BHIVA treatment guidelines for TB/HIV infection

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Summary of guidelines

These guidelines have been drawn up to help physicians manage adults with HIV/TB co-infection. We recommend that co-infected patients are managed by a multi-disciplinary team which includes physicians who have expertise in the treatment of both tuberculosis and HIV.

We recommend that the optimal regimen be used in the treatment of tuberculosis. In the majority of cases, this will necessitate use of rifampicin and isoniazid. In the treatment of HIV, there is more flexibility of choice for many patients starting highly active anti-retroviral therapy (HAART).

We recommend that if HIV treatment is started in patients who are on anti-tuberculosis therapy then HAART should be modified if necessary. TB treatment should only be modified when a patient has developed intolerance of, or severe toxicity from, HIV drugs or has evidence of genotypic resistance to specific HIV drugs thus limiting HAART therapy to agents whish are likely to interact with anti-tuberculosis therapy.

These factors (intolerance, toxicity and resistance) may sometimes necessitate prolongation of duration of TB treatment.

The gold standard for diagnosis of tuberculosis is microscopy followed by culture and drug sensitivity testing. Molecular diagnostics may be valuable in reducing the time patients spend in isolation facilities when tuberculosis is suspected clinically. Confirmation, by molecular diagnostics, that acid-fast bacilli are not *M. tuberculosis* may be useful for clinical management and infection control.

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.

TB treatment

We recommend daily tuberculosis treatment whenever possible. Treatment may be given 5 days a week, but should be intensively supervised. This option may be useful in hospital or other highly supervised settings. Three times a week directly observed therapy (DOT) should only be given to patients where local logistics enable this to be successfully undertaken.

We do not recommend twice-weekly DOT for treatment of HIV/TB co-infected patients, especially in those with CD4 counts <100 cells/uL.

Treatment should be started with four drugs (typically rifampicin, isoniazid, pyrazinamide and ethambutol) until sensitivities are known.
We recommend a 6 months treatment regimen for drug sensitive *Mycobacterium tuberculosis* outside of the central nervous system (CNS) [at least 182 doses of isoniazid and rifampicin and 56 doses of pyrazinamide and ethambutol]. In drug sensitive tuberculosis affecting the CNS we recommend 12 months of treatment. This usually consists of two months of a four-drug TB regimen, followed by 10 months of isoniazid and rifampicin. Drug resistant disease should be treated in line with BTS Guidelines

Drug interactions and toxicities.

Rifampicin is a powerful inducer of cytochrome P450-3A4 and therefore careful attention should be paid to potential drug/drug interactions between anti-tuberculosis drugs, HAART and other concomitant therapy. The alternative use of rifabutin may overcome some of the difficulties in co-administration of rifampicin with protease inhibitors and non-nucleosides.

Overlapping toxicity profiles, for example peripheral neuropathy with stavudine and isoniazid, or rash with non-nucleosides and rifampicin can complicate care , as ascribing a cause may be difficult. In some patients, for example those with chronic viral hepatitis, there is an increased rate of drug toxicity. In these patients we recommend more frequent monitoring of liver function tests.

Antiretroviral treatment

The following antiretroviral drugs may be used with rifampicin-based regimens of TB therapy. It is important to note that there is little long-term clinical outcome data to support use of these drugs in combination.

(i) Nucleoside / nucleotide reverse transcriptase inhibitors

There are no major interactions with rifampicin or rifabutin.

(ii) Non-nucleoside reverse transcriptase inhibitors

Efavirenz may be used at a dose of 800mg/day in patients weighing >50kg and the standard dose of 600mg/day in patients weighing <50kg. In patients experiencing side effects on these doses, therapeutic drug monitoring may be of value. We recommend that daily rifampicin should not be used with nevirapine.

NNRTI may be used with rifabutin, but the rifabutin dose is increased to 450mg/day when used with efavirenz. No dose modification is required when rifabutin is used with nevirapine, however we do not recommend use of this combination.

(iii) Protease inhibitors

Rifampicin should not be used with un-boosted protease inhibitors (PI). Data on boosted PI regimens eg lopinavir/ritonavir with rifampicin show an increased risk of hepatotoxicity and the need in some patients (based on therapeutic drug monitoring [TDM]) to increase the dose of lopinavir to 4 tablets bd. There is a lack of good clinical and virological outcomes using these combinations Boosted saquinavir should not be used with rifampicin as 11/28 (39.3%) subjects exposed to rifampicin 600 mg daily taken together with ritonavir 100 mg and saquinavir 1000 mg given twice daily (ritonavir boosted saquinavir) developed significant hepatocellular toxicity.

Rifabutin can be used with un-boosted PI but dose modifications of PI are needed and the dose of rifabutin halved to 150mg/day. There are few data to support use of rifabutin with a boosted PI but if it is used the dose of rifabutin needs to be reduced to 150mg three times a week. The dose of boosted PI remains unaltered. In these situations TDM should be used.

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.

Starting HAART

When to start anti-retroviral therapy in patients who have tuberculosis is a balance between potential overlapping toxicities, drug interactions and possible immune reconstitution versus the risk of further immune suppression with its associated increase in morbidity and mortality. We recommend that patients who have a CD4 count consistently >200 cells/uL while receiving treatment of tuberculosis should wait until their anti-tuberculosis therapy is completed before starting HIV therapy [see BHIVA HIV treatment guidelines].

For patients with CD4 counts between 100 and 200 cells/uL we recommend deferring starting HIV therapy until completion of the intensive phase of anti-tuberculosis treatment (after 2 months).

For patients with CD4 counts <100 cells/uL there are no data to support either immediate or deferred HAART. In this situation we recommend that patients should be recruited to clinical trials, which address this question. If that is not possible then patients should be started on HAART as soon as is practical after starting anti-tuberculosis therapy.

DOT

This is regarded as a gold standard for treatment of TB but it may not be possible to deliver all elements of the DOT package. Witnessed supervision of treatment may be impracticable in every case and it is important to remember that patient-centred management is the core of successful TB treatment. We recommend that DOT be used in all cases of multi-drug resistant TB.

Tuberculin skin test

Tuberculin skin testing is less useful in patients with HIV infection compared with HIV uninfected patients. We do not recommend tuberculin skin testing in patients with suspected HIV/TB co-infection or as a screening test for tuberculosis in HIV infected patients. New immune-based detection tests [such as those using gamma interferon production from TB specific T cells] appear to have better sensitivity than tuberculin tests, however correlation of positive results with outcome in patients with low CD4 counts is required.

Chemopreventative therapy

We do not recommend routine chemo-preventative therapy for HIV infected patients. Close contacts of people who have infectious TB should be followed up and offered chemo-preventative therapy [see BTS guidelines]. Data suggest that HAART is effective in reducing the incidence of new tuberculosis and we recommend that all HIV positive patients should be offered HAART [based on BHIVA HIV treatment guidelines].

Relapse and treatment failure

Patients with tuberculosis, with or without HIV infection, who appear to fail treatment or who relapse despite therapy pose particular management problems and should be referred to and discussed with clinical colleagues who have expertise in the management of HIV/TB.

Control & prevention of TB

Every hospital/Trust should have in place a policy for the control and prevention of TB. Specific consideration should be made to establishing protocols for prevention of transmission of TB to and from immunosuppressed patients.

1.0 Introduction

Worldwide, HIV infection is the foremost risk factor for development of active tuberculosis (TB). [1–4]

All patients with tuberculosis, regardless of their perceived risk of HIV infection should be offered an HIV test as part of their tuberculosis treatment package. In the United Kingdom, clinicians are caring for increasing numbers of HIV-TB co-infected patients. TB is now the second commonest opportunistic infection in the UK. In 2003 TB contributed to 27% of all AIDS diagnoses. [5–7]

The clinical and radiographic presentation of such individual's disease may be atypical. Compared to the immune competent general population, HIV infected patients with active pulmonary tuberculosis are more likely to have normal chest radiographs, or be smear negative/culture positive. [8–11]

The clinician caring for HIV infected patients, therefore, needs to have a high index of suspicion for tuberculosis in symptomatic individuals. As the investigation and treatment of both tuberculosis and HIV require specialist knowledge and expertise, it is mandatory to involve specialist HIV, Respiratory and Infectious Diseases physicians in patient care.

These guidelines have been drawn up in response to a perceived need for a clinical knowledge base covering the treatment of both HIV and tuberculosis in co-infected patients in the United Kingdom. These guidelines do not cover HIV infected children with tuberculosis, nor do they provide advice on HIV testing in adults with newly diagnosed tuberculosis. These treatment guidelines have been written to help physicians manage HIV infected patients with confirmed or suspected tuberculosis. They are based on evidence where it is available but some recommendations have to rely on expert opinion until data from trials are made available. These guidelines are not a manual for treatment of HIV/TB co infection and should be regarded as an adjunct to the BHIVA treatment of HIV guidelines and the BTS guidelines on tuberculosis.

These documents can be downloaded from:

http://www.bhiva.org

http://www.brit-thoracic.org.uk

BHIVA is aware of and involved in the creation of NICE guidelines on tuberculosis, which will be available in 2005 but felt that until that time some guidance on TB in HIV should be made widely available.

Recommendations for the treatment of tuberculosis in HIV infected adults are similar to those for HIV uninfected adults. However there are important exceptions.

1. Some intermittent treatment regimens are contra-indicated in HIV infected patients because of unacceptably high rates of relapse, frequently with organisms that have acquired rifamycin resistance. Consequently, patients with CD4 counts <100/μL should receive daily or a minimum of three times weekly anti-tuberculosis treatment
2. Adherence strategies including directly observed therapy (DOT) are especially important for patients with HIV related tuberculosis.
3. HIV infected patients are often taking medication, which might interact with antituberculosis medications for example rifampicin, which interacts with antiretroviral agents and other anti-infectives, for example fluconazole. Drug absorption may also be affected by the stage of HIV infection.
4. There are overlapping toxicity profiles and drug/drug interactions with some anti-tuberculosis and anti-retroviral drugs that further complicate the concurrent use of HAART and tuberculosis treatment.

5. There are also concerns about the timing of commencement of HAART in relation to the start of TB treatment in the context of preventing the risk of further HIV progression and the occurrence of paradoxical reactions.

2.0 Aims of TB treatment

It should be noted that the treatment of tuberculosis has benefits not only for the individual but also to the community.

The aim of TB therapy is:

1. To cure the patient of TB; and
2. To minimize the transmission of *Mycobacterium tuberculosis,* to both immune suppressed and immune competent persons.

3.0 Laboratory diagnosis

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

3.1 Microscopic smears

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

3.2 Cultures

These 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 grows M.tuberculosis in 7 to 28 days.

Identification of mycobacterium based on morphology, growth and biochemical characteristics are performed at mycobacterium reference centres. Rapid gene probes can be used but this should be fully discussed with the laboratory. These are less sensitive than culture and are used mainly on respiratory specimens. These are often requested when it is important to differentiate the diagnosis of MTB from other Mycobacteria for which treatment may be different and there are no infection control concerns. However, it should be noted that all specimens even those that are negative on PCR still require culture and that 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 Mycobacterium avium or Mycobacterium tuberculosis and often the physician will wait for the routine identification before altering the standard 4-drug regimen. Some physicians prefer to replace rifabutin for rifampicin in this situation. When opportunist mycobacteria are identified then the regimen can be modified appropriately.

3.3 Drug susceptibility tests

These are usually available within 10-21 days of the laboratory receipt of the isolates and are performed by standard assays. Molecular detection of rifampicin resistance (and pyrazinamide) is

available although it is not 100 percent sensitive. These molecular tests are useful when drug resistance is suspected, as about 95% of patients who are rifampicin resistant will also be isoniazid resistant.

Patients with gene probe positive rifampicin resistance should be treated as MDR-TB, until the full resistance profile from cultures are available.

3.4 Rapid detection of active and latent tuberculosis infection in HIV positive individuals.

The lack of sensitivity of the tuberculin test and the poor specificity because of antigenic cross-reactivity with BCG vaccination means that an accurate test for active or latent TB in HIV individuals is needed.

Tests using either whole blood or blood mononuclear cells have been developed which measure interferon gamma production from TB-specific T cells responding to *M. tuberculosis* antigens ESAT-6 or CFP-10.[12]

Using an enzyme linked immunospot [ELISPOT] assay, a study from Zambia and the UK diagnosed active TB in 90 percent of 39 individuals tested. Unfortunately, although this technology was better at picking up latent TB than PPD testing in HIV positive persons it was still not as sensitive when compared to HIV negative patients Larger studies are needed and correlations of Elispot responses with patient's CD4 counts need to be made. The reproducibility of the test also needs to be evaluated in HIV positive patients and long term outcomes measured.

4.0 Type and duration of TB treatment

4.1 Treatment regimens

Various treatment regimens are outlined in Figure 1. Because of the relatively high proportion of adult patients in the UK with tuberculosis caused by organisms that are resistant to isoniazid, four drugs are necessary in the initial phase for the 6 month regimen to be maximally effective. From Mycobnet data the overall isoniazid resistance rate in the UK is 6% and higher in non-white ethnic groups and those with prior treatment. The highest rates have been found in London. Thus, in most circumstances, the treatment regimen for all adults with previously untreated tuberculosis should consist of two phases;

1. A 2-month initial phase of isoniazid, rifampicin, pyrazinamide and ethambutol. If (or when) drug susceptibility test results are known and the organisms are fully susceptible, ethambutol need not be included.

Followed by:

A continuation phase of treatment is given for either four or seven months see figure 2. The 4-month continuation phase should be used in the majority of patients.

TB therapy can be given 5 times a week with standard doses Although there are no formal clinical trial data, considerable clinical experience suggests that 5 day-a-week drug administration by DOT is equivalent to 7 day-a-week treatment – and thus either may be considered "daily". **[AIII]**

2. The six months short course drug combination should be recommended to all HIV positive patients with pulmonary tuberculosis wherever possible. **[AII]** All patients should be given pyridoxine (vitamin B6) 10-25 mg with isoniazid dosing.

There are important exceptions.

4.2 Longer continuation phase [AII]

A seven months continuation phase is recommended for certain groups: e.g.

1. Patients with drug susceptible organisms whose initial phase of treatment did not include pyrazinamide.
2. Patients with cavitary pulmonary disease who remain sputum culture positive at month 2 of treatment

A ten month continuation phase is recommended for patients with central nervous system (CNS) involvement e.g. meningitis, tuberculomata.

4.3 Intermittent therapy [AII]

It is recommended that patients should receive daily therapy. However intermittent treatment is an option.[13,14] The indications for this in HIV positive individuals are almost the same as for patients without HIV infection. Intermittent therapy can be given three times per week with dose modification. Two dosing strategies should be avoided, as acquired rifamycin resistance has been associated with their use in HIV patients: [AII]

1. Once weekly isoniazid–rifapentine in the continuation phase should not be used in any HIV-infected patient; and
2. Twice weekly isoniazid–rifampicin or -rifabutin should not be used for patients with CD4 counts <100 cells/uL.

In two studies, patients with acquired rifamycin resistance had very low CD4 counts at the time of TB diagnosis (<60 cells/uL). [15-17]

These data have led the CDC in the USA to recommend that persons co-infected with HIV and TB who have CD4 cell counts <100 cells/uL should not be treated with highly intermittent (i.e. once or twice weekly) regimens. Patients already on highly intermittent regimens should switch over to daily or three times a week as soon as practicable.

4.4 Use of rifabutin [B11]

Rifabutin has been successfully used instead of rifampicin in treatment of TB in HIV negative patients. [18.19] In HIV patients receiving complex antiretroviral regimens, where there is a risk of drug/drug interactions with rifampicin, rifabutin may be substituted. Rifabutin showed similar efficacy to rifampicin in a single blind, randomized study of 50 HIV positive patients in Uganda and in a cohort study of 25 patients in the USA. [20.21]

Although rifabutin seems to be equivalent to rifampicin, there are no long-term data on which to make comparisons. Despite the paucity of data regarding use of rifabutin in HIV positive patients it is frequently used in the treatment of TB in HIV. This is because rifabutin may be administered with antiretroviral regimens that include protease inhibitors. However, non–protease inhibitor based regimens are possible, especially in HAART naïve patients.

We recommend that rifampicin should remain the drug of choice whenever possible.

4.5 Use of Rifapentine [DII]

Rifapentine has a long serum half-life, which theoretically would allow once weekly directly observed therapy during the continuation phase of TB treatment. In the initial phase of treatment of TB in HIV negative patients rifapentine has unacceptable 2-year microbiological relapse rates and

cannot be recommended. Data on its use in the continuation phase of treatment is encouraging, but this is accrued from studies of HIV negative patients.

There are few data regarding the interaction of rifapentine with HAART. Development of rifapentine resistance appears more frequent in TB/HIV co-infected patients and more data are needed before rifapentine can be recommended for use in this patient group. [22]

4.6 Duration and Effectiveness of TB treatment

In the absence of data from clinical trials, it is not known if duration of treatment of TB in HIV infected patients should be for longer than in HIV un-infected patients. The few data that exist suggest that in HIV infected patients duration of treatment for tuberculosis sensitive to first line therapy should be no different to HIV un-infected patients.

A review of six studies of patients with HIV infection and three studies of patients without HIV infection given treatment for six months (or longer) demonstrated considerable variability in published study design, eligibility criteria, site of disease, frequency and method of dosing, and outcome definitions. 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 co-infected patients other outcomes were comparable when 6 months regimens were used.

We recommend that for drug sensitive TB, not involving the CNS, regimens of 6 months should be given. [23-28] [AII]

Some or all of these factors have a role in explaining the differences in the present data. A multicentre study from the US found no difference between TB relapses with regimens of 6 and 9 months duration. However, very few patients relapsed (2 and 1 patients respectively). [29.30]

The risk of relapse of TB for HIV infected patients is the same as that for HIV uninfected patients if rifampicin is used throughout (for at least 6 months). Long-term randomized trials are needed to resolve the question of duration of TB therapy in HIV infected patients.

In HIV infected patients HAART may reduce the risk of relapse of TB[31-33]. This statement is supported by data showing a reduction in the incidence of TB with HAART and hence it might be hypothesized that there will be a reduced rate of exogenous reinfection and/or reactivation in patients who have HAART-induced improvements in CD4 count.

4.7 Baseline and follow up evaluations after starting TB treatment [AIII]

Monitoring of therapy is as follows:

1) A baseline absolute CD4 count and percentage should be obtained.
2) Baseline measurements of serum aminotransferases (aspartate aminotransferase [AST] and or alanine aminotransferase [ALT]), bilirubin, alkaline phosphatase, and serum creatinine, and a platelet count should be obtained. Liver function tests should be rechecked at 1-2 weeks if asymptomatic (see BTS Guidelines).
3) All patients should have serological tests for hepatitis B and C viruses at baseline.
4) Testing of visual acuity with Snellen charts should be performed when ethambutol is used (see BTS guidelines)
5) Patients with pulmonary TB who are not improving on treatment should have a repeat sputum smear and culture if the patient still has a productive cough after completing 2 months of treatment.

6) A chest radiograph should be performed if subsequent progress after 2 months is unsatisfactory. In pulmonary TB, a baseline and 'completion of treatment' chest radiograph are necessary.

7) Other evaluation e.g. additional chest radiographs, ultrasound or CT scans may be indicated, depending on the clinical need.

4.8 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. Therefore, determination of whether or not treatment has been completed should be based on the total number of doses taken—not solely on the duration of therapy.

For example 1) 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.

2) If the drugs are administered by DOT (5 days/week), the minimum number of doses of rifampicin and isoniazid is 130 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 a 6-month period. The 6-month regimen should therefore be completed by 9 months.

4.9 Interruptions of therapy [AIII]

These are common in the treatment of HIV associated tuberculosis. Data to support recommendations are scant. We agree with the CDC that there are few data to guide the management of interruptions. They suggest the following:

1) If the interruption occurs during the initial phase of treatment and the interruption is 14 days or more in duration, treatment should be restarted from the beginning.

2) If the interruption is less than 14 days, the treatment regimen should be continued.

NB In both 1) and 2) the total number of doses prescribed for the initial phase should be given.

3) For patients who were smear positive initially, continued treatment to complete the planned total number of doses is needed. Thus,

   i) If the patient has received less than 80% of the planned total doses and the lapse is 3 months or more in duration, treatment should be restarted from the beginning.

   ii) If the interruption is less than 3 months in duration, treatment should be continued to complete a full course. Studies have not been performed in HIV infected patients in order to confirm this observation and physicians should be cautious when treating patients who have had interruptions of therapy.

Regardless of the timing and duration of the interruption, DOT should be used.

If the patient was already being managed with DOT, additional measures may be necessary to ensure completion of therapy eg transport, food, social services.[34]

5.0 Drug/drug interactions (see Table 1 & 2)

Drug/drug interactions between HIV and TB therapy arise through shared routes of metabolism and are often due to enzyme induction or inhibition. [35,36]

One important family of enzymes is the hepatic cytochrome P450 (CYP) system. The isoform CYP3A4 is involved in the metabolism of many drugs including the protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTI), which makes up the core of most HAART regimens.

The non-nucleoside reverse transcriptase inhibitors and protease inhibitors have clinically important drug interactions with the rifamycins, as the latter are potent inducers of CYP3A4. [37,38]

However, the inducing effect of rifampicin not only takes at least 2 weeks to become maximal but will also persist for at least 2 weeks after rifampicin has been stopped. If antiretrovirals have been started or changed at the end of TB treatment this persistent effect on enzyme induction should be taken into consideration. In addition, rifampicin increases the activity of the efflux multi-drug transporter P-glycoprotein (P-gp) that contributes to the elimination of PI. [39,40]

Rifabutin is a less potent inducer of CYP3A4. Unlike rifampicin, it is also a substrate of the enzyme [41] Therefore any CYP3A4 inhibitors will increase the concentration of rifabutin but will have no effect on rifampicin metabolism. Thus, when rifabutin is given with PI, which are inhibitors of CYP3A4, its plasma concentration and that of its metabolites may increase and cause toxicity..

Individual drug/drug interactions between rifamycins and antiretroviral agents are shown in table 1 and 2. The complexity of drug/drug interactions requires expertise in use of both antiretroviral and anti-TB drugs. One particular drug interaction should be noted: the metabolism of corticosteroids is accelerated by rifampicin and therefore doses of such drugs e.g. prednisolone, which are commonly used in TB should be increased proportionately.

5.1 Rifamycins and nucleoside / nucleotide analogues

Most nucleosides have either unknown or little change in pharmacokinetics when given together with rifampicin based regimens. Rifampicin reduces the AUC and increases the clearance of zidovudine via the mechanism of increased glucuronidation of zidovudine. This is not clinically significant and dose alteration is not required. In contrast, rifabutin does not appear to affect the clearance of zidovudine. [42,43]

The previous formulation of didanosine contained a buffer, which affected the solubility and absorption of rifampicin and ingestion of the drugs had to be separated in time. This is no longer necessary as buffer-free enteric-coated didanosine is routinely used.

5.2 Rifamycins and protease inhibitors

5.2.1 Rifampicin

Rifampicin causes a 75 to 95% reduction in serum concentrations of PI other than ritonavir. Such reductions lead to loss of antiretroviral activity of PI-containing regimens and consequently can result in the emergence of resistance to one or more of the other drugs in the HAART regimen.

Currently, most patients are given combinations of PI, which includes low dose ritonavir [usually 100mg per dose] in order to take advantage of its enzyme inhibiting properties. In effect ritonavir boosts the concentrations of the other PI allowing easier and more tolerable dosing. Data from the drug/drug interaction of rifampicin with lopinavir/ritonavir suggest that ritonavir at this low dose may compensate for the induction effect of rifampicin on lopinavir metabolism. [44,45]

Preliminary data suggested that ritonavir 100mg twice daily may be used with daily rifampicin. Once daily saquinavir/ritonavir has also been used. [46] However recent studies of subjects exposed to

rifampicin twice daily together with ritonavir boosted saquinavir developed significant hepatocellular toxicity and this combination cannot be recommended. (alert letter Roche Pharmaceuticals Ltd, February 2005). Although there is CDC guidance on the use of PI with rifamycins, it is based on the limited available data, [47]

We recommend that until more data are available low dose ritonavir/PI combinations should not be given with rifampicin-based regimens. In these cases rifampicin should be substituted for rifabutin, or the protease inhibitor and ritonavir switched to an alternative antiretroviral if alternatives exist (see below).

5.2.2 Rifabutin

Rifabutin can be used with single (unboosted) PI except saquinavir. However, because of the balance between rifabutin induction and protease inhibition of CYP3A4, when this combination is used a modification in the dose of the PI may be required (see table 2) and the dose of rifabutin should be decreased by half to 150mg. If PI are used with 100mg ritonavir boosting then the dose of rifabutin should be reduced to 150mg and should only be given three times a week.

Complex interactions may occur when a rifamycin is given with salvage regimens such as two PI plus boosted ritonavir, or with a boosted or non-boosted PI and a NNRTI. These combinations are used in patients who have had virological failure or intolerance to simpler regimens. These multiple interactions have yet to be fully studied and there are no clear guidelines regarding dosing of rifabutin when given in this situation. Here TDM should be used

5.3 Rifamycins and NNRTI

The NNRTI nevirapine is both partially metabolized by CYP 3A4 and also induces this enzyme system. The other commonly used NNRTI efavirenz behaves in a similar way. Because of this inducing effect the clinical use of these drugs together with the rifamycins is complex.

5.3.1 Rifampicin

When Rifampicin is used with efavirenz-based regimens for patients >50kg an increase in the dose of efavirenz to 800mg/day is required. Standard doses of efavirenz are used if the patient weighs <50Kg.[48-50] **[AII]**

Rifampicin reduces the AUC and Cmax of nevirapine in HIV-infected patients by 31% and 36% respectively; Although no major impact on clinical and virological responses have been reported data suggest that rifampicin (two times a week) may be given with nevirapine-based regimens. [51-54]

These observations, have led some guideline committees to suggest that nevirapine may be co-administered with rifampicin in standard doses during the treatment of co-infection. However the numbers of patients studied are small and follow up is limited.

We recommend that daily rifampicin should not be used with nevirapine. **[AIII]**

5.3.2 Rifabutin

If rifabutin is used with efavirenz the rifabutin dose should be increased to 450mg/day because of the induction effect of efavirenz. Rifabutin and nevirapine have been given together with no adjustment in either of their dosages. More data are needed before this strategy can be recommended.

5.4 Isoniazid

Pharmacokinetic or clinical interactions between isoniazid and antiretroviral agents have not been extensively studied. In-vitro studies have shown that isoniazid, at clinically relevant concentrations, is a reversible inhibitor of CYP3A4 and CYP2C19, and that it mechanistically inactivates CYP1A2, CYP2A6, CYP2C19 AND CYP3A4 in human liver microsomes. Isoniazid, co-administered with drugs such as PI and NNRTI, which are metabolized by these isoforms, may result in significant drug-drug interactions.

These interactions might be significant when isoniazid is given alone to treat latent TB infection in an HIV co-infected patient who is receiving PI or NNRTI. The pharmacokinetic and clinical consequences of concurrent therapy with rifampicin (inducer) and isoniazid (inhibitor) together with PI and NNRTI on CYP3A4 have not been studied but may be clinically important. [55,56]

5.5 Non-rifamycin regimens

HIV related tuberculosis may be treated with non-rifamycin containing regimens. These should be only contemplated in patients with serious toxicity to rifamycins, where desensitization/reintroduction has failed, or in those with rifamycin-resistant isolates.

Drug/drug interactions might be fewer but a non-rifamycin regimen is inferior to a rifampicin-based regimen for the treatment of HIV-related tuberculosis.

It should be noted that high TB relapse rates, greater than 15%, have been seen when an initial 2 months rifampicin-containing regimen is then switched in the continuation phase to isoniazid and ethambutol

6.0 Overlapping toxicity profiles of antiretroviral drugs with anti-tuberculosis 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 antituberculosis drugs especially rifampicin, isoniazid and pyrazinamide. The NNRTI and co-trimoxazole may also cause similar features. The co-administration of these drugs can lead to difficult clinical management decisions if these side effects occur especially when 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.[57]

Adverse events led to cessation or interruption of either their TB or HIV therapy in 63 (34%) of the 183 patients. The most common 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%).

The majority of adverse reactions occurred within the first 2 months of starting concurrent therapies. Rifampicin was frequently implicated by the treating physicians, and was responsible for almost 2/3 of adverse events.

6.1 Hepatotoxicity

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

1) A serum AST or ALT level of more than three times the upper limit of normal in the presence of symptoms, or
2) A serum AST or ALT greater than five times the 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 versus about 2.3% in those older than 50 years. It is also more likely in those with a heavy alcohol intake, with hepatitis C co-infection and in those who are receiving therapy with rifampicin. High rates of adverse reaction requiring changes in therapy have been reported in HIV infected patients who are likely to have some or all of the other risk factors noted above. The rates of adverse reaction were 26% in one HIV cohort compared with 3% in the HIV uninfected group. Other studies have shown similar results. [144, 145,146]

If hepatitis develops then all potentially hepatotoxic drugs including isoniazid, rifampicin, pyrazinamide and others eg antivirals and co-trimoxazole, should be stopped immediately.

Serological testing for hepatitis viruses A, B, and C, if not already done, should be performed and the patient asked about any exposure to other possible hepatotoxins, especially alcohol.

As resolution of the hepatitis may be prolonged and until the cause of the hepatitis is identified then, if necessary, it would be reasonable to treat with two or more antituberculosis medications without significant risk of hepatotoxicity, such as ethambutol, streptomycin, amikacin/kanamycin, capreomycin, or a fluoroquinolone.

Monitoring of serum AST (or ALT) and bilirubin and any symptoms should be performed frequently and once the AST level drops to less than two times the upper limit of normal and symptoms have significantly improved, then first line medications can be restarted using a reintroduction regimen [Table 4].

If the drugs cannot be restarted or the initial reaction was life threatening then an alternative regimen can be used (see below).

6.2 Pre-existing liver disease

The risk of hepatotoxicity in these patients 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 due to chronic liver disease even before starting treatment, then other regimens can be used e.g.

1) Avoid pyrazinamide and treat with isoniazid and rifampicin for 9 months, adding ethambutol until isoniazid and rifampicin susceptibility are demonstrated **[AIII]**
2) Avoid isoniazid and treat with rifampicin, ethambutol, and pyrazinamide for 2 months, followed by 10 months of rifampicin and ethambutol. **[BIII]**
3) 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 however, there are no data to support this recommendation. **[CIII]**

In all patients with preexisting liver disease, frequent clinical and laboratory monitoring should be performed to detect drug induced hepatic injury.

Monitoring should be performed more frequently (at least 2 weekly initially) in those with underlying liver disease. This should include biochemical and hematological assessments and the prothrombin

time. Patients should be told to report to their physician if they develop symptoms such as anorexia, nausea, vomiting, abdominal pain or jaundice. [58,59]

6.3 Gastrointestinal side effects

These are common especially in the first 2-3 weeks after starting anti-tuberculosis therapy. If patients develop epigastric pain, vomiting or nausea with first line drugs, have no evidence of hepatic disease and are unresponsive to symptomatic treatment e.g. with anti-emetics, then they can:

1) take their treatment with meals unless on less than 600 mg rifampicin daily. Food delays or decreases the absorption of anti-tuberculosis drugs but these effects are moderate and of little clinical significance or
2) change the time of dosing.

Patients should avoid dividing doses or changing to alternative drugs if at all possible; however sometimes dividing the dose of e.g. pyrazinamide, can improve tolerability

6.4 Peripheral neuropathy

The nucleoside analogues ddI, ddC and d4T may all cause peripheral neuropathy and an additive toxicity of isoniazid when used with d4T has been demonstrated. These antiretroviral drugs can be avoided in the HAART naïve population and alternatives should be found if possible in those already on these drugs. **[AII]**

Pyridoxine 10-25mg daily should be used in all HIV positive patients receiving isoniazid. [57,60]

7.0 Drug absorption

7.1 Malabsorption of drugs

Malabsorption of antimycobacterial drugs with all first line therapies as well as ethionamide and cycloserine has been reported in co-infected persons.

Absorption of drugs may be less in those patients with a low CD4 count, whether it be due to HIV enteropathy or other specific HIV related gut diseases resulting in sub therapeutic serum and drug levels and consequently associated with treatment failure and drug resistance. Although some studies show lower peak concentrations of rifampicin and ethambutol as well as lower AUC compared with controls, there are other data suggesting that rifampicin is well absorbed in HIV patients even those with AIDS or with diarrhoea. [61-67]

7.2 Therapeutic drug monitoring (TDM)

TDM of TB drugs: [BII]

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

- patients who are at high risk of malabsorption of their TB drugs,
- in those who are responding inadequately to directly observed therapy with first line drugs
- in patients being treated for multi-drug resistant tuberculosis.

- In those who are on non-standard TB regimens or taking non-standard doses

One of the problems with monitoring anti-mycobacterial drugs in HIV positive patient is that the kinetics of absorption is not predictable. It is therefore difficult to know when to measure a peak serum level; and it is probably best to assess this in the individual patient by checking levels at more than one time point post dose eg 1, 2 and 4 hours. Decision re dosing may be difficult as there can be long delays in results returning to the physician. [61-67]

TDM of HIV drugs: [BII]

TDM may be relevant for PI and NNRTI especially when regimens are complex, when no formal PK data are available to guide the physician and when virological failure occurs.

8.0 When to start HAART

The optimal time to start HAART in TB/HIV patients is not known. Physicians have to balance the risk of HIV progression if HAART is delayed against the risk of having to discontinue therapies because of toxicities, side effects, paradoxical reactions or unforeseen drug/drug interactions if HAART is started. Similar routes of metabolism and elimination and extensive drug interactions may result in sub-therapeutic plasma levels of antiretroviral agents and furthermore, overlapping toxicity profiles may result in the interruption or alteration of TB and HIV regimens with potential subsequent microbiological or virological failure. In co-infected patients delaying the start of HAART can simplify patient management, limit the development of side effects and drug interactions and the risk of immune restoration reactions.

Deaths in the first month of TB treatment may be due to TB, while late deaths in co-infected persons are attributable to HIV disease progression. [68-70]

Patients with HIV disease and a CD4 cell count >200 cells/uL 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/uL. Some recommend that antiretroviral therapy be delayed until the first 2 months of tuberculosis therapy has been completed. Others would only recommend this strategy for those with CD4 counts >100 cells/uL, because of the short-term risk of developing further AIDS defining events and death[71-75]

One retrospective study has shown that 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. [57]Prospective data on these patients are needed.

8.1 Suggested timing of HAART in HIV/TB co-infection [AII]

CD4 count cells/uL	When to treat with HAART
<100	As soon as possible-dependent on physician assessment, [Some physicians delay up to 2 months]
100-200	After 2 months of TB treatment
>200	After completing 6 months TB treatment*

NB: regular 6-8 weekly CD4 count monitoring should be performed. If the CD4 count falls patient may need to start HAART.

* as per BHIVA treatment guidelines

9.0 Directly observed therapy (DOT)

The use of directly observed therapy is held up as the gold standard by WHO and CDC for the treatment of HIV related tuberculosis especially when using intermittent dosing. It is recommended that all patients with MDR-TB have DOT. **[AII]**

It should be noted that the superiority of DOT over self-administered therapy for the treatment of TB in developing countries is yet to be proven. Controlled, randomized trials performed in South Africa and Pakistan showed similar treatment completion and cure rates for DOT and self-administered TB treatment. [76-78]

In contrast, investigators in Thailand found higher treatment completion and cure rates in patients assigned to DOT compared to self-administered treatment, however special conditions pertained to the patients in this study. [79]

Patient centered care should be at the core of multidisciplinary management and should always include an adherence strategy that emphasizes DOT. This may include DOT/supervised therapy for antivirals. [80] **[BIII]**

However there are no published data on the utility and efficacy of combined HAART/TB DOT in treating co-infection.

DOT usually requires that patients be observed to ingest each dose of antituberculosis medication, to try and ensure the completion of therapy. Any treatment plan should be individualized to incorporate measures that facilitate adherence to the drug regimen. Such measures may include, for example, social service support, treatment incentives, housing assistance, referral for treatment of substance misuse, and co-ordination of tuberculosis services with those of other providers.

10.0 Tuberculin skin testing

In the pre-HIV era about 75% - 85% patients with newly diagnosed pulmonary tuberculosis had a positive response to 5 units [intermediate strength] PPD testing.

In HIV and TB co-infection there is a reduction in the proportion of those reacting to PPD as the CD4 count falls, from 50%-90% in those who have a CD4 count of ≥500 cells/uL down to 0% - 20%, in those patients who have AIDS or advanced HIV infection and a CD4 count of ≤200cells/uL. This limits the usefulness of the tuberculin test as a diagnostic tool.

Specific non-reactivity to PPD is difficult to distinguish from the general poor immune responsiveness seen in HIV infected patients and anergy testing using a panel of antigens gives inconsistent and ambiguous results and is not a recommended strategy.

HAART may improve immunological responses to tuberculosis but patients most likely to revert from a negative to a positive PPD are those with a rise in CD4 count of >200 cells/uL from baseline. [81-89]

10.1 Who should have tuberculin testing?

A tuberculin test is performed in order to identify those patients who may have latent TB infection so treatment may be given in order to prevent reactivation. US guidelines recommend that all newly diagnosed HIV patients should have a tuberculin skin test and those with a positive test (>5mm induration) should be given isoniazid or other chemo preventative therapy. Whether this policy has any long-term public health impact on TB control in countries where tuberculosis has a relatively low prevalence is not known. [90-97]

There are many factors that may affect the usefulness of such a broad strategy. These include the lower PPD positive rates in HIV positive patients, the effect of BCG immunization on PPD reactivity, the relative short term impact of chemo preventative therapy where there are high rates of exogenous infection and the effect of HAART in preventing tuberculosis reactivation and progression to infection. In newly diagnosed patients with CD4 counts <400 cells/uL the routine use of tuberculin testing is not recommended. **[DII]**

11.0 Chemo preventative therapy – HAART or antituberculosis drugs?

Widespread use of HAART has reduced the risk of developing clinical TB among persons infected with HIV and may help bring about further declines when integrated into TB programmes. The effect of HAART on the risk of TB among persons infected with HIV has been examined in several studies. The risk of TB was up to 80% lower among persons prescribed HAART and 40% lower among persons prescribed other non-HAART antiretroviral therapy than the risk in persons not prescribed antiretroviral therapy. The protective effect of HAART was greatest in symptomatic patients and those with advanced immune suppression but was not apparent in those with CD4 counts >350 cells/uL.[31-33] Its effect is almost certainly related to improvements in systemic immunity (measured by an increase in the CD4 count) to a point where the risk of new or reinfection is greatly diminished.

There have been several short-term controlled trials in HIV positive persons showing the protective effect of chemo preventative therapy. [98-110]

A protective effect of isoniazid is found only in those who are tuberculin skin test positive. This protective effect appears to only last 2 to 4 years as compared with 19 years or more in non-HIV populations. Such a short term effect in HIV positive patients studied especially in areas of high TB prevalence may be explained by the fact that the majority of the tuberculosis in HIV population arises from exogenous sources and thus are not from reactivation of latent TB but are new. Beyond recognized outbreaks, there is little evidence to suggest that re-infection (as opposed to reactivation) is a major factor in the UK.

A pragmatic but still theoretical approach in those HIV patients who are at increased risk of TB, eg immigrants, is to give isoniazid prophylaxis until the CD4 count has risen to above a reasonable threshold, say 200–300 CD4 cells/uL on HAART and then it could be stopped. Data are needed on what the threshold might be as patients may need to be on isoniazid for more than 1 year and the effects of this are relatively unknown.

The routine use of such chemo preventative therapy in this setting is not recommended. **[DI]**

11.1 The treatment of latent tuberculosis infection

The treatment of latent tuberculosis infection includes:

1. Isoniazid for a total of 6- 9 months
2. Rifampicin with isoniazid for a total of 3 months
3. Rifampicin alone for 4 months

Short courses of chemo preventative therapy using other drugs have been recommended to help overcome poor adherence. Unfortunately rifampicin and pyrazinamide given three times a week for 2 months has been associated with severe and fatal hepatic reactions in 5 non-HIV patients with a total of 21 cases of liver injury reported to CDC. [111]

However this complication was not been seen in the studies of HIV positive patients taking this regimen.

It is known from RFLP studies that many tuberculosis infections in HIV positive patients in TB endemic areas appear to be new infections rather than reactivation of the original TB. [112]Isoniazid may prevent such exogenous infection but would then have to be given long term or at least until there was a substantial CD4 rise on HAART[113-115]. There are no current data to support such a strategy.

12.0 Management of relapse, treatment failure and drug resistance

12.1 Relapse

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

1. Culture positive again or
2. Has clinical or radiographic deterioration that is consistent with active tuberculosis.

Every effort should be made to establish a diagnosis and to obtain microbiological confirmation of the relapse to enable testing for drug resistance.

Most relapses occur within the first 6–12 months after completion of therapy.

Patients whose initial tuberculosis was drug susceptible and who were treated with rifamycin containing regimens using DOT, relapse with susceptible organisms in nearly all cases. In patients who received self-administered therapy or a non-rifamycin regimen and who relapse, the risk of acquired drug resistance is substantial.

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

1) For patients with tuberculosis caused by drug susceptible organisms and who received DOT, initiation of the standard four-drug regimen is appropriate until the results of drug susceptibility tests are available. **[AII]**
2) For patients who have life threatening forms of tuberculosis, at least three additional agents to which the organisms are likely to be susceptible should be included even if the criteria in 1) are fulfilled. **[AIII]**
3) For patients with relapse who did not receive DOT, and/or who were not treated with a rifamycin based regimen, or who are known or presumed to have had irregular treatment, or poor adherence then it should be assumed that drug resistance is present and to treat with isoniazid, rifampicin, and pyrazinamide plus an additional two or three agents. Such agents would include a fluoroquinolone, an injectable agent such as streptomycin or amikacin,,with or without additional oral drugs such as para-aminosalicylic acid (PAS), cycloserine, prothionamide and clarithromycin. **[AIII]**

12.2 Treatment failure

Treatment failure is the presence of continued or recurrently positive cultures during the course of antituberculosis therapy. After 3 months of multi-drug therapy for pulmonary tuberculosis caused by drug susceptible organisms, 90–95% 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:

1. Non-adherence
2. Drug resistance
3. Malabsorption of drugs
4. Laboratory error and
5 A few patients take a long time to respond as part of extreme biological variation.

If treatment failure occurs the case should be referred to a regional centre[116]. *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 to which the patient has not been exposed and susceptibility thought likely should be added.

Empirical regimens usually include a fluoroquinolone and 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 according to the results.

12.3 MDR-TB

TB resistant to at least isoniazid and rifampicin (multi-drug resistant [MDR]) are at high risk of further acquired drug resistance. All such patients whatever their HIV status should be referred to regional treatment centres.

Although patients with strains resistant to rifampicin alone have a better prognosis than patients with MDR strains, they are also at increased risk for treatment failure and additional resistance and should be managed in consultation with an expert.

There are no definitive randomized or controlled studies to establish the best regimens for treating patients with various patterns of drug resistant tuberculosis. Such treatment recommendations are based on expert opinion. Surgical resection in the management of patients with pulmonary MDR tuberculosis has had mixed results and its role has not been established in randomized studies.

13.0 Pregnancy and breastfeeding

Because of the risk of tuberculosis to the fetus, treatment of tuberculosis in pregnant women should be initiated whenever the probability of maternal disease is moderate to high. The initial treatment regimen should consist of isoniazid, rifampicin, and ethambutol. Pyrazinamide can probably be used safely during pregnancy and is recommended by the WHO and the International Union against Tuberculosis and Lung Disease (IUATLD). Although all of these drugs cross the placenta, they do not appear to have teratogenic effects. Streptomycin has harmful effects on the human fetus (congenital deafness) and should not be used and prothionamide is teratogenic.

NB If pyrazinamide is not included in the initial treatment regimen, the minimum duration of therapy is 9 months.

As in the general population pyridoxine supplementation (10-25 mg/day) is recommended for all HIV positive patients taking isoniazid, including pregnant women.

14.0 Immune reconstitution inflammatory syndrome (IRIS) / paradoxical reactions

Some patients after starting antituberculosis treatment will develop an exacerbation of symptoms, signs, or radiological manifestations of tuberculosis. This has been well described in patients without HIV infection, but appears to occur more commonly in HIV positive patients. [117-136]

The etiology of these reactions is unknown, but it is presumed in HIV disease that they occur at least in part as a consequence of HAART-related reconstitution of immunity leading to an abnormal immune response to tubercle antigens released by dead or dying bacilli[137-42]

These reactions do not have a widely accepted definition. They are characterised by worsening or appearance of new signs, symptoms, or radiographic manifestations of tuberculosis that occur after initiation of HAART and are not the direct result of TB treatment failure or another disease process.

They are often defined as transient but can last many months. They are usually seen when the TB is microbiologically controlled but cases can occur with viable organisms isolated on culture. Such paradoxical reactions have been reported in immunocompetent patients before HIV became prevalent. Worsening of nodal disease occurred in around 10% of some populations and central nervous system disease with enlarging tuberculomata was sometimes seen.

14.1 Epidemiology

In the HAART era IRIS has been reported widely and occurred in 36% (12/33) and 32% (6/19) of patients in two of these studies but in another paradoxical worsening was not significantly more common in patients receiving HAART (3 of 28 cases or 11%) compared with 3 of 44 cases (7%) in patients not receiving antiretroviral treatment.

Reactions occur within a median of 15 days after HAART. IRIS does not appear to be associated with any particular antiretroviral regimen or drug class. Most patients with IRIS have advanced HIV infection (in one study the median baseline CD4 cell count was 35 cells/uL, and median HIV RNA load was approximately 580,000 copies/mL). Its relationship to the initiation of antiretroviral therapy suggests that, as the immune system recovers from profound immunosuppression, abnormal responses toward mycobacterial antigens occur.

IRIS most often presents with fever and increased or new lymphadenopathy. The skin over the nodes is often inflamed 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.

With such small data sets in the literature it is difficult to know who is at risk of IRIS but a low baseline CD4 cell count and a rapid recovery in CD4 numbers appear to be relevant. Cases with dissemination outside the lung may also be at increased risk. HAART started within the first 2 months of tuberculosis treatment was associated with an increased risk of IRIS. This may be due to the high burden of bacilli inducing immunologic changes associated with the rapid rise in CD4 cells.

14.2 Diagnosis and management of IRIS [AIII]

The diagnosis of IRIS must be one of exclusion as it can be confused with recrudescence of tuberculosis due to treatment failure and with drug hypersensitivity. Other infections common among immunocompromised patients should be excluded. The management of patients with 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*. It is not unusual for patients to be on these for prolonged periods of time and the dose to be increased again when IRIS relapses or recurs. Physicians should be aware of the metabolic side effects and potential to develop serious infections eg CMV retinitis in patients receiving high dose corticosteroids

Non-steroidal anti-inflammatory agents tend not to be helpful. Temporary discontinuation of antiretroviral therapy has also been advocated but can cause precipitous falls in CD4 counts. Recurrent needle aspiration of nodes or abscesses especially if they become tense and/or inflamed can prevent spontaneous rupture which, if occurs, can lead to long-term sinus formation and scarring. The use of steroids in this context may lead to necrosis and persistent discharge.

* After 2 or more weeks of rifampicin therapy this drug has an inducing effect on the metabolism of corticosteroids such that the corticosteroid is effectively reduced in efficacy by 33-50 %.

15.0 Prevention and control of transmission of HIV related tuberculosis

The guidelines for these are in the Interdepartmental Working Group on Tuberculosis published in 1998 by the Department of Health[116] and is available on the Department of Health and Health Protection Agency websites:

http://www.dh.gov.uk/PublicationsAndStatistics/fs/en

http://www.hpa.org.uk/infections/topics_az/tb/links/guidelines.htm

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

1. A recognition that tuberculosis is a potential diagnosis
2. That the diagnosis should be confirmed as soon as possible
3. That drug resistance should be considered early in non-responding patients or when patients have a history compatible with drug resistance
4. There should be no delay in starting treatment
5. Treatment should be started with appropriate drugs
6. Patients should have supervised therapy.

There should be appropriate accommodation for isolation of patients with potential tuberculosis and those with known tuberculosis. A risk assessment should always be made. There should be adequate isolation rooms and negative pressure facilities should be properly monitored. Aerosol generating procedures should not take place except in negative pressure rooms in patients with suspected or confirmed with tuberculosis. All patients with suspected or confirmed pulmonary tuberculosis should be considered potentially infectious until proven otherwise. There should be no intermingling of HIV infected or other immunosuppressed patients with patients who have potentially or infectious tuberculosis. [116]

All hospitals should have a TB control plan based on risk assessment. There should be 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.

Concerns over deductive disclosure of HIV status if the HIV treating physician notifies a patient can be overcome as any physician involved in the patients care can notify the patient.

Contact tracing should follow the BTS guidelines but requires considerable sensitivity.

16.0 Death and clinico-pathological audit of HIV-associated tuberculosis

Despite diagnosis and treatment, patients with HIV and tuberculosis still die.[143] It is important that as many such patients as feasible are examined by autopsy after death. This categorises the causes of death and enables audit of medical practice. The significant categories of pathology include:

1. death from active, progressive tuberculosis
2. death from IRIS affecting one or more critical organs (eg lung, brain), or from anti-TB drug toxicity
3. death from other HIV-related or non-HIV-related disease in a person who was effectively treated for tuberculosis
4. death from other disease in a person diagnosed with and treated for tuberculosis, without laboratory confirmation, who shows at autopsy no evidence of having had tuberculosis

If the interval between TB culture positivity and death is <=3 months, culture of tuberculous autopsy tissue should be performed to evaluate drug sensitivity and bacterial viability
Autopsies are either requested by clinicians or (in UK) commanded by a Coroner or Procurator Fiscal. If the autopsy is coronial, every endeavour should be made to obtain the autopsy report for clinical audit. Before any autopsy, contact with the appointed pathologist to discuss the clinico-pathological issues is recommended. *Pathology staff should adopt suitableuniversal infection control precautions against airborne and blood borne pathogens*

17.0 Tables

Table 1

Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BHIVA	British HIV Association
BTS	British Thoracic Society
CDC	Centers for Disease Control and prevention
CMV	cytomegalovirus
CNS	central nervous system
CXR	chest X-ray
CYP	cytochrome
d4T	stavudine
ddC	zalcitabine
ddI	didanosine,
DOT	directly observed therapy
E	ethambutol
H	isoniazid
HAART	Highly Active Anti-Retroviral Therapy
HIV	Human Immunodeficiency Virus
IRIS	Immune Reconstitution Inflammatory Syndrome
IUATLD	International Union against Tuberculosis and Lung Disease
MDR-TB	Multi Drug Resistant tuberculosis
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PAS	para-aminosalicylic acid
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PI	Protease inhibitor
PPD	purified protein derivative
R	rifampicin
TB	tuberculosis
TDM	therapeutic drug monitoring
WHO	World Health Organisation
Z	pyrazinamide

Table 2

Table rating system for the 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 that either are not randomized or were conducted in other populations

III. Expert opinion

Adapted from Gross PA, Barrett TL, Dellinger EP, Krause PJ, Martone WJ, McGowan JE Jr, Sweet RL, Wenzel RP. Clin Infect Dis 1994;18:421.

Table 3

Drugs used in the treatment of TB

First line drugs	Second line drugs
isoniazid	cycloserine
rifampicin*	prothionamide/ethionamide
pyrazinamide	levofloxacin*
ethambutol	moxifloxacin*
streptomycin	ofloxacin*
	ciprofloxacin*
	paraminosalicylic acid
amikacin/kanamycin*	capreomycin
rifabutin	

* rifabutin may be substituted for rifampicin in some situations eg drug/drug interactions

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

Table 4

Drug Interactions: For detailed information about HIV drug interactions see University of Liverpool at http://www.hiv-druginteractions.org/

Key for interaction tables.

No Interaction – dose as normal	♦
Potential Interaction – see advice	—
Definite interaction – do not combine	●

Reverse Transcriptase Inhibitors (NTI)

Anti-retroviral	Rifampicin	Rifabutin	Isoniazid	Pyrazinamide	Streptomycin	Amikacin	Clarithromycin	Azithromycin	Oflo xacin	Ciprofloxacin
NRTI										
Abacavir (ABC)	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
Didanosine EC capsules only (DDI)	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
Lamivudine (3TC)	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
Stavudine (D4T)	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
Zalcitabine (DDC)	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
Zidovudine (AZT)	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
NNRTI	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
Tenofovir	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦

Non-Nucleoside Reverse Transcription Inhibitors (NNRTI)

NNRTI	Rifampicin	Rifabutin	Isoniazid	Pyrazinamide	Streptomycin	Amikacin	Clarithromycin	Azithromycin	Ofloxacin	Ciprofloxacin
Delavirdine	● 96% ↓ in Delavirdine with Rifampicin no change in Rifampicin	● 80% ↓ in Delavirdine and highly significant change in Rifabutin levels	♦	♦	♦	♦	♦	♦	♦	♦
Efavirenz	— Dose of Efavirenz should be increased to 800mg OD. No dose adjustment required for Rifampicin	— In 1 small study Efavirenz reduced the AUC of Rifabutin by 38 %. No effect on Efavirenz. May consider increasing the dose of Rifabutin by 50% (450mg)	♦	♦	♦	♦	— 39% ↓ in AUC Clarithromycin. 11% ↑ in AUC Efavirenz. No clinical significance. There have been reports of ↑ frequency of rash. Consider Azithromycin as an alternative (no interaction)	♦	♦	♦

Nevirapine	● 58% ↓ in Nevirapine AUC no change in Rifampicin	— Dose both as normal 12%↑ in AUC with Rifabutin no significant changes to active metabolite of Rifabutin	♦	♦	♦	♦	— 30%↓ in AUC of Clarithromycin. 26% ↑ in Nevirapine AUC. No dose adjustment required.	♦	♦	♦

Protease Inhibitors (PI)

PI	Rifampicin	Rifabutin	Isoniazid	Pyrazinamide	Streptomycin	Amikacin	Clarithromycin	Azithro-mycin	Ofloxacin	Ciprofloxacin
Amprenavir	● 82% ↓ AUC for amprenavir	— Reduce dose of Rifabutin to half (150mg od) monitor for signs of neutropenia	♦	♦	♦	♦	♦	♦	♦	♦
Indinavir	● 89% ↓AUC for Indinavir	● ↓AUC 33% for Indinavir and ↑AUC 204% for rifabutin	♦	♦	♦	♦	♦	♦	♦	♦
Kaletra	● ↓ AUC for kaletra	— Reduce dose of Rifabutin to 150mg three times a week	♦	♦	♦	♦	— In renal impairment↓ Clarithromycin dose by 50% (clearance 30-60 mls/min) , and by 75% (clearance <30 mls/minute)	♦	♦	♦

PI	Rifampicin	Rifabutin	Isoniazid	Pyrazinamide	Streptomycin	Amikacin	Clarithromycin	Azithro-mycin	Ofloxacin	Ciprofloxacin
Nelfinavir	● 82% ↓ AUC for Nelfinavir	— Reduce dose by half (150mg) No dose adjustment needed for Nelfinavir	♦	♦	♦	♦	♦	♦	♦	♦
Ritonavir	● 35% ↓ AUC for Ritonavir	● 7-fold ↑AUC for Rifabutin at 500mg bd	♦	♦	♦	♦	— 77%↑ AUC Clarithromycin, reduce dose only if renal impairment	♦	♦	♦
Saquinavir	● 70% ↓ AUC of Fortovase (SG) and a 80% ↓ AUC for Invirase (HG)	● Co-administration results in significantly reduced plasma levels of Saquinavir	♦	♦	♦	♦	— Clarithromycin AUC↑ 34% Saquinavir AUC↑177% no dosage adjustment necessary	♦	♦	♦
PI	Rifampicin	Rifabutin	Isoniazid	Pyrazinamide	Streptomycin	Amikacin	Clarithromycin	Azithro-mycin	Ofloxacin	Ciprofloxacin
Boosted PI	●	— Very little information available. Consider using Rifabutin 150mg Three times a week as per Kaletra	♦	♦	♦	♦	— No information available but based on information available for single Proteases and Kaletra should be safe	♦	♦	♦

Table 5

Guidelines for the reintroduction of anti-tuberculous 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 / 600mg < 50kg _	
8	300mg	450mg/600mg	250mg
9	300mg	450mg/600mg	500mg
10	300mg	450mg/600mg	1g
11	300mg	450mg/600mg	1.5g > 50kg / 2g < 50kg
12	300mg	450mg/600mg	1.5g/2g
13	300mg	450mg/600mg	1.5g/2g

Add in ethambutol once all other 3 drugs are at full dose. If the reaction is severe start with one tenth of the first day dose for each drug. Commonly used modifications include those with 3 days between each drug being restarted after the full introduction of the previous drug.

Table 6

Definition of IRIS

- Apparent worsening/progression of tuberculosis.
- This may occur at the original site of the disease or at a more remote site.
- Symptoms, signs, laboratory or radiological findings consistent with another diagnosis excludes IRIS.
- IRIS may occur at any time point after initiation of TB treatment.
- The occurrence of IRIS is associated with commencing or continuing HAART.
- There must be no evidence of TB bacteriological relapse or recurrence. A positive AAFB smear does not exclude a diagnosis of IRIS.
- The patient should have had appropriate investigations to exclude concomitant disease due to other pathogens.
- Drug hypersensitivity is excluded.
- A response to corticosteroid treatment does not confirm a diagnosis of IRIS.

Box 1

Treatment of uncomplicated non-CNS tuberculosis
A four-drug regimen of isoniazid, pyrazinamide, ethambutol and rifampicin given for 2 months followed by 4 months of rifampicin and isoniazid is recommended

Box 2

Treatment of CNS or MDR tuberculosis
A prolonged treatment duration is recommended
Tuberculous meningitis is treated for 12 months
In patients with multi drug resistant tuberculosis 2 years or more treatment may be indicated

Box 3

Treatment of tuberculosis
A regimen of daily therapy is recommended
If three or five time a week therapy is given then this should be highly supervised, preferably by DOT

Box 4

Liver disease
Patients with concomitant liver disease should have close monitoring of their liver function tests and be warned to present immediately to healthcare facilities if symptoms of hepatitis occur eg jaundice, vomiting etc

Box 5

Molecular diagnostic techniques
These may be used for rapid identification of species and drug resistance
Results may inform important decisions regarding control of infection and choice of treatment regimen

Box 6

Notification of tuberculosis
All patients with tuberculosis, regardless of HIV status, should be notified

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