Perspective

Tuberculosis and HIV in the Caribbean: Approaches to Diagnosis, Treatment, and Prophylaxis

In the Caribbean region, the lifetime risk of active tuberculosis (TB) in purified protein derivative (PPD)-positive HIV-infected patients is 50%. Screening of individuals with cough who came to an HIV voluntary counseling and testing center in Haiti revealed active TB in 33% of patients. TB prophylaxis is effective in preventing active disease in HIV-infected individuals, and secondary prophylaxis has been shown to reduce recurrence in patients diagnosed with TB at more advanced stages of immunosuppression. Recommendations for anti-TB therapy differ according to whether antiretroviral therapy is available or not and according to whether the TB diagnosis is made while the patient is receiving antiretroviral therapy or not. This article summarizes a presentation by Jean William Pape, MD, at the first CHART Caribbean Conference on the Clinical Management of HIV/AIDS in Montego Bay, Jamaica in June 2004.

The populations in the developing world account for 95% of all cases of HIV-infection, more than 99% of HIV-related deaths, about 95% of all tuberculosis (TB) cases, and about 98% of TB-related deaths. In these areas, more than 85% of HIV deaths and 75% of TB deaths occur in the economically productive age group, ages 15 to 50 years. In the Caribbean region, some 40% to 90% of individuals are purified protein derivative (PPD)-positive. The lifetime risks of active TB are 5% to 10% among those without HIV infection and 50% in those with HIV infection.

Figure 1 shows a timeline of HIV disease in Haiti before the availability of antiretroviral therapy. The average time to AIDS (World Health Organization [WHO] HIV disease stage 4) was 6.5 years and average time to death was 7.4 years, representing disease progression in the absence of antiretroviral therapy approximately twice as rapid as that in developed countries. Similar findings have been made in Trinidad and Tobago. TB was the most common pre-AIDS manifestation in the Haitian cohort, occurring in 40% of patients prior to AIDS diagnosis. The most common AIDS-related illness was the wasting syndrome, which in many patients was associated with TB. The most common causes of death were wasting syndrome, TB, cryptococcal meningitis, and toxoplasmosis.

Diagnosis of TB

TB can occur at any time during the course of HIV infection. In a group of more than 1000 patients with HIV and TB seen at our site in Haiti, CD4+ cell count at TB diagnosis was above 350/µL in 56% of patients, between 200/µL and 350/µL in 23%, and below 200/µL in 21%. Pulmonary TB is still the most common form of the disease, with presentation depending on the degree of immunosuppression. Documented bacteriologic diagnosis is more difficult in HIV-infected patients than in those without HIV infection. In diagnosing TB, the disease manifestation in persons with early HIV infection closely resembles that in HIV-uninfected persons. Studies in Haiti have found that among patients with early HIV infection, chest x-ray often shows upper-lobe infiltrates and cavities, sputum smear is positive in 70% of patients, and 65% are PPD-positive. In contrast, in patients with late-stage HIV infection, chest x-ray may show lower-lobe infiltrates and no cavities, sputum smear is negative in 80% of patients, and PPD is negative in 80%. Blood culture may be helpful for diagnosis in HIV-infected patients who have lower concentrations of mycobacteria in sputum. Nucleic acid amplification assays can also be used in diagnosis; these assays are more reliable on positive smears from untreated patients (sensitivity of 95% and specificity of 98%) and least reliable in those receiving TB therapy.

Vigilance for TB must always be maintained in HIV-infected populations in the developing world. A high frequency of TB occurs among patients presenting with the wasting syndrome. Evaluation of 43 such patients via clinical assessment,

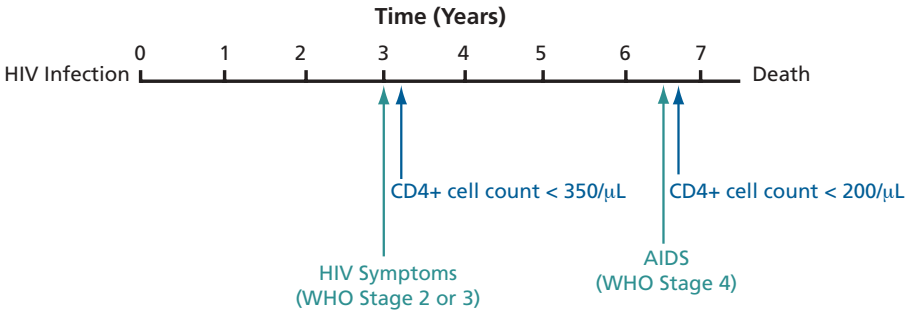

Figure **1**. Timeline of HIV infection in Haiti before the availability of antiretroviral therapy. WHO indicates World Health Organization.

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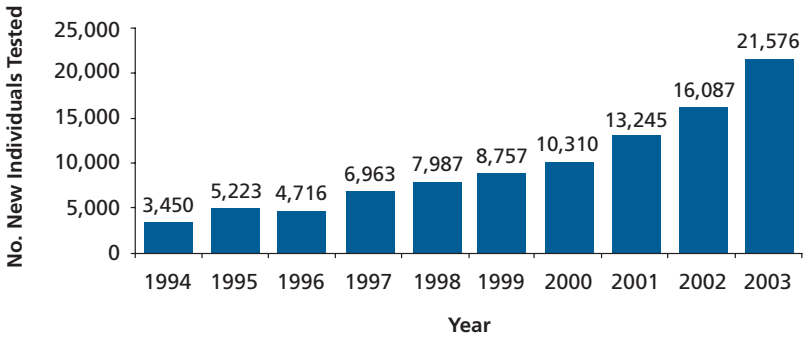

Figure **2**. Number of individuals newly tested for HIV at the Groupe Haitien d'Étude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) voluntary counseling and testing center in Haiti from 1994 to 2003.

chest x-ray, sputum smear, TB culture, and blood culture found that 16 patients (37%) had bacteremia and that TB accounted for 50% of these cases. Screening for TB through HIV voluntary counseling and testing in Haiti has produced an astounding yield in TB diagnoses. Figure 2 shows the increase in numbers of individuals coming to the Groupe Haitien d'Étude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) voluntary testing center in Haiti over the last 10 years; it is projected that more than 25,000 individuals will have presented during 2004. In a study conducted at the center, all persons coming for HIV testing who presented with cough underwent a work-up for TB with sputum smear, culture, and chest x-ray. Active TB was documented in 33% of all persons with cough and in 6% of all individuals who came to the center (Burgess et al, *AIDS*, 2001). More than 500 active TB cases per year are diagnosed this way and treated the same day, and more than 1000 persons per year coinfected with HIV and TB are put on isoniazid prophylaxis.

TB Prophylaxis

A number of studies in HIV-infected populations in the developing world have shown that isoniazid prophylaxis is effective in preventing active TB cases. In a study conducted by Pape and colleagues (*Lancet*, 1993), isoniazid prophylaxis for 1 year reduced the active TB rate from 10 cases to 1.7 cases per 100 person-years. Isoniazid prophylaxis had a beneficial impact on the natural history of HIV disease in PPD-positive patients, slowing progression to AIDS and to death; a similar effect was not observed in PPD-negative patients. In another study aimed at determining the appropriate length of isoniazid prophylaxis by the timing of TB recurrence in patients receiving primary isoniazid prophylaxis, time to diagnosis of active TB increased considerably with longer duration of prophylaxis. The median times to diagnosis of active TB from time of discontinuation of isoniazid prophylaxis were 8 months in those receiving 6 months of prophylaxis, 22 months in those receiving 12 to 24 months of prophylaxis, and 40 months in those receiving 24 to 36 months of prophylaxis (Fitzgerald et al, *Clin Infect Dis*, 2000).

The availability of potent antiretroviral therapy has a profound effect on rates of pulmonary and disseminated TB. Figure 3 shows rates of TB in Brazil prior to and after potent antiretroviral therapy became available around 1996.

TB Treatment

In general, the initial response to effective anti-TB treatment (absence of fever) occurs within 14 days even in patients with advanced AIDS. Persistent illness should raise concerns over drug-resistant TB, poor adherence, negative drug reactions involving TB medications, concomitant infections, or poor absorption of TB drugs, although the latter is infrequent in patients with AIDS.

Table 1 shows cure and recurrence rates in HIV-infected and HIV-uninfected patients with TB using different anti-TB regimens in developing countries. A study by Perriens and colleagues (*Am Rev Resp Dis*, 1991) showed an excessively high recurrence rate (14%) in patients receiving a regimen of isoniazid/streptomycin/thiacetazone for 2 months followed by isoniazid/thiacetazone for 10 months. In addition, many patients had Stevens-Johnson syndrome on this thiacetazone-containing regimen, with related fatalities occurring; thus, this regimen should not be used and thiacetazone avoided in HIV-infected patients. In another study by Perriens and colleagues (*N Engl J Med*, 1995), HIV-seropositive patients who received 12 months of treatment had an acceptable relapse rate of

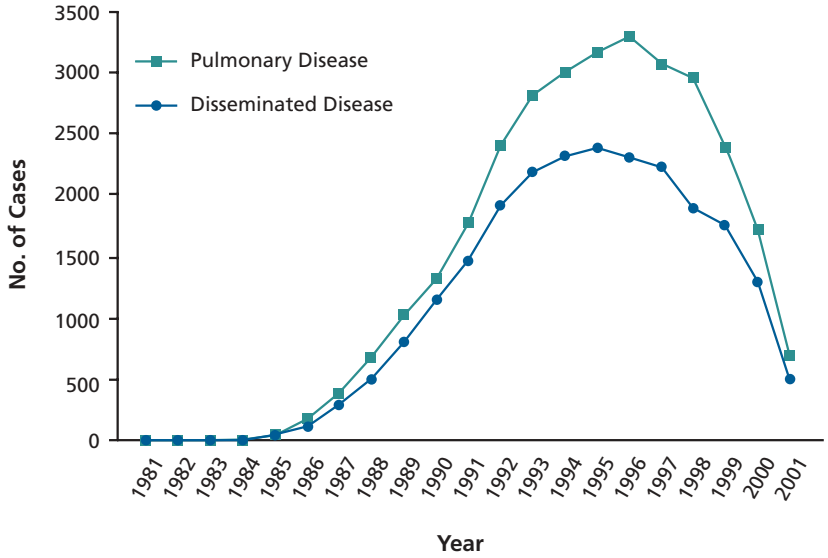

Figure **3**. Rates of pulmonary (green squares) and disseminated (blue circles) tuberculosis in patients with AIDS prior to and after availability of antiretroviral therapy in Brazil. Data from Brazilian Ministry of Health, 2002.

Table **1**. Anti-Tuberculosis Treatment Outcomes in HIV-Seropositive and HIV-Seronegative Patients

Study (location): Regimen	HIV-seropositive (%)		HIV-seronegative (%)	
	Cure	Relapse	Cure	Relapse
Perriens et al, *Am Rev Resp Dis*, 1991 (Zaire): 2 mo streptomycin, thiacetazone, isoniazid; 10 months thiacetazone/isoniazid[1]	84	14	87	5
Kassim et al, *AIDS*, 1995 (Ivory Coast): 2 mo isoniazid, rifampicin, pyrazinamide; 4 mo isoniazid, rifampicin	87	3	87	3
Perriens et al, *N Engl J Med*, 1995 (Zaire): 2 mo isoniazid, rifampicin/ pyrazinamide/ethambutol; 4-10 mo isoniazid, rifampicin	96	9, with 6 mo 1.9, with 12 mo	97	5.3
Ackah et al, *Lancet*, 1995 (Ivory Coast): 2 mo isoniazid, rifampicin, pyrazinamide; 4 mo isoniazid, rifampicin	93	—	92	—
Chaisson et al, *Am J Respir Crit Care Med*, 1996 (Haiti): 2 mo isoniazid, rifampicin, pyrazinamide, ethambutol; 4 mo isoniazid, rifampicin[2]	97	5.4	94	2.8
Desvarieux et al, *Am J PH,* 2001 (Haiti): 1 mo isoniazid, rifampicin, pyrazinamide; 4 mo isoniazid, rifampicin[3]	99	4	88	—

[1]Only regimen without rifampicin. [2]Directly observed therapy, thrice weekly regimen. [3]Modified directly observed therapy.

1.9%, compared with 9% among HIV-infected patients who only received 6 months of treatment. The Centers for Disease Control and Prevention (CDC) recommends treatment for 9 months in HIV-infected patients with a rifampicin-containing regimen.

In general, the highest initial cure rates are achieved in the setting of directly observed therapy. Initial cure rates are sometimes higher in HIV-infected patients than in HIV-uninfected patients. Survival in HIV-infected patients receiving anti-TB therapy is markedly better in those beginning treatment at higher CD4+ cell counts. One study in Abidjan showed that at 6 months after starting treatment, mortality rates were 10% in those with initial CD4+ cell counts below 200/µL, 4% in those with counts between 200/µL and 500/µL, and 3% in those with counts above 500/µL. A study in Kinshasa showed 18-month mortality rates of 67%, 22%, and 8%, respectively, in these CD4+ cell count categories.

Adverse reactions to anti-TB medications are common in HIV-infected patients, and serious adverse effects have been reported in 18% to 27% of patients in various studies (Small et al, *N Engl J Med*, 1991; Perriens et al, *N Engl J Med*, 1991; Perronne et al, *Tuber Lung Dis*, 1992; Nunn et al, *Lancet*, 1991). Common adverse reactions and the implicated drugs are shown in Table 2. Drug interactions are important to consider in treatment. For example, isoniazid and rifampicin decrease serum levels of ketoconazole and fluconazole, and that the latter 2 antimicrobials decrease absorption of rifampicin. As discussed below, the situation regarding drug interactions is especially complex when it comes to considering antiretroviral treatment, since some antiretroviral agents and anti-TB agents share metabolism via the cytochrome P450 (CYP450) enzyme pathways.

To determine the duration of response to anti-TB treatment and the potential benefit of secondary isoniazid prophylaxis, Fitzgerald and colleagues randomized 142 HIV-infected patients and 91 HIV-uninfected patients who had been treated for TB to placebo or secondary isoniazid prophylaxis (*Lancet*, 2000). All patients had normal chest x-ray findings and were culture-negative for TB after anti-TB treatment. Recurrence was statistically much higher in HIV-infected than in HIV seronegative patients. Among the HIV-infected patients, TB recurred in 12 of 74 placebo recipients and in 2 of 68 isoniazid recipients, rates (95% confidence interval) of 7.8 (4.1-13.3) and 1.4 (0.0-3.4) cases per 100 person-years, respectively. Among the HIV-uninfected patients, TB recurred in 0 of 40 placebo recipients and 1 of 51 isoniazid recipients, giving rates of 0.0 (0.0-4.0) and 0.7 (0.0-3.9) cases per 100 person-years, respectively. Further analysis showed that all cases of recurrence in the study were in patients with advanced HIV disease as indicated by CDC class B or C disease at the time of TB diagnosis. These findings

Table **2**. Adverse Reactions to Anti-Tuberculosis Therapy in HIV-Infected Patients

Reaction	Most frequently implicated drugs
Rash	thiacetazone, pyrazinamide, rifampicin, ethambutol
Stevens-Johnson syndrome	thiacetazone
Hepatitis	isoniazid, rifampicin, pyrazinamide
Gastrointestinal distress	rifampicin, pyrazinamide
Paresthesias	isoniazid
Optic neuritis	ethambutol
Arthralgias	pyrazinamide
Anaphylaxis	rifampicin

indicate that significant benefit may be achieved with secondary isoniazid prophylaxis after initial treatment in HIV-infected patients and that such prophylaxis should be provided following successful treatment for active TB in patients with advanced HIV disease at the time of TB diagnosis.

Santoro-Lopes and colleagues had similar findings from a study in a Brazilian cohort (*Clin Infect Dis*, 2002). As shown in Figure 4, the presence of TB is associated with decreased survival in patients with advanced HIV disease even in the context of antiretroviral therapy, indicating a role for such measures as secondary prophylaxis regardless of whether potent antiretroviral therapy is available. Survival was improved among patients with TB who received secondary TB prophylaxis.

TB relapse should be managed by reinstitution of the previous regimen if the organisms were susceptible to the regimen at the start of treatment. TB treatment failure (defined by persistence or worsening of TB-associated signs and symptoms, findings on chest radiograph, and/or smear-positive acid fast bacilli/positive culture for *M. tuberculosis*) should be managed by instituting a regimen with 3 drugs not previously used. In both cases, treatment should be conducted via directly observed therapy.

Antiretroviral Therapy in TB Patients

Should antiretroviral therapy be initiated in patients with active TB? In many cases, TB is the first opportunistic infection occurring in the HIV-infected patient, and may occur when CD4 + cell counts are relatively high—that is, before antiretroviral therapy needs to be initiated. Apart from this consideration, there are reasons to avoid initiating antiretroviral therapy in patients with active TB, including avoidance of potential drug interactions and toxicities and avoidance of the "paradoxical response" or "immune reconstitution inflammatory syndrome" to anti-TB therapy that can be caused by immune reconstitution under antiretroviral therapy. This response, which has been observed soon after initiation of antiretroviral therapy, is characterized by persistent or increasing fever, severe pulmonary inflammation, and lymphadenopathy. It may be associated with recovery of PPD-positivity and may respond to corticosteroid treatment. It is of interest that since antiretroviral therapy has become available in Haiti, few cases of TB immune reconstitution syndrome have been observed. The explanation for this phenomenon remains unclear.

Decisions to place patients on ART are often based on CD4 + cell count. However, TB in the absence of HIV can be associated with very low CD4 + cell counts that increase with anti-TB treatment. Thus, CD4 + cell count and response should be interpreted cautiously in HIV-infected patients undergoing anti-TB therapy. Concomitant therapy is also associated with a large pill burden that can threaten adherence to treatment regimens.

Drug interactions are a major consideration in decisions regarding concomitant antiretroviral therapy and anti-TB therapy. Rifampicin reduces blood levels of many antiretroviral agents, which can cause antiretroviral treatment failure and selection for antiviral drug resistance. Antiretroviral drugs metabolized by the liver, including nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), may cause liver toxicity, complicating patient management. Thus, antiretroviral drugs that should be avoided during anti-TB therapy include ones that undergo extensive CYP450 metabolism. These include the PIs nelfinavir, lopinavir/ritonavir, indinavir, amprenavir, and saquinavir, and the NNRTIs nevirapine, efavirenz, and delavirdine; however, nevirapine and efavirenz can be used with suitable dose adjustments. Interactions between anti-TB agents and antiretroviral agents are shown in Table 3. Antiretroviral drugs that can be safely

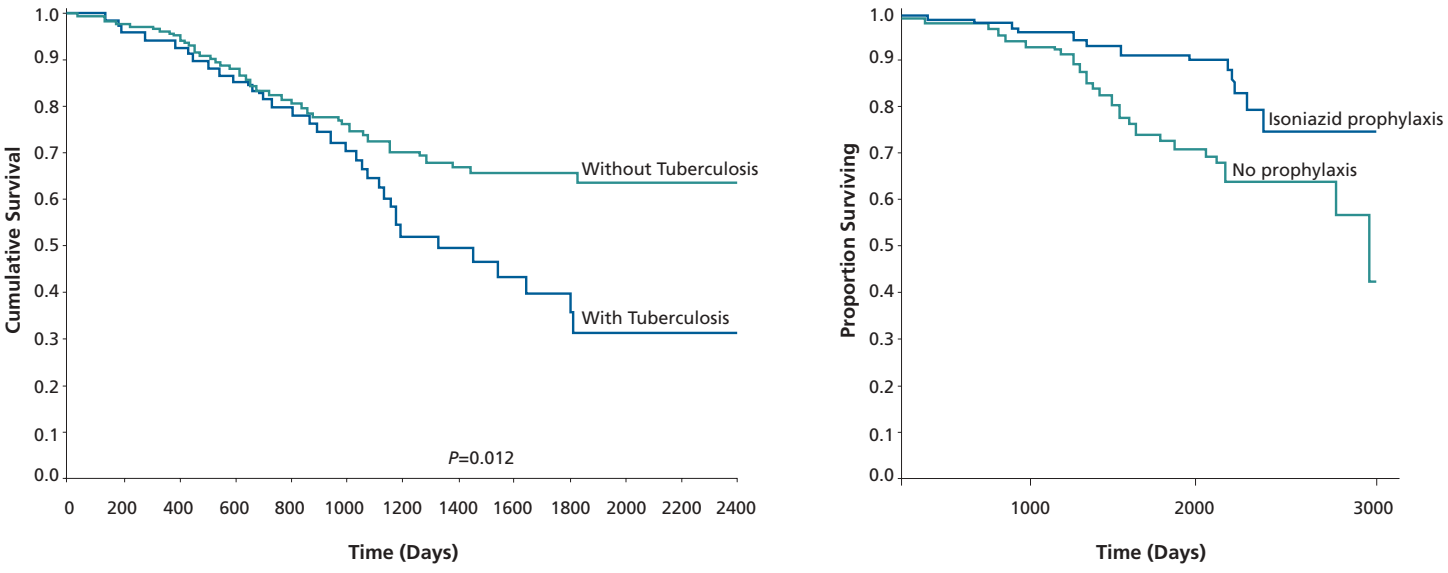

Figure **4**. Left: Survival among 312 patients in Brazil with advanced HIV disease (CD4+ cell percentage <15%) according to presence or absence of tuberculosis. Adapted from Santoro-Lopes et al, *Clin Infect Dis,* 2002. Right: Cumulative survival among those with tuberculosis according to use of isoniazid secondary prophylaxis or no prophylaxis. Adapted from Santoro-Lopes et al, *Clin Infect Dis*, 2002.

Table **3**. Drug Interactions Between Anti-Tuberculosis Agents and Nonnucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

Antimycobacterial	Nonnucleoside Reverse Transcriptase Inhibitor		
	Nevirapine	**Delavirdine**	**Efavirenz**
Rifampicin	Levels: nevirapine ↓ 37% Not recommended	Levels: delavirdine ↓ 96% Contraindicated	Levels: efavirenz ↓ 25% No dose adjustment
Rifabutin	Levels: nevirapine ↓ 16% No dose adjustment[1]	Levels: delavirdine ↓ 80% rifabutin ↑ 100% Not recommended	Levels: efavirenz unchanged; rifabutin ↓ 35% Dose: ↑ rifabutin dose to 450-600 mg qd or 600 mg 2-3x/week[1]; efavirenz: standard
Antimycobacterial	**Protease Inhibitor**		
	Indinavir	**Ritonavir**	**Saquinavir**
Rifampicin	Levels: indinavir ↓ 89% Contraindicated	Levels: ritonavir ↓ 35% Dose: No data Increased liver toxicity possible	Levels: saquinavir ↓ 84% Contraindicated, unless using ritonavir + saquinavir, then use rifampicin 600 mg qd or 2-3x/week
Rifabutin	Levels: indinavir ↓ 32%; rifabutin ↑ 2x Dose: ↓ rifabutin to 150 mg qd or 300 mg 2-3x/week Indinavir 1000 mg tid	Levels: rifabutin ↑ 4x Dose: ↓ rifabutin to 150 mg qd or dose 3x per week; Ritonavir: standard	Levels: saquinavir ↓ 40% No dose adjustment unless using ritonavir + saquinavir, then use rifabutin 150 mg 2-3x/week
Antimycobacterial	**Protease Inhibitor**		
	Nelfinavir	**Amprenavir**	**Lopinavir**
Rifampicin	Levels: ↓ 82% Contraindicated	Levels: amprenavir AUC ↓ 82% No change in rifampicin AUC Avoid concomitant use	Levels: Lopinavir AUC ↓ 75% Avoid concomitant use
Rifabutin	Levels: nelfinavir ↓ 32%; rifabutin ↑ 2x Dose: ↓ rifabutin to 150 mg qd or 300 mg 2-3x/week; ↑ nelfinavir dose to 1000 mg tid	Levels: amprenavir AUC ↓ 15%; rifabutin ↑ 193% Dose: no change in amprenavir dose; ↓ rifabutin to 150 mg qd or 300 mg 2-3x/week	Levels: rifabutin AUC ↑ 3-fold; 25-O-desacetyl metabolite ↑ 47.5-fold Dose: rifabutin dose to 150 mg qd; Lopinavir/ritonavir: standard

[1]Apply to regimens that do not include protease inhibitors. Adapted from Panel on Clinical Practices for Treatment of HIV Infection, US Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.* Oct. 29, 2004.
AUC indicates area-under-the-concentration curve.

used during anti-TB treatment in terms of drug interactions include zidovudine, lamivudine, stavudine, didanosine, abacavir, and tenofovir, all of which lack extensive CYP450 metabolism.

In general, recommendations for antiretroviral treatment in patients with active TB can be distinguished according to whether the patient is or is not receiving antiretroviral therapy when TB is diagnosed. For patients not receiving antiretroviral therapy, multidrug anti-TB therapy with isoniazid/rifampicin/ethambutol/pyrazinamide should be initiated, but antiretroviral therapy should be withheld initially. The clinical response to anti-TB therapy should be monitored—especially the fever curve over the initial 2 weeks—and indications for antiretroviral therapy should be evaluated after at least 2 to 4 weeks of anti-TB treatment. Initiation of antiretroviral therapy should be considered if the patient's condition worsens or if there is another indication to treat HIV infection. For patients already receiving antiretroviral therapy, such therapy generally may be continued during anti-TB treatment. If the patient is receiving PI treatment, consideration should be given to switching to a regimen consisting of all nucleoside reverse transcriptase inhibitors (NRTIs) or an NRTI plus NNRTI regimen. Alanine aminotransferase or aspartate aminotransferase level should be monitored every 2 to 4 weeks for signs of liver toxicity while the patient is receiving therapy, particularly if the patient is receiving an NNRTI or PI.

Summary

Management of TB in HIV-infected patients *without* access to antiretroviral therapy

1. HIV-infected patients can be effectively treated with rifampicin-containing, short-course regimens. The initial efficacy of treatment is comparable in HIV-infected and HIV-uninfected patients, but recurrence rates are higher in HIV-infected patients.
2. HIV-infected patients should receive a longer duration of therapy (9 months, as recommended by the CDC); another alternative for those with CDC class B or C disease at the time of TB diagnosis is to receive 6 months of therapy with 1 year of post-treatment isoniazid prophylaxis.
3. Treatment should be with at least 2 drugs to which the organism is sensitive, including rifampicin.
4. Adherence to treatment is the key to success. Directly observed therapy is the best choice; modified directly observed therapy protocols are acceptable with appropriate incentives.
5. Adverse drug reactions to anti-TB treatments are more common in HIV-infected patients than in patients not infected with HIV.
6. Drug interactions may interfere with blood levels of fluconazole, ketoconazole, rifampicin, and pyrazinamide.
7. The major determinant of TB mortality is the severity of immune deficiency at the time of TB diagnosis.

Management of TB in HIV-infected patients *with* access to antiretroviral therapy

1. If the patient is already receiving antiretroviral therapy, continue that therapy; if the patient is receiving a PI, consider switching to a less potentially toxic regimen.
2. If the patient is not receiving antiretroviral therapy, begin anti-TB therapy and delay antiretroviral therapy for at least 2 to 4 weeks if possible. Recommended antiretroviral regimens are nucleoside reverse transcriptase inhibitors (NRTIs) or an NRTI plus NNRTI regimen.
3. Monitor patients frequently for liver toxicity.

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