegravir	● Raltegravir levels ↓ 60% Even at 800mg bd use with caution C _{min} ↓ %	No data	
Maraviroc	■ Maraviroc levels ↓ Double maraviroc dose	◆ Use standard doses	
Enfuvirtide (T-20)	◆ No interaction Use standard doses	◆ No interaction Use standard doses	

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

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

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

Adapted from Girling DJ, Adverse effects of antituberculous drugs. *Drugs* 1982; **23**: 56.

Patients who are infectious should be treated with two active drugs whilst 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 non-infectious, 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 [184] and adopted by the Joint Tuberculosis Committee in 1998:

Once liver function is normal the original drugs can be reintroduced sequentially in the order isoniazid, rifampicin, pyrazinamide, with daily monitoring of the patient's condition and liver function. Isoniazid should be introduced initially at 50mg/day increasing sequentially to 300mg/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 75mg/day can be added, increasing to 300mg/day after 2–3 days, and then after a further 2–3 days without reaction to 450mg(<50kg) or 600mg(>50kg) per day as appropriate for the patient's weight, and then continued. Finally pyrazinamide can be added at 250mg/day, increasing to 1gm/day after 2–3 days and then 1.5gm (<50kg) or 2.0gm (>50kg) per day.

Example of alternative schedule

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

18.0 Key Points:

18.1 Treatment of uncomplicated non-CNS tuberculosis

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 3 or 5 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.

19.0 References

1. National Institute for Health and Clinical Excellence. *Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control*. 2006 London, UK. Available from www.nice.org.uk
2. World Health Organization. *Global tuberculosis control - surveillance, planning, financing*. Geneva: World Health Organization, 2008.
3. Ahmed AB, Abubakar I, Velpech V *et al*. The growing impact of HIV infection on the epidemic of tuberculosis in England and Wales. *Thorax* 2007; **62**: 672–676.
4. Anderson SA, Maguire H, Carless J. Tuberculosis in London: a decade and a half of no decline. *Thorax* 2007; **62**: 162–167.
5. Jones BE, Young SMM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis* 1993; **148**: 1292–1297.
6. Chaisson RE, Schechter GF, Theuer CP, Rutherford GW, Echenberg DF, Hopewell PC. Tuberculosis in patients with acquired immunodeficiency syndrome: clinical features, response to therapy, and survival. *Am Rev Respir Dis* 1987; **136**: 570–574.
7. Ackah AN, Coulibaly D, Digbeu H *et al*. Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Cote d'Ivoire. *Lancet* 1995; **345**: 607–610.
8. Collins KR, Quinones-Mateu ME, Toossi Z, Arts EJ. Impact of tuberculosis on HIV-1 replication, diversity and disease progression. *AIDS Rev* 2002; **4**: 165–176.
9. Holden M, Dubin MR, Diamond PH. Frequency of negative intermediate-strength tuberculin sensitivity in patients with active tuberculosis. *N Engl J Med* 1971; **285**: 1506–1509.
10. Graham NMH, Nelson KE, Solomon L *et al*. Prevalence of tuberculin positivity and skin test anergy in HIV-1-seropositive and seronegative intravenous drug users. *J Am Med Assoc* 1992; **267**: 369–373.
11. Markowitz N, Hansen NI, Wilcosky TC *et al*. Tuberculin and anergy testing in HIV-seropositive and HIV-seronegative persons. *Ann Intern Med* 1993; **119**: 185–193.
12. Huebner RE, Schein MF, Hall CA, Barnes SA. Delayed-type hypersensitivity anergy in human immunodeficiency virus-infected persons screened for infection with *Mycobacterium tuberculosis*. *Clin Infect Dis* 1994; **19**: 26–32.
13. Johnson MP, Coberly JS, Clermont HC *et al*. Tuberculin skin test reactivity among adults infected with human immunodeficiency virus. *J Infect Dis* 1992; **166**: 194–198.
14. Chapman AL, Munkanta M, Wilkinson KA *et al*. Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of *Mycobacterium tuberculosis*-specific T cells. *AIDS* 2002; **16**: 2285–2293.
15. Richeldi L, Losi M, Cerri S, Casali L, Fabbri LM, Ferrara G. Using ELISpot technology to improve the diagnosis of tuberculosis infection: from the bench to the T-SPOT.TB assay. *Expert Rev Resp Med* 2008; **2**: 253–260.

16. Rangaka MX, Diwakar L, Seldon R *et al.* Clinical, immunological, and epidemiological importance of T cell responses in HIV-infected Africans. *Clin Infect Dis* 2007; **44**: 1639–1646.
17. Brock I, Ruhwald M, Lundgren B *et al.* Latent tuberculosis in HIV positive, diagnosed by the *M. tuberculosis* specific interferon-gamma test. *Respir Res* 2006; **7**: 56.
18. The Interdepartmental Working Group on Tuberculosis. *The Prevention and Control of Tuberculosis in the United Kingdom*. DOH, 1998. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4006196.
19. Yanai H, Uthavivoravit W, Mastro TD *et al.* Utility of tuberculin and anergy skin testing in predicting tuberculosis infection in human immunodeficiency virus-infected persons in Thailand. *Int J Tuberc Lung Dis* 1997; **1**: 427–434.
20. Moreno S, Bavaia-Etxabury J, Bouza E *et al.* Risk for developing tuberculosis among anergic patients infected with HIV. *Ann Intern Med* 1993; **119**: 194–198.
21. Luetkemeyer AF, Charlebois ED, Flores LL *et al.* Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-infected individuals. *Am J Respir Crit Care Med* 2007; **175**: 737–742.
22. Mayanja-Kizza H, Jones-Lopez E, Okwera A *et al.* Immuno-adjunct prednisolone therapy for HIV-associated tuberculosis: a phase 2 clinical trial in Uganda. *J Infect Dis* 2005; **191**: 856–865.
23. Elliott AM, Luzzza H, Quigley MA *et al.* A randomized, double-blind, placebo-controlled trial of the use of prednisolone as an adjunct to treatment in HIV-1-associated pleural tuberculosis. *J Infect Dis* 2004; **190**: 869–878.
24. Thwaites GE, Nguyen DB, Nguyen HD *et al.* Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004; **351**: 1741–1751.
25. Hakim JG, Ternouth I, Mushangi E *et al.* Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. *Heart* 2000; **84**: 183–188.
26. Nahid P, Gonzales LC, Rudoy I *et al.* Treatment outcomes of patients with HIV and tuberculosis. *Am J Respir Crit Care Med* 2007; **175**: 1199–1206.
27. Chaisson RE, Clermont HC, Holt EA *et al.* Six-month supervised intermittent tuberculosis therapy in Haitian patients with and without HIV infection. *Am J Respir Crit Care Med* 1996; **154**: 1034–1038.
28. Alwood K, Keruly J, Moore-Rice K, Stanton DL, Chaulk CP, Chaisson RE. Effectiveness of supervised, intermittent therapy for tuberculosis in HIV-infected patients. *AIDS* 1994; **8**: 1103–1108.
29. Acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis with intermittent rifamycin-based regimens. *MMWR* 2002, **51**: 214–215.
30. El-Sadr WM, Perlman DC, Matts JP, Nelson ET, Cohn DL, Salomon N. Evaluation of an intensive intermittent induction regimen and duration of short course treatment for human immunodeficiency virus-related pulmonary tuberculosis. *Clin Infect Dis* 1998, **26**: 148–158.

31. Vernon A, Burman W, Benator D, Khan A, Bozeman L, Tuberculosis Trials Consortium. Acquired rifamycin mono-resistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. *Lancet* 1999; **353**: 1843–1847.
32. Nettles RE, Mazo D, Alwood K *et al*. Risk factors for relapse and acquired rifamycin resistance after directly observed tuberculosis treatment: a comparison by HIV serostatus and rifamycin use. *Clin Infect Dis* 2004; **38**: 731–736.
33. Burman W, Benator D, Vernon A *et al*. Tuberculosis Trials Consortium. Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am J Respir Crit Care Med* 2006; **173**: 350–356.
34. Gonzalez Montaner LJ, Natal S, Yonchaiyud P, Olliaro P. Rifabutin for the treatment of newly diagnosed pulmonary tuberculosis: a multinational, randomized, comparative study versus rifampicin. *Tuber Lung Dis* 1994; **75**: 341–347.
35. McGregor MM, Olliaro P, Womarans L *et al*. Efficacy and safety of rifabutin in the treatment of patients with newly diagnosed pulmonary tuberculosis. *Am J Respir Crit Care Med* 1996; **154**: 1462–1467.
36. Schwander S, Rusch-Gerdes S, Mateega A *et al*. A pilot study of antituberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis: a single-blind randomized evaluation in Ugandan patients with HIV-1 infection and pulmonary tuberculosis. *Tubercle Lung Dis* 1995; **76**: 210–218.
37. Narita M, Stambaugh JJ, Hollender ES, Jones D, Pitchenik AE, Ashkin D. Use of rifabutin with protease inhibitors for human immunodeficiency virus infected patients with tuberculosis. *Clin Infect Dis* 2000; **30**: 779–783.
38. Vernon A, Burman W, Benator D, Khan A, Bozeman L. Relapse with rifamycin mono-resistant tuberculosis in HIV-infected patients treated with supervised once-weekly rifapentine and isoniazid. *Lancet* 1999; **353**: 1843–1847.
39. Sterling TR, Alwood K, Gachuhi R *et al*. Relapse rates after shortcourse (6-month) treatment of tuberculosis in HIV-infected and uninfected persons. *AIDS* 1999; **13**: 1899–1904.
40. Kassim S, Sassan-Morokro M, Ackah A *et al*. Two-year follow-up of persons with HIV-1- and HIV-2-associated pulmonary tuberculosis treated with short-course chemotherapy in West Africa. *AIDS* 1995; **9**: 1185–1191.
41. El-Sadr WM, Perlman DC, Denning E, Matts JP, Cohn DL. A review of efficacy studies of 6-month short-course therapy for tuberculosis among patients infected with human immunodeficiency virus: differences in study outcomes. *Clin Infect Dis* 2001; **32**: 623–632.
42. Diel R, Wrighton-Smith P, Zellweger J-P. Cost-effectiveness of interferon- release assay testing for the treatment of latent tuberculosis. *Eur Resp J* 2007; **30**: 321–332.
43. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53**: 536–548.
44. Perriens JH, St. Louis ME, Mukadi YB *et al*. Pulmonary tuberculosis in HIV infected patients in Zaire: a controlled trial of treatment for either 6 or 12 months. *N Engl J Med* 1995; **332**: 779–784.

45. Centers for Disease Control and Prevention. Treatment of Tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. *MMWR* 2003; **52** (No.RR-11).
46. Li AP, Reith MK, Rasmussen A *et al.* Primary human hepatocytes as a tool for the evaluation of structure-activity relationship in cytochrome P450 induction potential of xenobiotics: evaluation of rifampicin, rifapentine, rifabutin. *Chemico-Biol Interact* 1997; **107**: 17–30.
47. Rae JM, Johnson MD, Lippman ME, Flockhart DA. Rifampin is a selective, pleiotropic inducer of drug metabolism genes in human hepatocytes: studies with cDNA and oligonucleotide expression arrays. *J Pharmacol Exp Ther* 2001; **299**: 849–857.
48. Boulle A, Van Cutsem G, Cohen K *et al.* Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA* 2008; **300**: 530–539.
49. Blanc FX, Havlir DV, Onyebujoh PC, Thim S, Goldfeld AE, Delfraissy JF. Treatment strategies for HIV-infected patients with tuberculosis: ongoing and planned clinical trials. *J Infect Dis* 2007; **196**: S46–S51.
50. Perucca E, Grimaldi R, Frigo GM, Sardi A, Monig H, Ohnhaus EE. Comparative effects of rifabutin and rifampicin on hepatic microsomal enzyme activity in normal subjects. *Eur J Clin Pharmacol* 1998; **34**: 595–599.
51. Sun E, Heath-Chiozzi M, Cameron DW *et al.* Concurrent ritonavir and rifabutin increases risk of rifabutin-associated adverse events. XI International Conference on AIDS, Vancouver, Canada, 1996 [Abstr. MoB171].
52. Gallicano KD, Sahai J, Shukla VK *et al.* Induction of zidovudine glucuronidation and amination pathways by rifampicin in HIV-infected patients. *Br J Clin Pharmacol* 1999; **48**: 168–179.
53. Burger DM, Meenhorst PL, Koks CHW, Beijnen JH: Pharmacokinetic interaction between rifampicin and zidovudine. *Antimicrob Agents Chemother* 1993, **37**: 1426–1431.
54. DART Virology Group and Trial Team. Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1 infected adults in Africa. *AIDS* 2006; **20**: 1391–1399.
55. Srikantiah P, Walusimbi MN, Kayanja HK *et al.* Early virological response of zidovudine/lamivudine/abacavir for patients co-infected with HIV and tuberculosis in Uganda. *AIDS* 2007; **21**: 1972–1974.
56. Gulick RM, Ribaud HJ, Shikuma CM *et al.* Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med* 2004; **350**: 1850–1861.
57. Moyle G, Higgs C, Teague A *et al.* An open-label, randomized comparative pilot study of a single-class quadruple therapy regimen versus a 2-class triple therapy regimen for individuals initiating antiretroviral therapy. *Antivir Ther* 2006; **11**: 73–78.
58. Lopez-Cortes LF, Ruiz-Valderas R, Viciano P *et al.* Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet* 2002; **41**: 681–690.

59. Soy D, Lopez E, Sarasa M *et al.* Population pharmacokinetic modeling in HIV patients with tuberculosis treated with efavirenz and rifampicin. Program and Abstracts of the 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec City, Canada, 28–30 April, 2005 [Abstr. 15].
60. Matteelli A, Regazzi M, Villani P *et al.* Multiple-dose pharmacokinetics of efavirenz with and without the use of rifampicin in HIV-positive patients. *Curr HIV Res* 2007; **5**: 349–353.
61. Manosuthi W, Kiertiburanakul S, Sungkanuparph S *et al.* Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. *AIDS* 2006; **20**: 131–132.
62. Pedral-Samapio D, Alves C, Netto E *et al.* Efficacy of efavirenz 600 mg dose in ARV therapy regimen for HIV patients receiving rifampicin in the treatment of tuberculosis. Tenth Conference on Retroviruses and Opportunistic Infections, Boston, 2003 [Abstr. 784].
63. Ribaldo H, Clifford D, Gulick R *et al.* Relationship between efavirenz pharmacokinetics, side effects, drug discontinuation, virologic response and race: results from ACTG A5095/A5097s. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, 8–11 February 2004 [Abstr. 132].
64. Haas D, Ribaldo H, Kim R *et al.* A common CYP2B variant is associated with efavirenz pharmacokinetics and central nervous system side effects: AACTG Study NWCS214. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, Feb 2004 [Abstr. 133].
65. Brennan-Benson P, Lys R, Harrison T *et al.* Pharmacokinetic interactions between efavirenz and rifampicin in the treatment of HIV and tuberculosis: one size does not fit all. *AIDS* 2005; **19**: 1541–1543.
66. Oliva J, Moreno S, Sanz J *et al.* Co-administration of rifampin and nevirapine in HIV-infected patients with tuberculosis. *AIDS* 2003; **17**: 637–638.
67. Ribera E, Pou L, Lopez RM *et al.* Pharmacokinetic interaction between nevirapine and rifampicin in HIV-infected patients with tuberculosis. *J Acquir Immune Defic Syndr* 2001; **28**: 450–453.
68. Robinson P, Lamson M, Gigliotti M *et al.* Pharmacokinetic interaction between nevirapine and rifampicin [abstract]. In: *Program and abstracts of the 12th World AIDS Conference*. Geneva: Switzerland, 1998. [Abstr. 60623]
69. Autar RS, Wit FWNM, Sankote J *et al.* Nevirapine plasma concentrations and concomitant use of rifampin in patients coinfecting with HIV-1 and tuberculosis. *Antiviral Ther* 2005; **10**: 937–943.
70. Cohen K, Van Cutsem G, Boule A *et al.* Effect of rifampicin-based antitubercular therapy on nevirapine plasma concentrations in South African adults with HIV-associated tuberculosis. *J Antimicrob Chemother* 2008; **61**: 389–393.
71. Ramachandran G, Hemanthkumar AK, Rajasekaran S *et al.* Increasing nevirapine dose can overcome reduced bioavailability due to rifampicin coadministration. *J Acquir Immune Defic Syndr* 2006; **42**: 36–41.
72. Avihingsanon A, Manosuthi W, Kantipong P *et al.* PK and 12 weeks efficacy of NVP 400 vs. 600 mg daily in HIV+ patients with active TB receiving rifampin. 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles, 2007 [Abstr. 576].

73. Van Cutsem G, Cohen K, Bedelu M *et al.* TB/HIV co-infected patients on rifampicin containing treatment have equivalent ART treatment outcomes, and concurrent use of nevirapine is not associated with increased hepatotoxicity. 3rd Conference on HIV Pathogenesis and Treatment 2005, Rio de Janeiro, 2005. [Abstr. WePp0303]
74. van Heeswijk R. The effects of CYP3A4 modulation on the pharmacokinetics of TMC278, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI). Programme and Abstracts of the 7th International Workshop on Clinical Pharmacology of HIV Therapy, Lisbon, 20–22 April 2006 [Abstr. 74].
75. Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivisto KT. Pharmacokinetic interactions with rifampicin: clinical relevance. *Clin Pharmacokinet* 2003; **42**: 819–850.
76. Moreno S, Podzamczar D, Blazquez R *et al.* Treatment of tuberculosis in HIV-infected patients: safety and antiretroviral efficacy of the concomitant use of ritonavir and rifampin. *AIDS* 2001; **15**: 1185–1187.
77. Bonfanti P, Valsecchi L, Parazzini F *et al.* Incidence of adverse reactions in HIV patients treated with protease inhibitors: a cohort study. Coordinamento Italiano Studio Allergia e Infezioneda HIV (CISAI) Group. *J Acquir Immun Defic Syndr* 2000; **23**: 236–245.
78. Veldkamp AI, Hoetelmans RMW, Beijnen JH, Mulder JW, Meenhorst PL. Ritonovir enables combined therapy with rifampin and saquinavir. *Clin Infect Dis* 1999; **29**: 1586.
79. Ribera E, Azuaje C, Lopez RM *et al.* Once-daily regimen of saquinavir, ritonavir, didanosine, and lamivudine in HIV-infected patients with standard tuberculosis therapy (TBQD study). *J Acquir Immun Defic Syndr* 2005; **40**: 317–323.
80. Ribera E, Azuaje C, Lopez RM *et al.* Pharmacokinetic interaction between rifampicin and the once-daily combination of saquinavir and low-dose ritonavir in HIV-infected patients with tuberculosis. *J Antimicro Chemother* 2007; **59**: 690–697.
81. Gray A, Abdool Karim SS, Gengiah TN. Ritonavir/saquinavir safety concerns curtail antiretroviral therapy options for tuberculosis-HIV-co-infected patients in resource-constrained settings. *AIDS* 2006; **20**: 302–303.
82. Bertz R, Hsu A, Lam W *et al.* Pharmacokinetic interactions between lopinavir/ritonavir (ABT-378r) and other non-HIV drugs. *AIDS* 2000; **14**(Suppl 4): S100.
83. La Porte CJ, Colbers EP, Bertz R *et al.* Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampin in healthy volunteers. *Antimicrob Agents Chemother* 2004; **48**: 1553–1560.
84. Nijland H, L'homme R, Rongen G *et al.* Unexpected high incidence of nausea, vomiting and asymptomatic elevations of AST/ALT enzymes in healthy volunteers receiving rifampin and adjusted doses of lopinavir/ritonavir tablets. International Workshop on Clinical Pharmacology of HIV Therapy, Budapest, 2007 [Abstr. 51].
85. Acosta E, Kendall M, Gerber J *et al.* and the A5213 Study Team. Effect of rifampin on pharmacokinetics and safety of twice-daily atazanavir: ACTG Protocol A5213. 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles, 2007 [Abstr. 575].
86. Burger DM, Agarwala S, Child M *et al.* Effect of rifampin on steady-state pharmacokinetics of atazanavir with ritonavir in healthy volunteers. *Antimicrob Agents Chemother* 2006; **50**: 3336–3342.

87. Mallolas J, Sarasa M, Nomdedeu M *et al.* Pharmacokinetic interaction between rifampicin and ritonavir-boosted atazanavir in HIV-infected patients. *HIV Med* 2007; **8**: 131–134.
88. Boehringer Ingelheim Pharmaceuticals Inc. Aptivus® package insert. Ridgefield, CT: Boehringer Ingelheim International, 2005.
89. Burman WJ, Gallicano K, Peloquin C. Therapeutic implications of drug interactions in the treatment of HIV-related tuberculosis. *Clin Infect Dis* 1999; **28**: 419–430.
90. Wang Y, Serradell N, Bolos J, Rosa E. MK-0518. *Drugs Fut* 2007; **32**: 118.
91. Abel S, Russell D, Ridgway C, Muirhead G. Overview of the drug–drug interaction data for maraviroc (UK-427,857). 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec, 28–30 April 2005 [Abstr. 76].
92. Centers for Disease Control and Prevention. *Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis*. 2007, Department of Health and Human Services, USA
93. Desta Z, Soukhova NV, Flockhart DA. Inhibition of cytochrome P450 (CYP450) by isoniazid: potent inhibition of CYP2C19 and CYP3A. *Antimicrob Agents Chemother* 2001; **45**: 382–392.
94. Wen X, Wang J-S, Neuvonen PJ, Backman JT. Isoniazid is a mechanism-based inhibitor of cytochrome P450 1A2, 2A6, 2C19, and 3A4 isoforms in human liver microsomes. *Eur J Clin Pharmacol* 2002; **57**: 799–804.
95. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomized trial. *Lancet* 2004; **364**: 1244–1251.
96. Okwera A, Whalen C, Byekwaso F *et al.* Randomised trial of thiacetazone and rifampicin-containing regimens for pulmonary tuberculosis in HIV-infected Ugandans. *Lancet* 1994; **344**: 1323–1328.
97. Dean GL, Edwards SG, Ives NJ *et al.* Treatment of tuberculosis in HIV-1 infected persons in the era of highly active antiretroviral therapy. *AIDS* 2002; **16**: 75–83.
98. Breen RA, Miller RF, Gorsuch T *et al.* Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. *Thorax* 2006; **61**: 791–794.
99. Yee D, Valiquette C, Pelletier M *et al.* Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *J Respir Crit Care Med* 2003; **167**: 1472–1477.
100. Devoto FM, Gonzalez C, Iannantuono R *et al.* Risk factors for hepatotoxicity induced by antituberculosis drugs. *Acta Physiol Pharmacol Ther Latinoam*. 1997; **47**: 197–202.
101. Ungo JR, Jones D, Ashkin D *et al.* Antituberculosis drug induced hepatotoxicity. The role of hepatitis C virus and the human immunodeficiency virus. *Am J Respir Crit Care Med* 1998; **157**: 1871–1876.
102. Sadaphal P, Astemborski J, Graham NM *et al.* Isoniazid preventive therapy, hepatitis C virus infection, and hepatotoxicity among injection drug users infected with *Mycobacterium tuberculosis*. *Clin Infect Dis* 2001; **33**: 1687–1691.

103. Breen RAM, Lipman MCI, Johnson MA. Increased incidence of peripheral neuropathy with co-administration of stavudine and isoniazid in HIV infected individuals. *AIDS* 2000; **14**: 615.
104. Peloquin CA, MacPhee AA, Berning SE. Malabsorption of antimycobacterial medications. *N Engl J Med* 1993; **329**: 1122–1123 (letter).
105. Patel KB, Belmonte R, Grove HM. Drug malabsorption and resistant tuberculosis in HIV-infected patients. *N Engl J Med* 1995; **332**: 336–337.
106. Berning SE, Huitt GA, Iseman MD, Peloquin CA. Malabsorption of antituberculosis medications by a patient with AIDS. *N Engl J Med* 1992; **327**: 1817–1818.
107. Perlman DC, Segal Y, Rosenkranz S *et al.* AIDS Clinical Trials Group 309 Team. The clinical pharmacokinetics of rifampin and ethambutol in HIV-infected persons with tuberculosis. *Clin Infect Dis* 2005; **41**: 1638–1647.
108. Tappero JW, Bradford WZ, Agerton TB *et al.* Serum concentrations of antimycobacterial drugs in patients with pulmonary tuberculosis in Botswana. *Clin Infect Dis* 2005; **41**: 461–469.
109. Peloquin CA, Nitta AT, Burman WJ *et al.* Low antituberculosis drug concentrations in patients with AIDS. *Ann Pharmacother* 1996; **30**: 919–925.
110. Sahai J, Gallicano K, Swick L *et al.* Reduced plasma concentrations of antituberculous drugs in patients with HIV infection. *Ann Intern Med* 1997; **127**: 289–293.
111. Taylor J, Smith PJ. Does AIDS impair the absorption of antituberculosis agents? *Int J Tuberc Lung Dis* 1998; **2**: 670–675.
112. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. *Drugs* 2002; **62**: 2169–2183.
113. Murray J, Sonnenberg P, Shearer SC, Godfrey-Faussett P. Human immunodeficiency virus and the outcome of treatment for new and recurrent pulmonary tuberculosis in African patients. *Am J Respir Crit Care Med* 1999; **159**: 733–740.
114. Nunn P, Brindle R, Carpenter L *et al.* Cohort study of human immunodeficiency virus infection in patients with tuberculosis in Nairobi, Kenya: analysis of early (6-month) mortality. *Am Rev Respir Dis* 1992; **146**: 849–854.
115. Churchyard GJ, Kleinschmidt I, Corbett EL, Murray J, Smit J, De Cock KM. Factors associated with an increased case-fatality rate in HIV-infected and non-infected South African gold miners with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2000; **4**: 705–712.
116. Moreno S. *World AIDS Conference, Barcelona Spain 2002*; [Abstract TuOr 171].
117. Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. *Am J Respir Crit Care Med* 2001; **164**: 7–12.
118. American Thoracic Society Documents. American Thoracic Society / Centers of Disease Control and Prevention / Infectious Diseases Society of America: treatment of tuberculosis. *Am J Respir Crit Care Med* 2003; **167**: 603–662.
119. World Health Organization. *Scaling up antiretroviral therapy in resource-limited settings: guidelines for a public health approach*. WHO 2004.

120. Navas E, Oliva J, Miralles P *et al.* Antiretroviral therapy in AIDS patient. *XIV International AIDS Conference, Barcelona*, 2002; [Abstr. ThPeB7271].
121. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS* 2007; **21**: 335–341.
122. Schiffer JT, Sterling TR. Timing of antiretroviral therapy initiation in tuberculosis patients with AIDS: a decision analysis. *J Acquir Immune Defic Syndr* 2007; **44**: 229–234.
123. Farmer P, Léandre F, Mukherjee J, Gupta R, Tarter L, Kim JY. Community-based treatment of advanced HIV disease: introducing DOT-HAART (directly observed therapy with highly active antiretroviral therapy). *Bull World Health Organization* 2001; **79**: 1145–1151.
124. Gandhi NR, Moll A, Sturm AW *et al.* Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006; **368**: 1575–1580.
125. Snider DE Jr, Layde PM, Johnson MW, *et al.* Treatment of tuberculosis during pregnancy. *Am Rev Respir Dis* 1980; **122**: 65–79.
126. Armstrong L, Garay S. *Tuberculosis and pregnancy*. In: Rom WN, Garay S, eds. *Tuberculosis*. New York, NY: Lippincott, 1996; 694–695.
127. Jones JL, Hanson DL, Dworkin MS, DeCock KM. HIV-associated tuberculosis in the era of highly active antiretroviral therapy. The Adult/Adolescent Spectrum of HIV Disease Group. *Int J Tuberc Lung Dis* 2000; **11**: 1026–1031.
128. Santoro-Lopes G, de Pinho AM, Harrison LH, Schechter M. Reduced risk of tuberculosis among Brazilian patients with advanced human immunodeficiency virus infection treated with highly active antiretroviral therapy. *Clin Infect Dis* 2002; **34**: 543–546.
129. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet* 2002; **359**: 2059–2064.
130. Gordin FM, Matts JP, Miller C *et al.* A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. *N Engl J Med* 1997; **37**: 315–320.
131. Jordon TJ, Levit EM, Montgomery EL, Reichman LB. Isoniazid as preventive therapy in HIV-infected intravenous drug abusers: a decision analysis. *JAMA* 1991; **265**: 2987–2991.
132. Warren RM, Van Helden PD. HIV-1 and tuberculosis infection. *Lancet* 2002; **359**: 1619–1620.
133. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons (Cochrane Review). In: *The Cochrane Library*, Issue 2. Oxford, 2002.
134. Quigley MA, Mwinga A, Hosp M *et al.* Long-term effect of preventive therapy for tuberculosis in a cohort of HIV-infected Zambian adults. *AIDS* 2001; **15**: 215–222.
135. Aisu T, Raviglione MC, van Praag E *et al.* Preventive chemotherapy for HIV associated tuberculosis in Uganda: an operational assessment at a voluntary counselling and testing centre. *AIDS* 1995; **9**: 267–273.

136. Gordin F, Chaisson RE, Matts JP *et al.* Rifampicin and pyrazinamide versus isoniazid for prevention of tuberculosis in HIV infected persons: an international randomized trial. *JAMA* 2000; **283**: 1445–1450.
137. Mwinga A, Hosp M, Godfrey-Faussett P *et al.* Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS* 1998; **12**: 2447–2457.
138. Halsey NA, Coberly JS, Desormeaux J *et al.* Randomized trial of isoniazid versus rifampicin and pyrazinamide for the prevention of tuberculosis in HIV-1 infection. *Lancet* 1998; **351**: 786–792.
139. Cohen T, Lipsitch M, Walensky RP, Murray M. Beneficial and perverse effects of isoniazid preventive therapy for latent tuberculosis infection in HIV-tuberculosis coinfecting populations. *Proc Natl Acad Sci USA* 2006; **103**: 7042–7047.
140. Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerg Infect Dis* [internet publication] 2006 May. Available from www.cdc.gov/ncidod/EID/vol12no05/05-0681.htm
141. Lawn SD, Wilkinson RJ, Lipman MC, Wood R. Immune reconstitution and “unmasking” of tuberculosis during antiretroviral therapy. *Am J Respir Critical Care Med* 2008; **177**: 680–685.
142. Chan ED, Iseman MD. Multidrug-resistant and extensively drug-resistant tuberculosis: a review. *Curr Opin Infect Dis* 2008; **21**: 587–595.
143. Blackmore TK, Manning L, Taylor WJ, Wallis RS. Therapeutic Use of Infliximab in Tuberculosis to Control Severe Paradoxical Reaction of the Brain and Lymph Nodes. *Clin Infect Dis* 2008; **47**: e83–e85.
144. Ijaz K, Jereb JA, Lambert LA *et al.* Severe or fatal liver injury in 50 patients in the United States taking rifampicin and pyrazinamide for latent tuberculosis infection. *Clin Infect Dis* 2006; **42**: 346–355.
145. Fitzgerald D, Desvarieux M, Severe P, Joseph P, Johnson W, Pape J. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomized trial. *Lancet* 2000; **356**: 1470–1474.
146. Fielding KL, Hayes RJ, Charalambou SS *et al.* Efficacy of secondary isoniazid preventative therapy among HIV infected South Africans. *XIV International AIDS Conference*, Barcelona, 2002; [Abstr. ThPeB7275].
147. Sonnerberg P, Murray J, Glynn JR, Shewer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet* 2001; **358**: 1687–1693.
148. Lopez-Cortes LF, Marin-Niebla A, Lopez-Cortez LE *et al.* Influence of treatment and immunological recovery on tuberculosis relapses in HIV-infected patients. *Int J Tuberc Lung Dis* 2005; **9**: 1385–1390.
149. Breen RA, Smith CJ, Bettinson H *et al.* Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax* 2004; **8**: 704–707.
150. Judson MA. Highly active antiretroviral therapy for HIV with tuberculosis: pardon the granuloma. *Chest* 2002; **122**: 399–400.

151. Crump JA, Tyrer MJ, Lloyd-Owen SJ *et al.* Military tuberculosis with paradoxical expansion of intracranial tuberculomas complicating human immunodeficiency virus infection in a patient receiving highly active antiretroviral therapy. *Clin Infect Dis* 1998; **26**: 1008–1009.
152. John M, French MA. Exacerbation of the inflammatory response to Mycobacterium tuberculosis after antiretroviral therapy. *Med J Aust* 1998, **169**, 473–474.
153. Kunimoto DY, Chui L, Nobert E *et al.* Immune mediated 'HAART' attack during treatment for tuberculosis: highly active antiretroviral therapy. *Int J Tuberc Lung Dis* 1999, **3**, 944–947.
154. Mofredj A, Guerin JM, Leibinger F *et al.* Paradoxical worsening in tuberculosis during therapy in an HIV-infected patient [letter]. *Infection* 1996, **24**, 390–391.
155. Ramdas K, Minamoto GY. Paradoxical presentation of intracranial tuberculomas after chemotherapy in a patient with AIDS [letter]. *Clin Infect Dis* 1994, **19**, 793–794.
156. Campbell IA, Dyson AJ. Lymph node tuberculosis: a comparison of various methods of treatment. *Tubercle* 1977, **58**, 171–179.
157. Chambers ST, Record C, Hendricks WA, Rudge WA, Smith H. Paradoxical expansion of intracranial tuberculomas during chemotherapy. *Lancet* 1984; **2**:181–184.
158. Afghani B, Lieberman JM. Paradoxical enlargement or development of intracranial tuberculomas during therapy: case report and review. *Clin Infect Dis* 1994; **19**: 1092–1099.
159. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med* 1998; **158**: 157–161.
160. Navas E, Martín-Dávila P, Moreno L *et al.* Paradoxical reactions of tuberculosis in patients with the acquired immunodeficiency syndrome who are treated with highly active antiretroviral therapy. *Arch Intern Med* 2002; **162**: 97–99.
161. Race EM, Adelson-Mitty J, Kriegel GR *et al.* Focal mycobacterial lymphadenitis following initiation of protease inhibitor therapy in patients with advanced HIV-1 disease. *Lancet* 1998; **351**: 252–255.
162. Foudraine NA, Hovenkamp E, Notermans DW *et al.* Immunopathology as result highly active antiretroviral therapy in HIV-1-infected patients. *AIDS* 1999; **13**: 177–184.
163. Choremis CB, Padiatellis C, Zoumboulakis D, Yannakos D. Transitory exacerbation of fever and roentgenographic findings during treatment of tuberculosis in children. *Am Rev Tuberc* 1955; **72**: 527–536.
164. Minguez C, Roca B, Gonzalez-Mino C *et al.* Superior vena cava syndrome during the treatment of pulmonary tuberculosis in an HIV-1 infected patient. *J Infect* 2000; **40**: 187–189.
165. Navos S, Moreno L, Martin-Davila V *et al.* TB reactivation in AIDS patients treated with HAART. *39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco*, 1999
166. Wendel KA, Alwood KS, Gachuhi R, Chaisson RE, Bishai WR, Sterling TR. Paradoxical worsening of tuberculosis in HIV-infected persons. *Chest* 2001; **120**: 193–197.

167. Furrer H, Malinverni R. Systemic inflammatory reaction after starting highly active antiretroviral therapy in AIDS patients treated for extrapulmonary tuberculosis. *Am J Med* 1999; **106**: 371–372.
168. Schluger NW, Perez D, Liu YM. Reconstitution of immune responses to tuberculosis in patients with HIV infection who receive antiretroviral therapy. *Chest* 2002; **122**: 597–602.
169. Price P, Morahan G, Huang D *et al*. Polymorphisms in cytokine genes define subpopulations of HIV-1 patients who experienced immune restoration diseases. *AIDS* 2002; **16**: 2043–2047.
170. Price P, Mathiot N, Krueger R, Stere S, Keane NB, French MA. Immune restoration disease in HIV patients given highly active antiretroviral therapy. *J Clin Virol* 2001; **22**: 279–287.
171. Stone SF, Price P, Brochier J, French MA. Plasma bioavailable interleukin-6 is elevated in human immunodeficiency virus-infected patients who experience herpes-virus associated immune restoration disease after start of highly active antiretroviral therapy. *J Infect Dis* 2001; **184**: 1073–1077.
172. Stone SF, Price P, Keane NM, Murray RJ, French MA. Levels of IL-6 and soluble IL-6 receptor are increased in HIV patients with a history of immune restoration disease after HAART. *HIV Med* 2002; **3**: 21–27.
173. Morlese JF, Orkin CM, Abbas R *et al*. Plasma IL-6 as a marker of mycobacterial immune restoration disease in HIV-1 infection. *AIDS* 2003; **17**: 1411–1413.
174. Perez D, Liu Y, Jung T *et al*. Reconstitution of host immunity to M tuberculosis in HIV-infected individuals. *Am J Respir Crit Care Med* 2000; **161**: A224
175. Colebunders R, John L, Huyst V *et al*. Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources *Int J Tuberc Lung Dis* 2006, **10**: 946–953.
176. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson M, Gazzard B. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. *Antivir Ther* 2005; **10**: 417–422.
177. Manosuthi W, Kiertiburanakul S, Phoorisri T, Sungkanuparph S. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. *J Infect* 2006; **53**: 357–363.
178. Gazzard BG on behalf of the BHIVA Treatment Guidelines Writing Group. British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV Medicine* 2008; **9**: 563–608.
179. Shelburne SA, Visnegarwala F, Darcourt J *et al*. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. *AIDS* 2005; **19**: 399–406.
180. Rajeswaran G, Becker JL, Michailidis C, Pozniak AL, Padley SPG. The radiology of IRIS (immune reconstitution inflammatory syndrome) in patients with mycobacterial tuberculosis and HIV co-infection: appearances in 11 patients. *Clin Radiol* 2006; **61**: 833–843.

181. Harwick C, White D, Morris E, Monteiro EF, Breen RA, Lipman M. Montelukast in the treatment of HIV associated immune reconstitution disease. *Sex Transm Infect* 2006; **82**: 513–514.
182. Pires A, Nelson M, Pozniak AL *et al.* Mycobacterial immune reconstitution inflammatory syndrome in HIV-1 infection after antiretroviral therapy is associated with deregulated specific T-cell responses: beneficial effect of IL-2 and GM-CSF immunotherapy. *J Immune Based Ther Vaccines* 2005; **3**: 7.
183. The Interdepartmental Working Group on Tuberculosis (1998). *The prevention and control of tuberculosis in the United Kingdom: UK guidance on the prevention and control of transmission of 1.HIV-related tuberculosis 2.drug-resistant, including multiple drug-resistant, tuberculosis*. London: Department of Health. Available from www.dh.gov.uk
184. Ormerod LP, Skinner C, Wales JM. Hepatotoxicity of antituberculosis drugs. *Thorax* 1996; **51**: 111–113.