Canadian Tuberculosis Standards

7th Edition

Chapter 10: Tuberculosis and Human Immunodeficiency Virus

To promote and protect the health of Canadians through leadership, partnership, innovation and action in public health.

— Public Health Agency of Canada

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CHAPTER 10

TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS

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KEY MESSAGES/POINTS

DIAGNOSIS OF HIV

- All patients with newly diagnosed TB who are not already known to be HIV-seropositive should undergo informed HIV serologic testing unless they persistently refuse testing (opt-out screening).

- TB programs should take advantage of contact tracing activities to offer provider-initiated HIV testing to at-risk individuals.

DIAGNOSIS OF LTBI

- Every patient with newly diagnosed HIV infection should be assessed with regard to history of active TB, previous tuberculin skin test (TST) results and known or likely TB exposure, including close contact with an infectious case or exposure to a community with high TB prevalence. A clinical assessment and chest radiography should be performed to look for features of previous or active TB**.**

- Unless there is a history of active TB or a well-documented previous positive TST or interferon gamma release assay (IGRA), every HIV-infected person should have a TST performed with 5 tuberculin units of purified protein derivative and read at 48-72 hours by a health care worker experienced in reading TSTs.

- Use of an IGRA as an additional test may be considered if the TST is negative, particularly if the patient is thought to have a high likelihood of TB exposure.

- TST induration of $\geq$5 mm should be considered indicative of TB infection in HIV-infected individuals.

- Anergy testing is *not* recommended.

- A TST should be repeated annually in patients at markedly increased risk of ongoing TB exposure, e.g. homeless shelter exposure or return travel to high TB endemic countries.

- In patients with an initial negative TST, repeat TST should be considered after institution of antiretroviral therapy (ART) and immune reconstitution indicated by an increase in the CD4 cell count.

- HIV-infected patients found to be TST- or IGRA-positive or with well-documented previous positive TST should be evaluated for the presence of active TB by clinical assessment, chest radiography and any other investigations suggested by the clinical findings. Even when the chest x-ray is normal, sputum should be obtained for *M. tuberculosis* smear and culture.

ART INITIATION AND LTBI DIAGNOSIS

- TST or IGRA positivity may be considered as factors favouring earlier ART initiation.

TREATMENT OF LTBI

Recommendations for the treatment of LTBI in HIV-infected individuals are similar to those for non HIV-infected patients and are reviewed in detail in Chapter 6. It is important to remember that the risk of disease reactivation from LTBI is substantially higher, and drug interactions need to be considered for those taking ART.

- Except when there is a well-documented history of completed treatment of LTBI or completed treatment of active TB, treatment of LTBI should be strongly recommended for every HIV-infected patient with a TST reaction $\geq$5 mm or positive IGRA test, regardless of age or BCG (Bacille Calmette-Guérin**)** vaccination status, after exclusion of active TB.

- HIV-infected people thought to have had recent close contact with an infectious TB patient should receive treatment for presumed LTBI regardless of the TST result.

- In HIV-infected individuals for whom treatment of LTBI is indicated, the recommended regimen is the same as that recommended for HIV-uninfected patients: daily self-administered isoniazide (INH) for 9 months.

- Continuation of INH beyond 9 months is not recommended in Canada, given the relatively low exposure rates.

- Daily rifampin (RMP) for 4 months is an alternative regimen in cases of INH intolerance in the patient or INH resistance in the exposure source, or in patients for whom the shorter duration is felt to be critical to the likelihood of completion, as long as it is compatible with the patient's antiretroviral regimen.

- Daily RMP plus isoniazid is an alternative (Chapter 6) but is associated with the potential toxicity of isoniazid and the potential drug interactions of RMP.

- The 3-month regimen of *supervised* once weekly rifapentine and weekly isoniazid is a promising alternative but is NOT currently recommended for HIV-infected patients.

- The combination of RMP and pyrazinamide (PZA) is NOT recommended for treatment of LTBI, regardless of HIV serostatus.

- It is recommended that consideration be given to practical measures such as clinic hours, staff attitudes, inducements, social supports, close follow-up and linking with adherence supports that may be in place for ART.

- For HIV-infected patients with predictors of poor adherence, such as unstable housing, active substance abuse or major psychosis, or those who have demonstrated poor adherence, consideration should be given, along with other supports, to providing directly observed twice weekly treatment of LTBI; twice weekly regimens should always be given under direct supervision.

- HIV-infected people who are candidates for preventive therapy but who do not receive it for any reason should have regular clinical follow-up. TB should be considered in the differential diagnosis and mycobacterial cultures of appropriate specimens included in the investigation of any unexplained illness.

- In an HIV-infected pregnant woman for whom treatment of LTBI is indicated, it should be initiated as soon as active disease has been excluded and not delayed until after the delivery.

DIAGNOSIS OF ACTIVE TB

- Health care workers caring for patients with HIV infection should maintain a high index of suspicion for TB, particularly in patients with an increased epidemiologic likelihood of either recent or remote TB exposure, when investigating any unexplained illness, especially persistent fever or lung disease, even in the absence of typical features of TB.

- An HIV-infected patient in whom a respiratory tract specimen is found to contain acid-fast bacilli should generally be managed as a suspected TB case until such time as the organism has been shown *not* to be *M. tuberculosis.*

TREATMENT OF ACTIVE DISEASE

TB treatment

- Treatment of TB in HIV-infected patients should be guided by a physician with expertise in the management of both diseases or in close collaboration with a physician expert in HIV care.

- Anti-TB therapy should be initiated immediately upon the diagnosis of TB, irrespective of ART considerations.

- A standard rifamycin (RMP or RBT)-containing regimen should be used unless the organism is rifamycin resistant or the patient is intolerant of rifamycins (Chapter 5).

- The TB program should achieve successful completion of treatment using measures outlined in Chapter 5, as determined by the patient's requirements, which may include directly observed therapy.

- A treatment duration of 8 months, including INH and RMP for 8 months and PZA for the first 2 months, is recommended in patients with HIV infection who decline or for other reasons do not take ART.

- As in the preferred regimen for HIV-uninfected patients, the first 2 months (intensive phase) should be administered daily in HIV-infected patients and the continuation phase given daily (if self-administered) or thrice weekly, but not twice weekly (if on DOT) in HIV-infected patients, particularly those with CD4 cell counts $\leq$100 x 10^6/L.

- If cavitation is present on the chest x-ray or if treatment response is delayed (culture positive at 2 months), treatment may need to be prolonged from 6 to 9 months (see Chapter 5).

- In patients for whom PI-based ART is judged most appropriate, dose-adjusted rifabutin should be substituted for RMP in standard treatment regimens. (RMP should be switched to rifabutin 2 weeks before ART is initiated to allow for "washout" of the hepatic enzyme induction.)

- Routine measurement of serum concentrations of antituberculous drugs, particularly rifabutin, is suggested, especially in any patient with chronic diarrhea and advanced HIV disease, in whom a drug interaction is suspected to be lowering anti-TB drug levels or who is demonstrating a suboptimal response to TB therapy.

Antiretroviral treatment

- A diagnosis of TB in an HIV-infected individual constitutes an indication for ART.

- In patients not receiving ART at the time TB treatment is initiated, if the CD4 count is <50 x 10^6/L, ART should be initiated within 2 weeks of starting anti-TB treatment; if the CD4 count is >50, ART should be started within 8 weeks.

- For most patients taking standard RMP-containing TB therapy who are not already receiving ART, an efavirenz-based regimen combined with two nucleoside or nucleotide analogues (avoiding the additive peripheral neuropathy risk of stavudine or didanosine) is recommended unless contraindicated by drug resistance, concern over pregnancy risk or intolerance.

- In patients already receiving effective combination ART at the time of the TB diagnosis, a switch to an efavirenz-based regimen may be considered if there are no contraindications.

- Use of a PI-based regimen requires that RMP be replaced by RBT.

- In exceptional circumstances when neither an efavirenz-based or PI-based regimen can be used, a quadruple nucleoside regimen, nevirapine-based regimen or possibly an integrase inhibitor based regimen can be considered.

- In patients with a suboptimal virologic response to ART in whom an interaction with a TB drug is a possible explanation, after optimizing adherence and ruling out antiviral resistance, monitoring of serum antiretroviral concentrations should be considered.

- A "paradoxical IRIS reaction" following initiation of ART should be suspected in a patient with a low initial CD4 count on the basis of fever and localized findings following ART initiation, after exclusion of other possible causes. Corticosteroid therapy (prednisone 1 mg/kg daily) may be considered if the reaction is severe. Neither antituberculous drugs nor ART should be discontinued for an IRIS reaction.

- Patients with CD4 cell counts less than 200 cells x 10^6/L should receive prophylaxis against pneumocystis pneumonia according to current guidelines.

- Pyridoxine supplementation should be given to HIV-infected TB patients receiving INH.

- Treatment for central nervous system (CNS) and pericardial TB should follow guidelines (Chapter 6) for HIV-uninfected patients. After ART initiation patients with CNS TB should have very close monitoring for potentially serious manifestations of adverse neurologic changes due to IRIS.

BCG

- BCG vaccine should not be given to individuals (of any age) known or suspected to have HIV infection or to children of mothers with HIV infection.

Infection control

- Hospitals, hospices, clinics, correctional institutions and other settings where HIV-infected individuals may be concentrated should establish policies and implement the necessary practices to allow early identification and effective isolation of patients with possible infectious TB and to minimize the likelihood of exposure of HIV-infected patients to those with infectious TB.

- TB and HIV control programs and care providers should collaborate closely in the care of individual patients and in prevention activities.

INTRODUCTION

The HIV epidemic has had a dramatic impact on tuberculosis (TB) rates and TB control in both industrialized and low-income countries where both infections are prevalent. HIV is the most powerful known risk factor for the development of active TB disease in individuals infected with *Mycobacterium tuberculosis* (see Table 1 of Chapter 6, Treatment of Latent Tuberculosis Infection). TB increases mortality in patients with HIV, particularly in the absence of antiretroviral therapy (ART); globally, TB is the most common cause of death in HIV-infected individuals.[1] In Canada, HIV/TB coinfection is seen disproportionately in immigrants and refugees from TB- and HIV-endemic countries and in Aboriginal peoples (Chapter 1, Epidemiology of Tuberculosis in Canada).

PATHOPHYSIOLOGY

The predominant immunologic effect of HIV is on cell-mediated immunity, the arm of the immune system most important in mediating an effective response against *M. tuberculosis.* The immune deficiency induced by HIV infection decreases the immunologic containment of latent infection, new infection[2] and reinfection with *M. tuberculosis.* It also alters the delayed-type hypersensitivity reaction involved in the tuberculin skin test (TST) and the clinical and radiologic features of TB, which are partly determined by the host response. Although TB can occur at any stage in the course of HIV infection,[3] the risk increases with advancing immune suppression and decreases in patients receiving effective ART.[4,5] The interaction between the two infections is bidirectional; treatment of *M. tuberculosis* decreases HIV replication.[6]

DIAGNOSIS OF HIV INFECTION IN TB PATIENTS

HIV prevalence is markedly increased among TB patients relative to the Canadian population because of both the overlapping of risk groups and the powerful biologic effect of HIV on *M. tuberculosis* activation. Hence HIV screening of TB patients is justified on epidemiologic grounds. Establishing a diagnosis of HIV benefits the individual patient through earlier initiation of HIV care, including ART, and contributes to the public health benefit of reduced onward transmission risk.

RECOMMENDATIONS FOR DIAGNOSIS OF HIV

- **All patients with newly diagnosed TB who are not already known to be HIV-seropositive should undergo informed HIV serologic testing unless they persistently refuse testing (opt-out screening).**

  (Strong recommendation, based on strong evidence)

- **TB programs should take advantage of contact tracing activities to offer provider-initiated HIV testing to at-risk individuals.**

  (Conditional recommendation, based on weak evidence)

DIAGNOSIS OF TB INFECTION IN HIV-INFECTED INDIVIDUALS

Among the HIV and *M. tuberculosis* coinfected, the annual risk of active TB may be as high as 10 per 100 person years in the absence of ART,[7,8] so that identification and treatment of latent TB infection (LTBI), along with early detection of active TB, provide both clinical and public health benefits.

The sensitivity of the TST decreases with decreased CD4 cell counts. Falsely negative TST results may become positive on retesting after the patient has experienced a degree of immunologic reconstitution due to ART.[9] Interferon-gamma release assays (IGRAs) have not been shown to perform better than the TST in HIV-infected individuals.[10]

HIV-infected patients are more likely than HIV-uninfected individuals to have active TB with atypical clinical or radiologic features,[11] hence the need for rigorous efforts to exclude active disease before initiating treatment of LTBI. In patients with absolute CD4 counts of ≤50 x 10^6/L a blood culture for mycobacteria is useful to exclude *M. avium* complex infection and will identify some patients with disseminated *M. tuberculosis.*

RECOMMENDATIONS FOR DIAGNOSIS OF LTBI

- Every patient with newly diagnosed HIV infection should be assessed with regard to history of active TB, previous TST results and known or likely TB exposure, including close contact with an infectious case or exposure to a community with high TB prevalence. A clinical assessment and chest radiography should be performed to look for features of previous or active TB.

  (Strong recommendation, based on moderate evidence)

- Unless there is a history of active TB or a well-documented previous positive TST or IGRA, every HIV-infected person should have a TST performed with 5 tuberculin units of purified protein derivative and read at 48-72 hours by a health care worker experienced at reading TSTs.

  (Strong recommendation, based on strong evidence)

- Use of an IGRA as an additional test may be considered if the TST is negative, particularly if the patient is thought to have a high likelihood of TB exposure.

  (Conditional recommendation, based on weak evidence)

- TST induration of $\geq$5 mm should be considered indicative of TB infection in HIV-infected individuals.

  (Strong recommendation, based on moderate evidence)

- Anergy testing is *not* recommended.

  (Strong recommendation, based on moderate evidence)

- A TST should be repeated annually in patients at markedly increased risk of ongoing TB exposure, e.g. homeless shelter exposure or return travel to countries highly TB endemic.

  (Conditional recommendation, based on moderate evidence)

- In patients with an initial negative TST, repeat TST should be considered after institution of ART and immune reconstitution as indicated by an increase in the CD4 cell count.

  (Conditional recommendation, based on moderate evidence)

- HIV-infected patients found to be TST or IGRA positive or with a well-documented previous positive TST should be evaluated for the presence of active TB by clinical assessment, chest radiography and any other investigations suggested by the clinical findings. Even when the chest x-ray is normal, sputum should be obtained for *M. tuberculosis* smear and culture.

  (Strong recommendation, based on strong evidence)

PREVENTING THE DEVELOPMENT OF ACTIVE TB: ART AND TREATMENT OF LATENT TUBERCULOSIS INFECTION

ART reduces the incidence of active TB in adults by 65%, with the greatest impact in those with lowest CD4 counts[12–14] and in children,[15] although the incidence remains higher than that of HIV-uninfected individuals even after normal CD4 cell count levels are attained.[13]

Treatment of LTBI in TST-positive, HIV-infected adults has significantly reduced the risk of development of active TB by about 32%, but a reduction in mortality has not been clearly shown.[16] Some studies suggest that protection may wane in the years after treatment of LTBI, possibly as a result of reinfection in communities with high rates of transmission,[17,18] which might be less relevant to most Canadian environments, where the risk of re-exposure is expected to be low. Provision of treatment of LTBI in tuberculin-negative or anergic HIV-infected individuals has not been shown to be beneficial in several randomized trials.[16,19]

The benefit of INH treatment of LTBI appears to be additive to that of ART in reducing the incidence of active TB in adults[20] and children.[21]

RECOMMENDATIONS FOR ART INITIATION AND LTBI

- TST or IGRA positivity may be considered as factors favouring earlier ART initiation.
  (Conditional recommendation, based on weak evidence)

Completion rates for a full course of preventive therapy in Canadian programs vary widely.[22] Many HIV-infected candidates for preventive therapy are likely to have one or more characteristics associated with poor adherence, such as substance use or unstable housing. A variety of supports and/or incentives may improve treatment completion rates. Directly observed preventive therapy, usually twice weekly, for example in a methadone clinic or by an outreach worker, has been predicted to be cost-effective or cost-saving under a variety of conditions.[23,24]

A 6-month duration has shown proven efficacy in HIV-infected patients in at least five studies, but experience in HIV-uninfected patients indicates that 9 months is the optimal duration (Chapter 6, Treatment of Latent Tuberculosis Infection).

While twice weekly isoniazid (INH) has not been compared with daily chemoprophylaxis, it has been used in two published studies[17,18] and, on the basis of its efficacy in treatment, is generally thought to be comparable.

Two studies, one using daily and the other twice weekly dosing, of RMP and PZA for 2 months in HIV-infected individuals demonstrated efficacy comparable with that of 6 months of INH.[17,25] Subsequent experience with this regimen in another study, which included HIV-uninfected individuals, has revealed a high rate of serious hepatotoxicity.[26,27] This regimen is no longer recommend in HIV-infected or uninfected people (see also Chapter 6).

A 4-month regimen with daily RMP alone (Chapter 6) has not been studied in HIV-infected individuals. For patients unable to take RMP because of its interaction with protease inhibitors rifabutin is the recommended alternative and appears to have comparable efficacy in the treatment of *active* TB,[28] although it is associated with higher rates of hematologic toxicity and has not been studied as treatment for LTBI.

Of two studies, both in settings with very high TB transmission, which examined the benefit of prolonged treatment for LTBI, one showed benefit of extending isoniazid to 36 months[29] and one did not.[30]

In a study of over 7,000 patients receiving treatment for LTBI, of whom 2.7% in the RPT/INH arm were HIV-infected,[31] a 3-month course of directly observed weekly RPT (not currently available in Canada) and isoniazid was at least equivalent to a standard regimen of 9 months of self-administered daily isoniazid alone, with a lower risk of hepatitis but higher rates of overall adverse effects, including allergic or hypersensitivity reactions. The implications of potential interactions with antiretroviral drugs have not been determined.

RECOMMENDATIONS FOR TREATMENT OF LATENT TB INFECTION

Recommendations for the treatment of LTBI in HIV-infected individuals are similar to those for non HIV-infected patients and are reviewed in detail in Chapter 6. It is important to remember that the risk of disease reactivation from LTBI is substantially higher and drug interactions need to be considered for those taking ART.

- Except when there is a well-documented history of completed treatment of LTBI or completed treatment of active TB, treatment of LTBI should be strongly recommended for every HIV-infected patient with a TST reaction $\geq$5 mm or positive IGRA test, regardless of age or BCG (Bacille Calmette-Guérin) vaccination status, after exclusion of active TB.

  (Strong recommendation, based on strong evidence)

- HIV-infected people thought to have had recent close contact with an infectious TB patient should receive treatment for presumed LTBI regardless of the TST result.

  (Conditional recommendation, based on weak evidence)

- In HIV-infected individuals for whom treatment of LTBI is indicated, the recommended regimen is the same as that recommended for HIV-uninfected patients: daily self-administered INH for 9 months.

  (Strong recommendation, based on moderate evidence)

- Continuation of INH beyond 9 months is not recommended in Canada, given the relatively low exposure rates.

  (Conditional recommendation, based on weak evidence)

- Daily RMP for 4 months is an alternative regimen in cases of INH intolerance in the patient or INH resistance in the exposure source, or in patients for whom the shorter duration is felt to be critical to the likelihood of completion, as long as it is compatible with the patient's antiretroviral regimen.

  (Conditional recommendation, based on moderate evidence)

RECOMMENDATIONS FOR TREATMENT OF LATENT TB INFECTION - *Continued*

- Daily RMP plus isoniazid is an alternative (Chapter 6) but is associated with the potential toxicity of isoniazid and the potential drug interactions of RMP.

  (Conditional recommendation, based on weak evidence)

- The 3-month regimen of *supervised* once weekly rifapentine and weekly isoniazid is a promising alternative but is NOT currently recommended for HIV-infected patients.

  (Strong recommendation, based on moderate evidence)

- The combination of RMP and PZA is NOT recommended for treatment of LTBI, regardless of HIV serostatus.

  (Strong recommendation, based on moderate evidence)

- Consideration should be given to practical measures such as clinic hours, staff attitudes, inducements, social supports, close follow-up and linking with adherence supports that may be in place for ART.

  (Conditional recommendation, based on weak evidence)

- For HIV-infected patients with predictors of poor adherence, such as unstable housing, active substance abuse or major psychosis, or those who have demonstrated poor adherence, consideration should be given, along with other supports, to providing directly observed twice weekly treatment of LTBI; twice weekly regimens should always be given under direct supervision.

  (Conditional recommendation, based on weak evidence)

- HIV-infected people who are candidates for preventive therapy but who do not receive it for any reason should have regular clinical follow-up. TB should be considered in the differential diagnosis and mycobacterial cultures of appropriate specimens included in the investigation of any unexplained illness.

  (Strong recommendation, based on moderate evidence)

- In an HIV-infected pregnant woman for whom treatment of LTBI is indicated, it should be initiated as soon as active disease has been excluded and not delayed until after the delivery.

  (Conditional recommendation, based on weak evidence)

DIAGNOSIS OF ACTIVE TB

The clinical presentation of TB may be altered in the presence of HIV infection, particularly in those with more advanced immunosuppression. Extrapulmonary TB is more common, lymph nodes being the most common site, but pleural and pericardial TB, TB meningitis and TB involving more than one organ have all been found to be more common in HIV-infected than uninfected patients.

The radiologic features of TB may be altered in approximate proportion to the individual's degree of immunosuppression.[32] Upper lobe predominance and cavitation are less common, and intrathoracic adenopathy, pleural effusions, disseminated disease or a normal chest x-ray are more common in the HIV-infected, especially in patients with more advanced immune suppression.

Laboratory diagnosis of TB may also be affected by the presence of HIV infection. The rate of sputum smear positivity tends to be lower in those with pulmonary TB who are coinfected with HIV.[33] Characteristic granulomas may be absent or altered on histologic examination of tissue.[34] *M. tuberculosis* bacteremia, uncommon in the absence of HIV, is much more common in advanced HIV disease, so that blood culture may be a useful diagnostic tool in these patients.[35] Acid-fast staining of lymph node aspirates is more sensitive in HIV-coinfected than HIV-negative patients with TB lymphadenitis.[36] Infection with nontuberculous mycobacteria is relatively common in advanced HIV infection; polymerase chain reaction techniques can rapidly confirm or exclude *M. tuberculosis* in a patient with acid-fast bacilli detected on microscopy or culture; this has important clinical and public health implications.

RECOMMENDATIONS FOR DIAGNOSIS OF ACTIVE TB

- Health care workers caring for patients with HIV infection should maintain a high index of suspicion for TB, particularly in patients with an increased epidemiologic likelihood of either recent or remote TB exposure, when investigating any unexplained illness, especially persistent fever or lung disease, even in the absence of typical features of TB.

  (Strong recommendation, based on moderate evidence)

- An HIV-infected patient in whom a respiratory tract specimen is found to contain acid-fast bacilli should generally be managed as a suspected TB case until such time as the organism has been shown *not* to be *M. tuberculosis.*

  (Conditional recommendation, based on weak evidence)

TREATMENT OF TB

TB recurrence is more common among the HIV-infected.[37] When molecular techniques have been used to distinguish between relapse and reinfection, in communities with high levels of ongoing transmission the rates of relapse with the original strain have been similar, whereas reinfection with a new strain of *M. tuberculosis* is more frequent among the HIV-infected.[38] Mortality is higher among HIV-infected TB patients and correlates with the degree of immune suppression.[39] However, with appropriate anti-tuberculosis therapy and timely initiation of ART, the difference in outcomes attributable to HIV can be greatly decreased.

A number of studies have found decreased serum concentrations of antituberculous agents in patients with HIV infection, thought to be due to decreased absorption.[40,41]

Findings from recent randomized trials[42] and a recent meta-analysis suggest that regimens containing RMP for ≤8 months may be associated with higher rates of treatment failure and, particularly, of relapse in HIV-infected individuals who are not receiving ART;[43] the risk of relapse was lower and the benefit of therapy >6 months in duration less clear among TB patients receiving ART.[44]

Several investigators have found that continuation of INH ("secondary prophylaxis") after completion of standard TB therapy was associated with lower rates of TB recurrence in HIV-infected patients, but this may be attributable to prevention of reinfection in settings of high transmission.[45,46]

Treatment failure with acquired RMP monoresistance has been observed during TB treatment in HIV-infected patients with once weekly INH and rifapentine and in twice weekly RMP-based regimens, associated with low serum INH levels. This phenomenon has been observed particularly among patients with CD4 counts <100 x 10^6/L and with twice weekly administration of TB therapy in the intensive phase.[47-51]

TIMING OF INITIATION OF ART

In the HIV-infected patient with active TB, establishment of effective TB treatment is the first priority. If the two therapies were initiated simultaneously, the problems of overlapping drug adverse effects and pill burden, as well as drug interactions and the immune reconstitution inflammatory syndrome (IRIS), could result in unacceptable obstacles to successful TB treatment initiation. On the other hand, undue delay in the initiation of effective ART results in a significant risk of HIV-related death among patients with advanced immune suppression.

Three recent randomized controlled trials found that early initiation of ART, within 2-4 weeks of TB therapy initiation, reduced the mortality and/or incidence of AIDS-defining illness.[52–54] In two of the three studies, this effect was limited to patients with CD4 counts of <50 x 10^6/L. Deferring the initiation of ART in patients with higher CD4 counts until 8 weeks of therapy reduced the risk of IRIS without increasing the risk of HIV progression or death. The advantage of early initiation of ART is less clear in cases of TB meningitis,[55] perhaps because of the unique risks of IRIS reactions in the closed space of the cranium.

DRUG INTERACTIONS

Drug interactions between antiretrovirals and antituberculous drugs may be complex and sometimes bidirectional. Experience and recommendations continue to evolve, even with older agents such as efavirenz, but particularly with newer drugs. Current information can be obtained from several regularly updated websites:

- HIV Insite (San Francisco, CA), see http://hivinsite.ucsf.edu/insite?page=ar-00-02
- Liverpool (UK), see http://www.hiv-druginteractions.org/
- Toronto General Hospital, see http://www.hivclinic.ca/main/drugs_interact.html

ANTIRETROVIRAL DRUGS

Antiretroviral drugs, particularly those in the protease inhibitor (PI) class but also the non-nucleoside reverse transcriptase inhibitor (NNRTI) group, demonstrate major and sometimes bidirectional interactions with rifamycin antituberculous agents. Clinically important interactions with antituberculous agents have not been found with any of the nucleoside or nucleotide analogues (zidovudine, didanosine, stavudine, lamivudine, abacavir, emtricitabine or tenofovir). Although clinical experience is limited, integrase inhibitors and CCR5 receptor blockers also interact with RMP.

RIFAMYCINS

Critical to the success of short-course TB treatment, these are the only antituberculous agents found to have clinically significant interactions with antiretroviral drugs. Lesser degrees of interaction are seen with RBT than with RPT, which in turn interacts less than RMP.

Specific interactions with rifamycins

Extensive experience has shown that the NNRTI efavirenz at standard dosing of 600 mg/day remains effective when used with RMP, particularly in populations with relatively low body mass, in spite of variable reduction in efavirenz serum concentrations.[56] An increase in dose to 800 mg in those ≥50 kg was recommended in 2012 by the Food and Drug Administration on the basis of kinetics studies.

No PI dosing regimen has been found to be safe and effective in combination with RMP. Rifabutin can be substituted for RMP in TB treatment to permit the use of PIs[28] but is associated with higher rates of hematologic toxicity. Rifabutin concentrations are increased to varying degrees by concomitant therapy with different PIs.

Rifabutin, *with appropriate dose reduction*, can be used together with most ritonavir "boosted" PIs. Rifabutin concentrations may vary when given with lopinavir/ritonavir, and higher than standard recommended doses of rifabutin may be required to achieve effective serum concentrations.[57,58]

RMP reduces serum concentrations of nevirapine to a greater degree than efavirenz concentrations.[59,60] Reports of virologic suppression by nevirapine-based regimens in combination with RMP are conflicting.[61] Nevirapine taken once a day has been shown to be inferior to efavirenz when administered with RMP.[62] There is no published information on the combination of nevirapine and rifabutin.

Therapy with the combination of four nucleoside/nucleotide reverse transcriptase inhibitors zidovudine, lamivudine, abacavir (coformulated as Trizivir) and tenofovir appears comparable in limited studies to standard ART regimens and is not expected to be associated with significant drug interactions.[63]

Although clinical experience remains limited with the newer integrase inhibitor drug class, such as raltegravir,[64,65] dose adjustments are recommended when used with RMP but not if used with rifabutin. Metabolism of the CCR5 receptor blocker maraviroc is also induced by RMP, and dosage increases of maraviroc are also recommended. The manufacturer currently recommends against concomitant use of etravirine and RMP, but use of RBT may be considered in spite of modest decreases in the levels of both drugs. Recommendations regarding these newer agents are likely to evolve.

Because of the possibility of reduced drug absorption, the potential for complex and difficult-to-predict drug interactions and the serious consequences (treatment failure, drug resistance) of inadequate treatment of either active TB or HIV infection, therapeutic drug monitoring of antituberculous[66] (see Chapter 5, Treatment of Tuberculosis Disease) and antiretroviral drug levels is assuming an increasing role in the management of TB in the HIV-infected, particularly when a non-efavirenz based regimen is used or when the response to therapy is poorer than expected or the therapies selected in an individual patient have been less well studied.[67]

TREATMENT OF DRUG-RESISTANT TB, INCLUDING MULTIDRUG-RESISTANT AND EXTENSIVELY DRUG-RESISTANT TB WITH HIV COINFECTION

(See Chapter 8, Drug-resistant Tuberculosis)

HIV is not clearly associated with increased risk of multidrug-resistant TB (MDR TB) overall but may be associated with nosocomially transmitted MDR disease outbreaks.[68] The early experience with MDR and subsequently extensively drug-resistant TB (XDR TB) and HIV showed very high mortality.[69] Early diagnosis of drug resistance and initiation of ART appear to contribute to improved outcomes.[70,71] There are few data on interactions between second-line anti-TB drugs and ARVs.[72]

IMMUNE RECONSTITUTION REACTIONS

Immune reconstitution inflammatory syndrome may occur during TB therapy, after ART initiation (paradoxical reactions) or following ART initiation in patients with unrecognized TB ("unmasking").[73] Paradoxical IRIS has been reported with a frequency ranging from 8% to 43%.[74] These reactions may present as fever and clinical and radiologic disease progression at involved sites, e.g. enlarging lymph nodes, worsening pulmonary infiltrates or exacerbation of inflammatory changes at other sites.[75-77] Almost all affected patients have low initial CD4 cell counts, typically below 50-100 x 10^6/L.[75–80] Onset has been described between 2 and 40 days after ART initiation.[77,79] Paradoxical reactions can occur even when ART is initiated more than 2 months after starting TB treatment, but the risk may be higher with early ART initiation. Diagnosis is often difficult and requires exclusion of other possible causes of the observed clinical findings, including treatment failure due to drug resistance[81] or development of a different opportunistic infection. A standardized definition of IRIS has been proposed.[82] Mortality attributed to IRIS appears to be uncommon except in cases with neurologic involvement. If the reaction is severe enough to warrant therapy, corticosteroids such as prednisone at doses in the range of 1 mg/kg of body weight have been shown effective in a randomized trial.[83] In almost all cases, patients can be managed successfully without interruption of ART or TB treatment.

Although less well studied in the HIV-infected, available evidence suggests a benefit of adjunctive corticosteroids in TB meningitis and pericarditis.[84-86]

HIV-infected individuals are at increased risk of neuropathy due to HIV or specific antiretroviral agents and may be more susceptible to INH-associated neuropathy.

RECOMMENDATIONS FOR TREATMENT OF ACTIVE DISEASE

TB treatment

- Treatment of TB in HIV-infected patients should be guided by a physician with expertise in the management of both diseases or in close collaboration with a physician expert in HIV care.
  (Strong recommendation, based on strong evidence)

- Anti-TB therapy should be initiated immediately upon the diagnosis of TB, irrespective of ART considerations.
  (Strong recommendation, based on strong evidence)

- A standard rifamycin (RMP or RBT)-containing regimen should be used unless the organism is rifamycin resistant or the patient is intolerant of rifamycins (See Chapter 5).
  (Strong recommendation, based on strong evidence)

- The TB program should achieve successful completion of treatment using measures outlines in Chapter 5, as determined by the patient's requirements, which may include directly observed therapy.
  (Strong recommendation, based on strong evidence)

- A treatment duration of 8 months**,** including INH and RMP for 8 months and PZA for the first 2 months, is recommended in patients with HIV infection who decline or for other reasons do not take ART.
  (Conditional recommendation, based on moderate evidence)

- As in the preferred regimen for HIV-uninfected patients, the first 2 months (intensive phase) should be administered daily in HIV-infected patients and the continuation phase given daily (if self-administered) or thrice weekly, but not twice weekly (if on DOT) in HIV-infected patients, particularly those with CD4 cell counts $\leq$100 x 10^6/L.
  (Strong recommendation, based on moderate evidence)

- If cavitation is present on the chest x-ray or if treatment response is delayed (culture positive at 2 months), treatment may need to be prolonged from 6 to 9 months (see Chapter 5).

- In patients for whom PI-based ART is judged most appropriate, dose-adjusted rifabutin should be substituted for RMP in standard treatment regimens.
  (Strong recommendation, based on strong evidence)

  RMP should be switched to RBT 2 weeks before ART is initiated to allow for "washout" of the hepatic enzyme induction.

- Routine measurement of serum concentrations of antituberculous drugs, particularly RBT, is suggested, especially in any patient with chronic diarrhea and advanced HIV disease, in whom a drug interaction is suspected to be lowering anti-TB drug levels or who is demonstrating a suboptimal response to TB therapy.
  (Conditional recommendation, based on moderate evidence)

RECOMMENDATIONS FOR TREATMENT OF ACTIVE DISEASE - *Continued*

Antiretroviral treatment

- A diagnosis of TB in an HIV-infected individual constitutes an indication for ART.
  (Strong recommendation, based on moderate evidence)

- In patients not receiving ART at the time TB treatment is initiated, if the CD4 count is <50 x 10^6/L, ART should be initiated within 2 weeks of starting anti-TB treatment; if the CD4 count is >50, ART should be started within 8 weeks.
  (Strong recommendation, based on strong evidence)

- For most patients taking standard RMP-containing TB therapy who are not already receiving ART, an efavirenz-based regimen combined with two nucleoside or nucleotide analogues (avoiding the additive peripheral neuropathy risk of stavudine or didanosine) is recommended unless contraindicated by drug resistance, concern over pregnancy risk or intolerance.
  (Strong recommendation, based on strong evidence)

- In patients already receiving effective combination ART at the time of the TB diagnosis, a switch to an efavirenz-based regimen may be considered if there are no contraindications.
  (Conditional recommendation, based on weak evidence)

- Use of a PI-based regimen requires that RMP be replaced by RBT.
  (Strong recommendation, based on strong evidence)

- In exceptional circumstances when neither an efavirenz-based or PI-based regimen can be used, a quadruple nucleoside regimen, nevirapine-based regimen or possibly an integrase inhibitor based regimen can be considered.
  (Conditional recommendation, based on weak evidence)

- In patients with a suboptimal virologic response to ART in whom an interaction with a TB drug is a possible explanation, after optimizing adherence and ruling out antiviral resistance, monitoring of serum antiretroviral concentrations should be considered.
  (Conditional recommendation, based on weak evidence)

- A "paradoxical IRIS reaction" following initiation of ART should be suspected in a patient with a low initial CD4 count on the basis of fever and localized findings following ART initiation, after exclusion of other possible causes. Corticosteroid therapy (prednisone 1 mg/kg daily) may be considered if the reaction is severe. Neither antituberculous drugs nor ART should be discontinued for an IRIS reaction.
  (Conditional recommendation, based on moderate evidence)

- Patients with CD4 cell counts less than 200 cells x 10^6/L should receive prophylaxis against pneumocystis pneumonia according to current guidelines.
  (Strong recommendation, based on strong evidence)

- Pyridoxine supplementation should be given to HIV-infected TB patients receiving INH.
  (Conditional recommendation, based on weak evidence)

- Treatment for central nervous system (CNS) and pericardial TB should follow guidelines (Chapter 6) for HIV-uninfected patients. After ART initiation patients with CNS TB should have very close monitoring for potentially serious manifestations of adverse neurologic changes due to IRIS.

Table 1. Summary of compatible antituberculous and antiretroviral regimens
(see text and recommendations for consideration of monitoring serum drug concentrations)

	TB regimen	ARV regimen
1st line	2 months daily INH/RMP/PZA/EMB daily for 2 months, followed by *INH*RMP daily or 3x weekly for 4 months *daily or 3x weekly in continuation phase*	Efavirenz 600 mg* and two nucleoside/nucleotide analogues (not stavudine or didanosine) *Consider efavirenz 800 mg if weight >50 kg or suboptimal virologic response*
Alternative	2 months daily INH/PZA/EMB rifabutin 150 mg q 2 days, followed by: 6 months *INH*PZA*EMB RBT 150 mg q 2 days *daily or 3x weekly in continuation phase*	Ritonavir "boosted" protease inhibitor and two nucleoside/nucleotide analogues

INH = isoniazid, RMP = rifampin, PZA = pyrazinamide, EMB = ethambutol, RBT = rifabutin

BACILLE CALMETTE-GUÉRIN

BCG vaccination is associated with a substantial risk of disseminated disease,[87] and its efficacy appears to be markedly reduced in HIV-infected infants.[88]

RECOMMENDATION FOR BCG

- BCG vaccine should not be given to individuals (of any age) known or suspected to have HIV infection or to children of mothers with HIV infection.
  (Strong recommendation, based on strong evidence)

CONTROL OF TB TRANSMISSION TO HIV-INFECTED INDIVIDUALS: PROGRAM COORDINATION

Outbreaks of TB, including MDR TB, in HIV-infected patients and health workers have been associated with hospitals and clinics caring for HIV-infected patients[69] and with correctional institutions.

RECOMMENDATIONS FOR INFECTION CONTROL

- Hospitals, hospices, clinics, correctional institutions and other settings where HIV-infected individuals may be concentrated should establish policies and implement the necessary practices to allow early identification and effective isolation of patients with possible infectious TB and to minimize the likelihood of exposure of HIV-infected patients to those with infectious TB.

  (Strong recommendation, based on moderate evidence)

- TB and HIV control programs and care providers should collaborate closely in the care of individual patients and in prevention activities.

  (Strong recommendation, based on moderate evidence)

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