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Tuberculosis in HIV-infected patients: a comprehensive review

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ABSTRACT

The incidence of tuberculosis (TB) is currently increasing in HIV-infected patients living in Africa and Asia, where TB endemicity is high, reflecting the susceptibility of this group of patients to mycobacteria belonging to the TB group. In this population, extension of multiple resistance to anti-tuberculous drugs is also a matter of anxiety. HIV-induced immunosuppression modifies the clinical presentation of TB, resulting in atypical signs and symptoms, and more frequent extrapulmonary dissemination. The treatment of TB is also more difficult to manage in HIV-infected patients, particularly with regard to pharmacological interactions secondary to inhibition or induction of cytochrome P450 enzymes by protease inhibitors with rifampicin or rifabutin, respectively. Finally, immune restoration induced by highly active anti-retroviral therapy (HAART) in developed countries may be responsible for a paradoxical worsening of TB manifestations.

Keywords AIDS, HAART, HIV, *Mycobacterium tuberculosis*, tuberculosis

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INTRODUCTION

Airborne transmission of *Mycobacterium tuberculosis* is responsible for primary tuberculosis (TB) infection which can evolve in immunocompetent, but more frequently in immunocompromised hosts into TB. The number of TB cases has increased dramatically worldwide, reflecting the susceptibility of HIV-infected patients to the *M. tuberculosis* complex. Because of this, pulmonary TB was considered in the 1993 Centers for Disease Control classification of AIDS as a true AIDS-defining illness in HIV-infected patients, similar to *Pneumocystis carinii* pneumonia, cerebral toxoplasmosis or extra-pulmonary systemic mycoses. However, in contrast to most of these other AIDS-classifying opportunistic infections, TB may occur relatively early in the course of HIV infection. It should be noted that there is a mutual interaction between *M. tuberculosis* and HIV. Indeed, the immunosuppression induced by HIV modifies the clinical presentation of TB and its management, while immune restoration induced by highly active anti-retroviral therapy (HAART) may be associated with paradoxical manifestations related to immune reconstitution. On the other hand, TB influences the prognosis of HIV infection, and anti-tuberculous drugs interfere with anti-retroviral drugs, including protease inhibitors and non-nucleoside reverse-transcriptase inhibitors (NNRTIs).

PATHOPHYSIOLOGY

TB results from infection by a pathogen belonging to the *M. tuberculosis* complex, primarily *M. tuberculosis* (Koch's bacillus), and rarely *Mycobacterium bovis* or *Mycobacterium africanum*. After penetration into the respiratory tract, these bacilli infect macrophages, while $CD4^+$ T-lymphocytes and Tγδ-lymphocytes produce interferon gamma (IFN-γ), interleukin-2, tumour necrosis factor alpha (TNFα), and macrophage colony-stimula-

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ting factor, which activate macrophages and cytotoxic cells to inhibit their intracellular growth. TB appears when the immune response inducing granuloma is insufficient to limit the growth of mycobacteria. IFN-γ plays a pivotal role at this stage. Indeed, people harbouring genetic defects that result in reduced production of either IFN-γ or its cellular receptors develop severe and fatal TB [1]. During HIV infection, IFN-γ production is decreased dramatically in parallel with the reduction of $CD4^+$ T-lymphocytes, which leads finally to a markedly increased risk of developing reactivation or reinfection by *M. tuberculosis* in these patients [2,3].

Conversely, TB may also influence HIV evolution. Proinflammatory cytokine production by tuberculous granulomas (in particular TNFα) has been associated with increased HIV viraemia, which might accelerate the course towards severe immunosuppression [4]. The risk of death in HIV-infected patients with TB is twice that in HIV-infected patients without TB with matched CD4 cell counts, with most deaths caused by progressive HIV infection, rather than TB [5].

EPIDEMIOLOGY

It has been estimated that at least 10.7 million persons were coinfected with HIV and *M. tuberculosis* in 1997, and that HIV-1-infected patients represent 8% of the worldwide total of TB cases [6]. More than 30% of TB cases in Africa are also coinfected by HIV [6]. During HIV infection, an increased risk of developing TB has been found in males, and in those living in areas such as sub-Saharan countries and Maghreb, where malnutrition and social deprivation are factors [3,7]. Most TB cases are found in southern Asia [6]. The incidence of TB does not vary according to the route of HIV transmission, but the risk of developing TB after an infectious contact has been estimated to be 5–15%/year in HIV-infected patients (compared to 5–10% during the lifetime of HIV-negative patients) [8]. The incidence of TB has been found recently to be as high as 10.4/100 000 HIV-infected patients/year in Cape Town [9]. The TB mortality rate also increased at the beginning of the HIV pandemic in areas hyper-endemic for both HIV and TB, particularly in Africa and Asia [10,11], where TB can develop early after infectious contact even in non-severely immunocompromised patients. In Ivory Coast, as well as in several other African countries, TB is the leading cause of mortality in the HIV-infected population [12,13]. During an autopsy study, active TB was found in 50% of HIV-infected individuals examined [14]. In Western countries, HIV infection led to an increased incidence of TB in the early 1990s, often resulting from reactivation of a latent focus at a later stage of immunodeficiency (mean CD4 = 77/mm^3 in Spain and 162/mm^3 in France) [10,15]. Between January 1994 and June 2001, > 2800 TB cases were declared in HIV-infected patients in France [16]. A recent study in New York City has documented clearly that TB observed in HIV-infected patients born abroad resulted from recent transmission of the bacillus [17]. Moreover, overcrowding and deprivation, present in large cities such as New York, contribute to TB dissemination.

Marked decreases in both the incidence and mortality of TB have been reported in countries with access to HAART [18,19]. In France during 2000, the results of HIV serology were known in 39% of total declared TB cases, giving an overall estimation of the total number of cases associated with HIV as 4.8% [19]. However, TB was still the first AIDS-classifying infection in 16.1% of cases reported in France in 2001 [16]. Finally, a French study performed in 1998 which investigated 31 cases of multidrug-resistant (MDR) TB, with 21 patients being born abroad and ten in France, showed a higher prevalence of HIV coinfection in the former subgroup [20].

CLINICAL PRESENTATION AND DIAGNOSIS OF TB

In Western countries, TB develops typically from reactivation of a latent infection and rarely from a primary infection, with the incubation period being difficult to assess. During a nosocomial epidemic of TB, 12 HIV-infected patients (37% of residents exposed to the bacteria) developed TB, with a mean time between contamination and diagnosis of 106 days [21]. The prolonged insidious evolution found in 93% of cases, consisting of the association of sub-acute fever, nocturnal sweats and weight loss, could explain such a delay in diagnosis [22].

The clinical presentation differs according to the degree of immunity. Indeed, the classic picture of pulmonary TB is seen mainly in non-severely immunocompromised patients

(CD4 > 200/mm^3), and is secondary to a recent infection. Pulmonary involvement (70–93% of TB cases) is associated with cough, sputum and, more rarely, haemoptysis, thoracic pain and dyspnoea [22,23]. Atypical features, consisting of lower lobe involvement with a trend towards diffuse infection rather than cavitation, are seen frequently. Cavitary lesions are encountered rarely in patients with a CD4 T-lymphocyte count < 200/mm^3 [24,25]. In contrast, pulmonary basal involvement, tuberculous pneumonia, hilar or mediastinal lymphadenopathies and miliary TB are seen more frequently in severely immunocompromised HIV-infected patients [24–26]. Pleural effusions are found in 5% of cases, and could present uni- or bilaterally. It should also be remembered that chest radiography is normal in 8–20% of TB cases despite the presence of *M. tuberculosis* in sputum [22,24,25].

The association of pulmonary and extrapulmonary localisations occurs in 9–40% of cases [22,23]. All varieties of extrapulmonary TB have been described in HIV-infected patients (bone marrow infiltration, and bone, hepatic, splenic, cerebral, vertebral, meningeal, spinal and kidney involvements). Isolated extrapulmonary localisations are described in 53–63% of TB cases in HIV-infected patients, and more frequently in severely immunocompromised HIV patients than in HIV-seronegative individuals [22,23]. These presentations are secondary to reactivation of a latent infection. In one study, focal cerebral lesions related to TB were more frequent in HIV-infected patients than in seronegative individuals [27]. Computed tomography scanning is useful to search for extrapulmonary lesions [28]. Finally, persistent unexplained fever is the only symptom that might lead to the prescription of anti-tuberculous treatment [29].

TB diagnosis is confirmed by a positive culture of *M. tuberculosis*. The search for acid-fast bacilli in sputum smears is positive in 30–60% of AIDS-related TB cases (compared to 57% in HIV-seronegative patients) [22,23,25]. Blood cultures are positive in 0–42% of TB cases developing in HIV-infected patients [22,30,31]. However, these results should be interpreted in the light of the immune status (Table 1).

The contribution of skin tests to TB diagnosis depends on the immune status. Indeed, reaction to a tuberculin skin test and the presence of a granulomatous reaction in tissues requires a functional Th1 cytokine response. During active TB, the tuberculin skin test is positive (> 5 mm diameter in the absence of previous BCG vaccination and >10 mm diameter in those who have been vaccinated with BCG) in 30% of HIV-infected patients with a CD4 cell count < 200/mm^3, and in 50% of those who present with >200/mm^3 [23]. The presence of a tuberculous granuloma varies from 60% to 100% of cases, depending on the immune status (Table 1) and the site of sampling [23,32,33]. Bronchial aspiration obtained by fibroscopy, trans-bronchial biopsy or bronchoalveolar lavage makes a diagnostic contribution in 70% of cases [22,32]. Nucleic acid amplification tests are costly and have poor sensitivity (95.5% for positive sputum smears; 70% for negative sputum smears) [34], and should be limited to situations where the results will affect the decision to give anti-TB or anti-non-TB *Mycobacterium* therapy. Such tests are particularly helpful when CD4 lymphocytes are <100/mm^3 [34].

TB TREATMENT IN HIV PATIENTS

Each of the major anti-tuberculous drugs varies in its capacity to kill *M. tuberculosis* and prevent the emergence of drug resistance. Isoniazid is the most potent bactericidal drug, killing > 90% of bacilli within 7 days by acting on metabolically active bacilli. It is also quite effective in preventing the emergence of drug resistance. Rifampicin is also a bactericidal drug with a potent sterilising effect and the ability to prevent emergence of drug resistance. Pyrazinamide, although bactericidal, is used mainly for its sterilising effect, and is effective for killing bacilli sequestered by macrophages in an acid environment. Ethambutol and streptomycin are less potent, and ethambutol is probably only bactericidal at high concentrations. The latter two drugs are less effective in

Table 1. Bacteriological and histological results observed during HIV-associated TB as a function of immune status

	CD4 < 200/mm^3	CD4 > 200/mm^3	References
Positive tuberculin skin test reaction (> 5 mm without BCG)	30%	50%	[23]
Acid-fast bacilli on smear	56–60%	50–58%	[22,23,25]
Acid-fast bacilli on biopsy	60–65%	50–56%	[22]
Granuloma in biopsy	60–75%	67–100%	[23,31,32]
Mycobacteraemia	20–49%	0–7%	[22,30]

preventing emergence of resistance to rifampicin and isoniazid. A fourth drug (ethambutol, streptomycin or, potentially, amikacin) can play a role in HIV-infected patients who present with an increased risk of drug resistance. Such drugs might be included in the initial phase of anti-TB therapy [35].

Rifapentine has been approved recently as part of a combination regimen for pulmonary TB when given weekly with isoniazid in the continuation phase (after 2 months of four-drug treatment with isoniazid, rifampicin, pyrazinamide and streptomycin) [36]. The potential advantages over rifampicin are once-weekly dosage in the continuation phase, and a better adverse reactions profile. However, it is not recommended for use in HIV-infected patients because of the high rate of relapse with rifamycin-resistant organisms [37].

In HIV-infected patients with TB, the priority is to treat TB because of public health issues, especially in smear-positive cases, before the initiation of HAART in anti-retroviral-naive patients. The standard 6-month regimen results in prompt sterilisation of sputum and low rates of treatment failure, similar to those obtained in HIV-negative persons [38–40]. In various studies, relapse rates were 3–5% after a follow-up of 18–22 months [38–40]. However, two studies have documented higher rates of relapse in HIV patients who received anti-TB therapy for 6 months, as compared with 9–12 months [41,42]. However, the latter studies are limited and their results remain a matter of debate. The most recent guidelines of the Centers for Disease Control recommend that HIV-infected patients with drug-susceptible TB be treated with rifampicin, isoniazid, ethambutol and pyrazinamide for 6 months, a similar regimen to that used currently in HIV-negative patients (Table 2) [43,44]. Therefore, if the clinical or bacteriological response is slow, treatment for pulmonary TB should be continued for a total of 9 months, or for 4 months after culture becomes negative [43,44]. Moreover, when patients are not observed while taking therapy, or when they are severely immunosuppressed, treatment might be for a total of 9 months. For extra-thoracic or disseminated TB, treatment should be given for 9–12 months. Therapy for at least 12 months is recommended for patients who have miliary, meningeal or skeletal TB [43,44]. Such recommendations mean that, if possible, bacterial eradication should be assessed systematically in HIV-infected patients.

TB drug regimens with rifabutin instead of rifampicin appear to offer the best alternative for the treatment of active TB among patients taking or requiring anti-retroviral therapy that includes protease inhibitors (PIs) or NNRTIs. Standard anti-TB therapy could be administered more simply with a triple nucleoside reverse-transcriptase inhibitor (NRTI) combination, with anti-retroviral therapy being changed if necessary after anti-TB therapy. To reduce the risk of sub-therapeutic levels of PIs, an alternative is to treat TB with regimens that do not include rifampicin. These regimens have demonstrated efficacy only in HIV-negative patients, and their utility is limited by toxicity, increased duration (18 months) and non-adherence to therapy [3,43,45].

The major obstacle to controlling TB is probably non-compliance. If non-compliance is anticipated or is suspected, fully supervised intermittent, directly administered ambulatory therapy should be initiated [38,46]. Drug dosages can help to ensure compliance, in association with measurement of uricaemia in pyrazinamide-treated patients and the observation of the orange colour of urine resulting from rifampicin treatment.

Table 2. Anti-TB regimens recommended for HIV-infected patients (adapted from [3])

Drug resistance	Patients without HIV infection	Patients with HIV infection
None	IRPE for 2 months, IR for 4 months[a]	IRPE for 2 months, IR for 4–7 months[b] *or* IPE plus rifabutin for 2 months, I + rifabutin for 4–7 months
Isoniazid[b]	RPE for 6 months	RPE for 6–9 months *or* rifabutin + PE for 6–9 months
Rifampicin	IPE for 18–24 months	IPE for 18–24 months *or* IPSE for 2 months, IPS for 7–10 months

I, isoniazid; R, rifampicin; P, pyrazinamide; E, ethambutol; S, streptomycin.
[a]Ethambutol may be omitted only if rates of isoniazid resistance in the community are known to be <4%.
[b]Therapy for a total of 12 months is recommended for patients who have miliary or skeletal tuberculosis, with or without HIV infection.

TOLERANCE TO TREATMENT

In a Kenyan cohort, drug intolerance has been recorded in 26% of HIV-infected patients taking a four-drug anti-tuberculous regimen, and often occurs early after the initiation of therapy (before the second month). The most frequent drug intolerance is observed with rifampicin (10%), followed by isoniazid (3–6%) and, more rarely, ethambutol and pyrazinamide [47]. Drug intolerance may present as a febrile skin rash, digestive disorders, liver toxicity, especially in patients coinfected chronically with hepatitis B or C, or isolated fever. In one study, drug intolerance led to the discontinuation of anti-TB treatment in 6% of cases [48]. Some secondary effects can be increased by HAART, such as peripheral polyneuropathy secondary to isoniazid in combination with didanosine (ddI), zalcitabine (ddC) or stavudine (d4T), and hepatotoxicity related to isoniazid and/or pyrazinamide in combination with nevirapine, efavirenz or PIs.

CO-ADMINISTRATION OF ANTI-TB AND ANTI-RETROVIRAL THERAPY

New anti-retroviral treatment (HAART) has improved the prognosis of HIV infection dramatically, but has complicated the therapeutic management of TB. PIs and NNRTIs exhibit significant interactions with rifampicin (Tables 3 and 4). These drug–drug interactions result principally from changes in the metabolism of anti-retroviral agents and rifamycin secondary to induction or inhibition of the hepatic cytochrome P450 (CYP-450) enzyme system (Tables 3 and 4) and the P-glycoprotein. Cytochrome P450 proteins are membrane haemoproteins, found mostly in the liver and intestinal tissues, which metabolise endogenous and exogenous substances. P-Glycoprotein is a drug efflux pump system that depends on ATP, present in the liver. The P-glycoprotein system is coded by *mdrI* and confers resistance to chemotherapy, or reduces the efficacy of PIs, by diminishing the intracellular disposability of drugs. Rifampicin induces CYP-450 activity, which lowers the concentrations of PIs (saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir/ritonavir and atazanavir) and NNRTIs (nevirapine, efavirenz and delavirdine) to sub-therapeutic levels. Low trough plasma levels of these anti-retroviral drugs may be associated with incomplete viral suppression and the emergence of drug resistance. Concomitant administration of rifampicin with these drugs often requires modification of the anti-retroviral drug dosage (Table 5). For example, rifampicin causes a 13% decrease in efavirenz (NNRTI) concentrations, suggesting that, to obtain therapeutic levels in patients, it would be advisable to increase the efavirenz daily dose to 800 mg [49].

Table 3. Pharmacokinetic interactions between rifampicin or rifabutin and protease inhibitors (adapted from [43,44])

	Rifampicin		Rifabutin	
PI	**R's effect on PI**	**PI's effect on R**	**RFB's effect on PI**	**PI's effect on RFB**
Saquinavir	80% decrease saquinavir level	Data not reported	45% decrease saquinavir level	Data not reported
Ritonavir	35% decrease ritonavir level	Unchanged R level	Data not reported	293% increase RFB level
Indinavir	92% decrease indinavir level	Data not reported	34% decrease indinavir level	173% increase RFB level
Nelfinavir	82% decrease nelfinavir level	Data not reported	32% decrease nelfinavir level	200% increase RFB level
Lopinavir + ritonavir	75% decrease lopinavir level	Data not reported	Data not reported	300% increase RFB level
Amprenavir	81% decrease amprenavir level	Unchanged R level	14% decrease amprenavir level	200% increase RFB level

R, rifampicin; RFB, rifabutin, PI, protease inhibitor.

Table 4. Pharmacokinetic interactions between rifampicin and non-nucleoside reverse-transcriptase inhibitors (adapted from [43,44])

	Rifampicin		Rifabutin	
NNRTI	**R's effect on NNRTI**	**NNRTI's effect on R**	**RFB's effect on NNRTI**	**NNRTI's effect on RFB**
Efavirenz	13–36% decrease efavirenz level	Unchanged R level	Decrease efavirenz level	38% decrease RFB level
Nevirapine	37% decrease nevirapine level	Unchanged R level	16% decrease nevirapine level	Decrease RFB level
Delavirdine	96% decrease delavirdine level	Unchanged R level	80% decrease delavirdine level	342% increase RFB level

R, rifampicin; RFB, rifabutin, NNRTI, non-nucleoside reverse-transcriptase inhibitors.

Table 5. Dosage recommendations for co-administration of rifampicin and anti-retroviral drugs (these dosage recommendations are for patients receiving one of the anti-retroviral agents listed in this table only, in combination with an NRTI; measurement of rifampicin and anti-viral drug serum levels is always recommended)

Anti-retroviral treatment	Anti-tuberculosis treatment
Ritonavir: 400–600 mg twice-daily (adjust to serum levels)	Rifampicin: 600 mg/day
Amprenavir: not recommended in combination with NRTI	Rifampicin: not recommended in combination with amprenavir
Indinavir: not recommended in combination with NRTI	Rifampicin: not recommended in combination with indinavir
Nelfinavir: not recommended in combination with NRTI	Rifampicin: not recommended in combination with nelfinavir
Saquinavir: not recommended in combination with NRTI	Rifampicin: not recommended in combination with saquinavir alone
Saquinavir: 400 mg × 2 + ritonavir 400 mg twice-daily	Rifampicin: 600 mg/day
Lopinavir + ritonavir: not recommended in combination with NRTI	Rifampicin: not recommended in combination with lopinavir + ritonavir
Delaverdine: not recommended in combination with NRTI	Rifampicin: not recommended in combination with delaverdine
Efavirenz: 600–800 mg/day (serum levels)	Rifampicin: 600 mg/day
Nevirapine: not recommended in combination with NRTI	Rifampicin: not recommended in combination with nevirapine
NRTI: not necessary to adapt dosages	Rifampicin: not necessary to adapt dosages
Tenofovir: not necessary to adapt dosages	Rifampicin: not necessary to adapt dosages

NRTI, nucleoside reverse-transcriptase inhibitors.

Rifampicin can be used with ritonavir alone as it does not impair the anti-viral effect of full-dose ritonavir [50], and with the combination of ritonavir + saquinavir. Twice-daily use of 100 mg of ritonavir to boost plasma concentrations of other PIs does not block the effect of rifampicin on CYP-450.

Rifabutin is a less potent inducer of CYP-450 than rifampicin. It can be administered in combination with PIs (indinavir or nelfinavir, amprenavir, lopinavir/ritonavir, atazanavir), and with NNRTIs (nevirapine or efavirenz) [51], but anti-retroviral and rifabutin dosages need to be assessed, as reductions in the area-under-the-curve of 10–20% of the PI concentrations are unlikely to affect the efficacy of HIV therapy. On the contrary, PIs such as ritonavir increase concentrations of rifabutin and result in increased rates of toxicity (arthralgia, uveitis, decolourised skin and leukopenia). A reduced dose of rifabutin (150 mg once-daily) is recommended (Table 6). Rifabutin should not be used with hard gel saquinavir or delavirdine [51,52]. The use of rifabutin with NNRTIs should be approached cautiously. Rifabutin reduces delavirdine levels by 80%, and should not be used [53]. For patients treated with efavirenz, the rifabutin daily dose should be increased from 300 to 450 mg. In contrast to PIs and the NNRTIs, the other class of available anti-retroviral agents, NRTIs (zidovudine, didanosine, zalcitabine, stavudine, lamivudine and abacavir) and tenofovir, are not metabolised by CYP-450. Thus, concurrent use of NRTIs and rifamycin is not contraindicated (Tables 3 and 4).

In clinical practice, the use of PIs in a combined anti-retroviral strategy should be discouraged for TB patients. If patients are treated successfully with PIs, rifabutin is preferable to rifampicin for the treatment of TB. However, a drug dosage adaptation may be required according to serum drug levels (Tables 5 and 6).

DRUG-RESISTANT TB

The risk of drug-resistant TB is higher among HIV-infected persons than in HIV-seronegative patients. HIV-infected patients with TB who were born in the USA, and who had not been treated previously for TB, were infected by bacterial isolates with an incidence of isoniazid resistance of 11.3% and rifampicin resistance of 8.9% [54]. These figures are nearly double those seen in the HIV-negative population. In four studies, rifampicin resistance was associated independently with non-adherence to therapy, severe immunodeficiency, a positive acid-fast sputum smear, rifabutin use, co-prescription of antifungal therapy, and diarrhoea [54–57]. The mechanisms involved in the development of acquired rifampicin resistance are not understood clearly. Malabsorption of anti-mycobacterial drugs (rifampicin and ethambutol) in HIV-infected patients, associated with acquired drug resistance leading to treatment failure, has been reported [58]. Measurement of serum drug levels is, therefore, indicated in patients who seem to adhere to anti-TB therapy, but who do not exhibit objective responses to anti-tuberculous drugs [58,59]. MDR TB (defined as combined resistance to at least isoniazid and rifampicin) arises initially in patients who do not adhere to anti-TB therapy. Multiresistance is predictive of a poor outcome because these drugs are the two main components of anti-TB treatment. The

Anti-retroviral treatment	Anti-tuberculosis treatment
Ritonavir: 600 mg twice-daily	Rifabutin: 300 mg/week
Amprenavir: 1200 mg twice-daily	Rifabutin: 150 mg/day *or* 300 mg twice-weekly
Indinavir: 1000–1200 mg three times a day	Rifabutin: 150 mg/day *or* 300 mg twice-weekly
Nelfinavir: 1000 mg three times a day *or* 1250–1500 mg twice-weekly	Rifabutin: 150 mg/day *or* 300 mg twice-weekly
Saquinavir: 1600 mg three times a day	Rifabutin: 300 mg/day
Saquinavir hard gel: not recommended in combination with NRTI	Rifabutin: not recommended in this combination
(Saquinavir 400 mg + ritonavir 400 mg) twice-daily	Ribabutin: 150 mg three times a week
Lopinavir + ritonavir: 400 + 100 mg twice-daily	Rifabutin: 150 mg twice-weekly
Other PI with ritonavir 100 mg twice-daily	Rifabutin: 150 mg three times a week
Delaverdin: not recommended in combination with NRTI	Rifabutin: not recommended in this combination
Efavirenz: 600–800 mg/day (serum levels)	Rifabutin: 450–600 mg/day (serum levels)
Nevirapine: not necessary to adapt doses	Rifabutin: not necessary to adapt doses
NRTI: not necessary to adapt doses	Rifabutin: not necessary to adapt doses
Tenofovir: not necessary to adapt doses	Rifabutin: not necessary to adapt doses

NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor.

Table 6. Dosage recommendations for co-administration of rifabutin and anti-retroviral drugs (these dosage recommendations are for patients receiving one of the anti-retroviral agents listed in this table only, in combination with an NRTI; serum levels of rifabutin and anti-viral drugs should always be monitored)

continued decline in the rates of MDR TB hinges on the allocation of adequate public health resources to ensure that patients complete their anti-TB therapy. The optimal regimen for treatment of MDR TB in AIDS patients remains controversial. Most drug regimens used currently to treat MDR TB include an aminoglycoside (streptomycin, kanamycin, amikacin or capreomycin) and fluoroquinolones (sparfloxacin, ofloxacin, levofloxacin, moxifloxacin or ciprofloxacin) in combination with *p*-aminosalicylic acid, cycloserine or ethionamide for 18 months [55].

TB RELAPSE AFTER TREATMENT WITHDRAWAL

Excepting non-compliant patients, TB relapses are observed rarely in HIV-infected patients, but, relapses are more frequent in HIV-infected patients (mainly in severely immunocompromised patients) than in seronegative individuals. Indeed, the relapse rate in Africa has been shown to be 5% in HIV-infected individuals, compared to 0.4% in the HIV-negative population [60–62]. However, such data have been obtained in areas where TB endemicity is very high, the risk of recontamination is high, the compliance with anti-tuberculous therapy is difficult to measure, and HAART is not available [63]. In South Africa, HIV infection has been shown recently to be a risk factor for recurrence caused by reinfection rather than relapse of a previous episode [64]. Several other studies did not find a higher risk of relapse in HIV-infected people [38,40,65], but the follow-up was frequently short (< 2 years), while relapses are, classically, often observed after a longer period than 2 years [38–41].

PARADOXICAL REACTIONS WITH HAART DURING ANTI-TB THERAPY

A paradoxical worsening of signs and symptoms of TB may occur when HIV-infected patients are treated effectively for their TB and have commenced HAART. These paradoxical reactions consist of a hectic fever, the occurrence or enlargement of lymphadenopathies, worsening of chest infiltrates, and an increase of pre-existing TB lesions (cutaneous and peritoneal) [66–69]. However, these reactions are related to immune restoration and not to a failure to control infection. Paradoxical reactions were related more temporally to the initiation of combination anti-retroviral therapy (mean 15 ± 11 days afterwards) than to the initiation of anti-TB treatment (mean 109 ± 72 days afterwards). In one study, paradoxical worsening of disease developed in 36% of patients who received TB treatment and combination anti-retroviral therapy, and in only 7% of patients who received anti-tuberculous drugs alone (and < 2% of non-immunocompromised patients) [68]. These reactions occurred while peripheral blood $CD4^+$ T-cell counts remained at < 200 cells/mm^3. A substantial reduction in the HIV viral load and a marked increase in reactivity on tuberculin skin testing accompanied these paradoxical reactions, suggesting that they represent the inflammatory process resulting from a stronger immune response to *M. tuberculosis* under HAART. Indeed, immune restoration, mainly of memory CD4 lymphocytes and then naive CD4 lymphocytes induced by HAART, restores an effective Th1 immune response to tuberculous antigens (as well as to atypical mycobacteria, *Cryptococcus neoformans* and viruses such as cytomegalovirus and

varicella zoster) [61,69–75]. As a consequence, use of HAART might not be appropriate during the first weeks of anti-tuberculous therapy in naive HIV-infected patients. For patients receiving anti-retroviral therapy, this regimen should be continued or changed, and TB should be treated with an appropriate regimen (Fig. 1). Paradoxical reactions are self-limited and generally last for 10–40 days. However, some reactions are severe and may require a short course of glucocorticoids in order to attenuate the granulomatous reaction [68].

PRIMARY PROPHYLAXIS OF TB IN HIV-INFECTED PATIENTS

Primary prophylaxis is indicated for HIV-infected patients with a positive tuberculin skin test who have never been treated for TB, and for patients who have been in recent close contact with someone with active TB. Several regimens are recommended to treat latent TB infection in HIV-infected patients. Daily or twice-weekly isoniazid preventive therapy for 9 months is often recommended [43,76], and has been shown to be effective in a large population, without interactions in association with HAART [77–79]. A 6-month course was less effective than longer regimens, but courses lasting >12 months did not provide an additional benefit. Other prophylactic regimens recommended currently are daily pyrazinamide and either rifampicin or rifabutin for 2 months [43,76,80,81]. However, fatal and severe hepatitis associated with rifampicin or pyrazinamide, used alone or in combination, for the treatment of latent TB has been observed in non-HIV-infected patients [82]. Such a combination might be used cautiously in HIV-infected patients who are chronic alcoholics and in those coinfected chronically with hepatitis viruses. Chemoprophylaxis for an HIV-infected person exposed to a patient with MDR TB should include at least two drugs with activity against the drug-resistant isolate. Notably, isoniazid preventive therapy has not been shown to reduce the incidence of TB in anergic HIV-infected patients. Finally, it should be kept in mind that the immunological efficacy of HAART has been associated recently with a reduction in the incidence of HIV-1-associated TB of >80% in areas endemic for both TB and HIV-1, such as South Africa and Brazil [83,84].

SECONDARY PROPHYLAXIS OF TB IN HIV-INFECTED PATIENTS

Secondary prophylaxis of TB is not recommended for HIV-infected patients because relapses are rare when anti-tuberculous agents have been

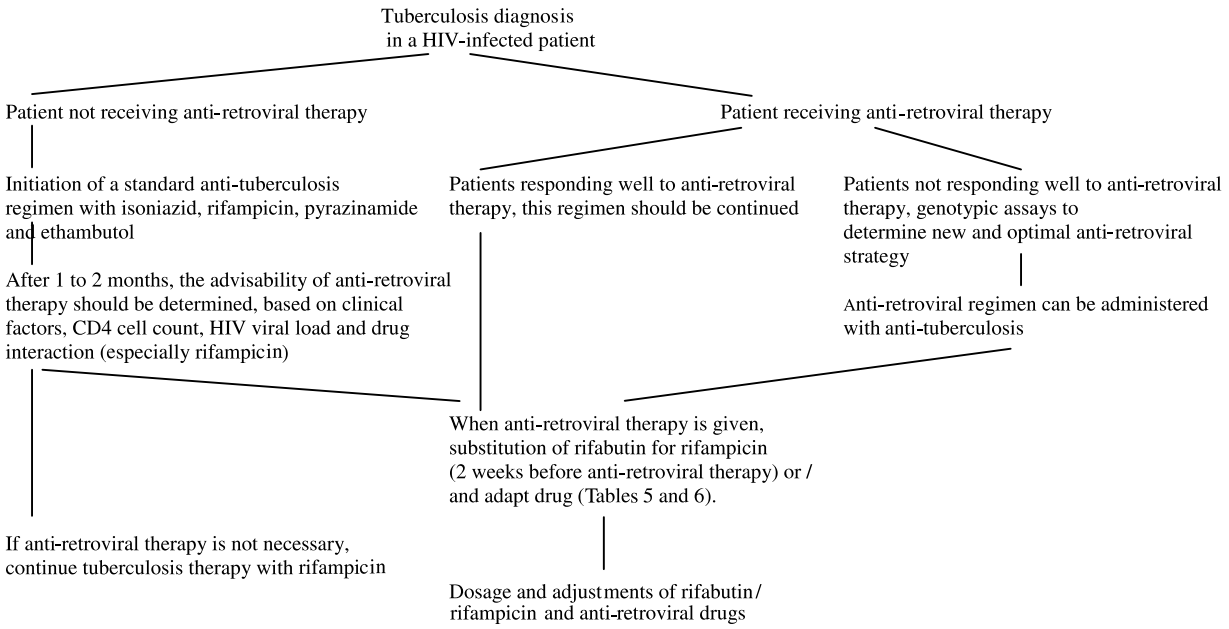

Fig. 1. Practical approach to anti-tuberculosis and anti-retroviral therapy.

taken properly [79]. However, secondary prophylaxis could be interesting in areas highly endemic for TB, as suggested by the results of a recent study conducted in Haiti, where the reinfection risk appeared to be very high and the relapse rate decreased from 7.8% to 1.4% in HIV patients [63]. As for other opportunistic infections, correction of the immune deficiency appears to be the best strategy to prevent TB relapse. Nevertheless, in developing countries, the use of both primary and secondary prophylaxis is not as frequent as it should be because of cost and logistical limitations. Indeed, feasibility studies have demonstrated that such interventions are ineffective [85]. In addition, the risk of poor compliance should also be considered.

CONCLUSIONS

The worldwide incidence of TB is increasing currently, particularly in areas of the southern hemisphere where HIV epidemics are devastating because anti-retroviral therapies are not available. HIV-infected patients are at extremely high risk for progression from latent TB to active disease, and unusual clinical manifestations of TB should not be ignored in this high-risk group. Patients receiving HAART may have significant drug–drug interactions when rifampicin is used with PIs or NNRTIs, and also risk developing severe paradoxical reactions attributable to immune restoration. Finally, the dramatic extension of anti-TB drug resistance, caused partially by the HIV epidemics, as seen currently in Southeast Asia, India, sub-Saharan Africa and South America, should be taken into account by international public health authorities.

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