Antiretroviral Drugs and the Treatment of Tuberculosis

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SUMMARY

This document provides updated recommendations by the New York City Bureau of Tuberculosis Control for the treatment of tuberculosis (TB) in patients co-infected with TB and the human immunodeficiency virus (HIV).

Rifamycins remain essential for adequate treatment of TB. However, treatment of TB in the presence of HIV infection is complicated by drug-drug interactions between the rifamycins used to treat TB and the protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) classes of drugs used to treat HIV infection. Previous recommendations specifically contraindicated the use of rifampin with any of the PIs or NNRTIs. However, new data indicate that rifampin can be used for the treatment of active TB in patients whose antiretroviral regimen includes efavirenz with two or more NRTIs. A nevirapine- based regimen may be used in selected settings as well. Use of rifampin with boosted saquinavir at any dose appears contraindicated.

Rifabutin can be used with regimens containing efavirenz or nevirapine, or a single PI, except saquinavir alone, with some dose adjustments. It can also be used with lopinavir/ritonavir combination or the fosamprenavir/ritonavir combination. Data is lacking on the use of rifabutin in antiretroviral regimens containing combinations of NNRTIs and PIs or multiple PIs and should be used with caution.

TB treatment should not be given less than three times per week in HIV-infected patients with a CD4 T-lymphocyte cell count of <100/mm3 because of the increased risk of development of acquired rifamycin resistance. Patients with a CD4 T-lymphocyte cell count of <100/mm3 should be treated with a daily regimen in the intensive phase of TB treatment and either daily or thrice weekly regimens in the continuation phase. We recommend that patients with CD4 count >100 cells/mm3 at the time of TB diagnosis be treated with a daily regimen in the intensive phase and either twice or thrice weekly regimens in the continuation phase. All HIV-infected patients should receive TB treatment with directly observed therapy.

Given the challenges of managing drug interactions and overlapping toxicities when treating both infections, it is essential that treatment of such patients be coordinated between the TB and HIV care providers to ensure optimal treatment for both diseases.

TB remains a common and preventable opportunistic infection in HIV-infected patients. Providers can arrange for directly observed therapy (DOT) to ensure better completion of treatment for latent TB infection (LTBI). Please call the TB Hotline at 212-788-4162 to access all TB related services offered by the Health Department.

NEW IN THIS ISSUE

- Correction to Table 2 and text of the document, regarding rifabutin dosing with Atazanavir
- Updated Figure 1

INTRODUCTION

The rapid increase in the number of drugs used to treat HIV requires that physicians keep up-to-date with the latest developments and the potential interactions these drugs may have with drugs used to treat TB and other infections that afflict HIV/AIDS patients. As new antiretroviral drugs are developed and more data become available, recommendations for the use of these drugs with anti-TB medications change (1, 2).

An enormous amount of information comes with these changes; therefore, the management of HIV-associated TB in patients taking PIs or NNRTIs should be directed by or conducted in consultation with a physician experienced in the care of patients with both HIV and TB. Close attention should be paid to the possibility of TB treatment failure, antiretroviral treatment failure, paradoxical reactions of TB, unique and synergistic overlapping adverse effects for all drugs used, and drug toxicities associated with increased serum concentrations of rifabutin.

ANTIRETROVIRAL DRUGS AND RIFAMYCINS

Treatment of TB in the presence of HIV infection is complicated by drug-drug interactions between the rifamycin class of antimycobacterial drugs (rifampin, rifabutin and rifapentine), and the PI and the NNRTI classes of drugs used to treat HIV infection (1, 2). Both PIs and NNRTIs are metabolized by hepatic CYP3A, specifically the CYP3A4 isozyme. Rifamycins are inducers of the CYP3A family of enzymes, which includes the CYP3A4 isozyme. Maximal drug levels (represented by C_{max}) or total drug exposure over time (represented by AUC, area under the concentration-time curve) of antiretroviral agents may be reduced when these drugs are co-administered with rifamycins. This will adversely affect the ability of the antiretroviral regimen to adequately suppress the virus, which is the goal of antiretroviral treatment regimens.

Rifamycins are inducers of the CYP3A system but rifampin is not metabolized by this system. Of the three available rifamycins, rifampin is the most potent inducer of CYP3A and rifabutin is the least potent, with rifapentine falling somewhere in between (1). Rifapentine should not be used for the treatment of TB in HIV-infected individuals because of the increased rate of acquired rifamycin resistance associated with its use in this population at the currently recommended dose (3).

Rifabutin has been used extensively in the developed world as a substitute for rifampin in the treatment of active TB since the mid 1990's, when highly active antiretroviral treatment (HAART) became widely available. Clinical experience shows outcomes are similar with rifampin or rifabutin. However, it is not available in most countries with large HIV and TB epidemics and is not on the WHO essential medicines list. Rifabutin is metabolized by the CYP3A system and rifabutin exposure is affected by the co-administration of PIs and NNRTIs. Rifabutin dosing has to be adjusted according to the choice of the co-administered antiretrovirals. Because the exposure of the active metabolite of rifabutin (25-O-desacetyl rifabutin) is also affected, the recommended dosages for rifabutin also take this into consideration.

Protease Inhibitors
The currently approved PIs (indinavir, nelfinavir, saquinavir, ritonavir, amprenavir, fosamprenavir, atazanavir, tipranavir/ritonavir or darunavir/ritonavir administered together, and lopinavir/ritonavir fixed combination) and the rifamycins have opposite effects on CYP3A family of enzymes in the liver. This causes the following types of drug-drug interactions when PIs are taken together with rifamycins:

- PI serum concentrations and overall exposure may decrease to subtherapeutic levels because rifamycins accelerate the metabolism of PIs by inducing the CYP3A enzymes.
- Rifampin levels are not affected since it is not metabolized by the CYP3A.
- Rifabutin exposure may increase to toxic levels because PIs decrease its metabolism.

Rifampin and PIs
Previous recommendations specifically contraindicated the use of rifampin with any of the PIs (4). However, some data indicate that rifampin may be used for the treatment of active TB in patients whose antiretroviral regimen includes ritonavir (600/mg twice daily) as the only PI (plus two or more NRTIs), though this may lead to loss of virologic response as ritonavir AUC is reduced 30% when co-administered with rifampin. However, the manufacturer does not make any recommendations on the use of rifampin with ritonavir (5). In addition, the utility of these high doses of ritonavir is limited by its poor tolerability in many patients.

Low dose ritonavir (100 mg bid) has gained utility as a booster for other PIs. The combination drug lopinavir/ritonavir (Kaletra ®; Abbott Laboratories, Chicago, IL) is an example. However, the low-dose ritonavir does not seem to ameliorate rifampin-mediated reduction in lopinavir concentration (6) and this likely applies to other PIs as well. The administration of rifampin with indinavir and low-dose ritonavir has lead to subtherapeutic concentrations of indinavir (7). Rifampin should not be administered together with the atazanavir/ritonavir 300/100 mg once daily. Even in the presence of a low dose of ritonavir, there is a clinically significant reaction between atazanavir and rifampin (8, 9). Some authorities have advised against using rifampin with any antiretroviral regimens containing low-dose ritonavir (10).

Tipranavir was FDA approved for use in a ritonavir boosted combination. It is contraindicated with rifampin. Tipranavir is actually a CYP3A inducer, but when administered with ritonavir, as currently approved, the induction effect is negated by the potent inhibitory effect of ritonavir on CYP3A (11). Darunavir is also an inhibitor of CYP3A and is approved for use in a ritonavir boosted combination. Co-administration of darunavir/ritonavir is contraindicated with rifampin (12).

Some data had indicated that rifampin may be co-administered with ritonavir (400 mg twice daily) given with saquinavir 400 mg twice daily (13). However, recent data show that 39.3% of normal subjects exposed to rifampin 600 mg once daily taken together with ritonavir 100 mg/saquinavir 1000 mg given twice daily developed significant hepatotoxicity during the 28-day study period. Among these subjects, transaminase elevations of up to >20X upper limit of normal values were noted, and one subject was admitted to the hospital with marked

transaminase elevations. Based on this, the manufacturer does not recommend co-administration of rifampin with any ritonavir/saquinavir combinations (14).

Rifabutin and PIs

Rifabutin can be used with regimens containing a single PI (except saquinavir alone) with some dose adjustments Rifabutin can also be used with atazanavir and the lopinavir/ritonavir, fosamprenavir/ritonavir, tipranavir/ritonavir or darunavir/ritonavir combinations; all are FDA approved combinations. Rifabutin should not be used with ritonavir alone because of high rate of adverse effects (15). For any boosted regimen containing ritonavir, the dose of rifabutin should be reduced to 150 mg three times per week (see below under Treatment Options and table 2 and figure) (16-21).

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

The NNRTIs—delavirdine, nevirapine, and efavirenz—are all metabolized by the hepatic CYP3A. Therefore, NNRTI levels are adversely affected by the rifamycins. The effect of NNRTIs on the CYP3A is less uniform; delavirdine inhibits the CYP3A, whereas nevirapine and efavirenz induce the CYP3A (Table 1 and 3). Delavirdine should not be used with either rifampin or rifabutin because both rifamycins greatly diminish the levels of delavirdine (22, 23).

Rifampin and NNRTIs

Efavirenz. Clinical experience supports the use of efavirenz and rifampin together. Rifampin modestly decreases the efavirenz exposure. Therefore, it is probably safe to use rifampin concomitantly with efavirenz at a slightly higher dose (800 mg of efavirenz instead of the usual 600 mg) (24), though some investigators report that there appears to be no need to increase efavirenz dose when administered with rifampin, especially if the patient weighs less than 60 kilos (25, 26).

Nevirapine. Nevirapine exposure is reduced by rifampin (27-29). Several small observational studies have shown a favorable clinical response for patients receiving rifampin and nevirapine (30, 31). Co-administration of nevirapine and rifampin may be particularly useful in resource-poor countries for pregnant patients since efavirenz cannot be used in pregnancy and use of a PI based regimen is limited because rifabutin is generally not available. If used under these circumstances, close clinical and virologic monitoring should be performed (see Treatment Options). (27).

Rifabutin and NNRTIs

Efavirenz. Efavirenz exposure is not significantly affected by rifabutin, but efavirenz does decrease rifabutin exposure. Therefore, the rifabutin dosage must be increased (from the usual dosage of 300 mg to a daily dose of 450-600 mg or twice or thrice weekly dose of 600 mg) when it is given with efavirenz (32-34). An increased dose of rifabutin given daily should be used with caution since adverse events, including anterior uveitis and reduction in the white blood cell count, have been reported with high-dose rifabutin when it was used in regimens that included a macrolide to treat disseminated *Mycobacterium avium* complex infections. Monthly monitoring with a CBC is recommended.

Nevirapine. Nevirapine exposure is slightly decreased by rifabutin, and nevirapine also slightly decreases rifabutin exposure. Therefore, nevirapine can be used with rifabutin, both at their usual doses (35).

Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Other Antiretroviral Agents
NRTIs include zidovudine, lamivudine, didanosine, zalcitabine, stavudine, emticitabine, tenofovir, and abacavir. There is a slight decrease in the level of zidovudine and probably abacavir when co-administered with rifampin. The clinical significance of this interaction is unclear. The other NRTIs do not interact significantly with rifamycins. Rifamycins can therefore be included in the anti-TB regimen if a PI- or NNRTI-sparing antiretroviral regimen is chosen. A regimen of triple NRTIs is less potent and should be used only if alternatives are not possible (36).

The fusion inhibitor T20, also known as enfuvirtide, is not known to be a substrate for the CYP450 enzymes or to have any effect on the levels of these enzymes and can be used with all anti-TB drugs.

Using More Than one PI and/or NNRTI
Drug-drug interactions between rifamycins and antiretroviral regimens containing two PIs, two NNRTIs, or both a PI and an NNRTI have not been well studied, with the exception of ritonavir (see above). However, based on knowledge of metabolic pathways, some authors have recommended the use of efavirenz or nevirapine plus a PI (other than ritonavir) with rifabutin at its usual dose of 300 mg daily or three times a week (14). It must be kept in mind that these recommendations are based on theoretical considerations and are not backed by hard data. Avoiding antiretroviral regimens that contain more than one PI (with the exception of ritonavir boosted regimens) or a PI and an NNRTI when given simultaneously with a rifamycin-containing regimen for the treatment of TB seems prudent until more data are available.

OTHER ANTI-TUBERCULOSIS AGENTS

The other major anti-TB drugs (isoniazid, pyrazinamide, ethambutol, the aminoglycosides [streptomycin, kanamycin, and amikacin], capreomycin, para-amino salicylic acid, and the fluoroquinolones) are not primarily metabolized by CYP3A. Therefore, they do not have clinically important interactions with current PIs and NNRTIs. However, ethionamide is primarily metabolized by CYP3A, and its AUC may increase if it is co-administered with PIs or delavirdine; efavirenz and nevirapine may decrease levels of ethionamide (1). The clinical significance of this interaction is unknown.

TREATMENT OPTIONS (*See Figure 1*)

For drug-sensitive TB, several rifamycin-containing anti-TB regimens can be safely administered with effective antiretroviral therapy. Rifampin and rifabutin are the preferred rifamycins for HIV-infected patients taking PIs or NNRTIs (37, 38).

The importance of rifamycins must be strongly emphasized. Regimens that include rifampin are much shorter (6-9 vs. 18-24 months) and have faster sputum conversion rates, higher cure rates,

and lower relapse rates than regimens that do not include rifampin. Regimens that have used only two months of rifampin (or rifamycin) have been shown to have much higher relapse rates, particularly for HIV-infected patients (39). Rifabutin may be substituted for rifampin (either initially or during the continuation phase of treatment). Rifabutin should be substituted at least two weeks before the planned initiation of a PI or an NNRTI to allow for the resolution of the effect of rifampin on CYP3A. Rifabutin can be administered with all the currently approved PIs (except saquinavir alone) as well as efavirenz and nevirapine. The dose and frequency of rifabutin depends on the PI or NNRTI with which it is being co-administered (Tables 1 and 2, and Figure 1). Rifampin exposure is not affected by the co-administration of the PIs or NNRTIs and rifampin dosing does not need to be adjusted.

The following regimens can be used. Details on which antiretroviral drugs can be administered with these regimens are provided in Figure 1 and the tables.

- 2 months isoniazid, rifampin, pyrazinamide, ethambutol, then 4 months isoniazid, rifampin
- 2 months isoniazid, rifabutin, pyrazinamide, ethambutol, then 4 months isoniazid, rifabutin
- 2 months isoniazid, rifampin, pyrazinamide, ethambutol, then 4 months isoniazid, rifabutin
- 9 months isoniazid, pyrazinamide, streptomycin

General Considerations

Most patients with TB in NYC have CD4 T-lymphocyte counts below 200 cells/mm^3 and are eligible for antiretroviral treatment (36). For patients who are not already taking antiretrovirals at the time of TB diagnosis, physicians should consider deferring the initiation of an antiretroviral regimen until after the intensive phase of TB therapy (the first two months of treatment for drug-susceptible TB). This allows the clinician to manage the adverse effects associated with TB drugs without having to deal with the complexities introduced by antiretroviral drugs and it may minimize the likelihood of immune reconstitution syndrome (IRIS; see below). Patients may also find the pill burden more tolerable when the antiretroviral drugs are started after some of the anti-TB medications have been discontinued in the continuation phase (40, 41). If the patient is unable to tolerate or manage the multiple drugs needed to treat both conditions, it may be necessary to defer HIV treatment until TB treatment is completed.

If a patient is already on a PI- or an NNRTI-containing antiretroviral regimen that is not compatible with rifamycins, consideration should be given to changing the antiretroviral regimen. Currently, treatment interruptions are not recommended for most patients taking antiretroviral therapy and in some patients this practice may be associated with worse treatment outcomes (36); an expert in the management of HIV disease should be consulted.

Alternatively, for patients undergoing therapy with complex combinations of PIs and/or NNRTIs, the use of anti-TB regimens that do not contain rifamycins can be given. Only one regimen without a rifamycin-nine months of isoniazid, pyrazinamide, and streptomycin has been shown (in HIV-seronegative patients) to have high efficacy in < 12 months (42).

If an isoniazid-resistant, rifampin-susceptible organism is isolated, it is essential to try to adjust the regimen so that a rifamycin can be used. Otherwise, the patient will need at least 18-24 months of treatment with one of the weaker, more toxic regimens used for multidrug-resistant TB (43).

Women of child bearing potential and during pregnancy

In pregnancy, treatment for HIV and TB is challenging. Efavirenz is contraindicated in pregnancy and in women of childbearing potential who are not on adequate contraception. The only other HAART regimen that can be administered with rifampin is nevirapine. However, nevirapine is associated with an increased risk of severe hepatotoxicity in women with CD4 T-lymphocyte counts above 250 cells/mm^3 and is a relative contraindication. In such women who are pregnant, HAART regimen will be difficult to administer during TB treatment in areas where rifabutin is not available. If nevirapine is used with rifampin, close clinical, hepatic and virologic monitoring should be performed (36, 44, 45).

Length of Therapy

Recommended treatment regimens and length of therapy are similar for HIV-infected and non-HIV-infected individuals. The length of therapy is not affected by antiretroviral use, and short course therapy is possible if a standard rifamycin-containing regimen is used. The clinical, radiographic, and microbiologic responses to therapy are similar irrespective of HIV status. Relapse rates are low. Though several studies have shown that relapse rates are higher in HIV-infected individuals (46, 47), others have shown similar relapse rates in HIV-infected and HIV-negative individuals (48, 49). If cultures remain positive after two months of rifamycin based treatment, the therapy should be extended to nine months (50).

Intermittent Regimens Containing Rifamycins

Regimens should not be given at a frequency of less than three times per week in HIV-infected TB patients with CD4 cell counts less than 100/mm^3; administering rifabutin-containing regimens twice a week has been associated with the development of acquired rifamycin resistance. The CDC suspended enrollment of patients into Study 23 (a study designed to evaluate the efficacy of twice-weekly rifabutin-based regimens for treatment of HIV-associated TB) because seven cases of acquired rifamycin resistance occurred among study patients. They had all received a biweekly rifabutin-containing regimen at some point during the treatment of TB with a drug-susceptible organism(37, 51, 52). In addition, the NYC experience confirms that use of intermittent rifamycin-containing regimens in the intensive phase of treatment is associated with development of acquired rifampin resistance in patients with very low CD4 cell counts (53).

As a result, it is now recommended that patients with HIV-associated TB and CD4 cell count of less than 100/mm^3 receive daily therapy during the intensive phase, and daily or thrice weekly therapy during the continuation phase, regardless of whether they are also receiving antiretroviral drugs (37). Rifabutin doses should be adjusted accordingly.

For patients with a CD4 cell count of less than 100/mm^3 receiving lopinavir/ritonavir or any other ritonavir boosted regimen, TB therapy should be daily during the intensive phase, with the

exception of the rifabutin component. Isoniazid, pyrazinamide, and ethambutol should be given daily at standard doses; rifabutin should be given as 150 mg three times per week. During the continuation phase of therapy, isoniazid and rifabutin can both be given three times per week.

We recommend that patients with CD4 count >100 cells/mm^3 at the time of TB diagnosis be treated with a daily regimen in the intensive phase and either twice or thrice weekly regimens in the continuation phase.

Indinavir, nelfinavir, amprenavir and fosamprenavir can all be administered with daily rifabutin (150 mg/day) as well as with twice or thrice weekly regimens (during the continuation phase only) at a dose of 300 mg. Atazanavir can be administered with rifabutin (150mg/day) three times per week. Efavirenz can be given with rifabutin 450-600 mg daily or 600 mg two or three times a week). An increased dose of rifabutin given daily should be used with caution (54). Monthly monitoring with a CBC is recommended.

ANTI-TUBERCULOSIS DRUGS AND MEALS

Rifampin and isoniazid should be taken on an empty stomach whenever possible. Absorption of rifapentine is improved when taken with meals; however, rifapentine is not recommended for HIV-infected persons. Rifabutin, pyrazinamide and ethambutol can be taken with food. Isoniazid should not be dissolved in or ingested with beverages high in glucose or lactose. Isoniazid, ethambutol, and fluoroquinolones should be given an hour before or two hours after magnesium or calcium-containing antacids as they may interfere with absorption of these drugs.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

The term paradoxical reaction, coined in the pre-AIDS era, describes the development of new manifestations of TB or worsening of existing signs and symptoms of TB in patients on appropriate anti-TB therapy. It is thought to be due to a reversal of a TB induced state of anergy by effective chemotherapy. Immune reconstitution inflammatory syndrome (IRIS), a term coined in the AIDS era, broadly encompasses a range of inflammatory manifestations temporally related to HAART initiation resulting either in unmasking a previously occult opportunistic pathogen or in provoking an intensified inflammatory reaction to a concurrent opportunistic pathogen. Presumably HAART-induced partial immune restoration permits a heightened inflammatory response. This theory is strengthened by the observation that patients with HIV-associated TB who are started on antiretroviral regimens seem to be at a particularly increased risk of developing this syndrome. Thus the timing of HAART initiation in patients with TB is further complicated by the potential for a paradoxical or IRIS reaction.

The frequency of IRIS reaction varies from 11% to 45 % (55-60) and occurs more often in patients with lower CD-4 counts, extra-pulmonary disease (56, 61, 62), disseminated disease (61) and with a shorter interval from TB diagnosis to HAART initiation (58). Temporally, paradoxical reaction occurs within a few weeks of starting HAART and coincides most closely with viral load decline (57). The frequency of IRIS was least (13%) in a cohort in whom HAART initiation was delayed until at least 5 weeks after TB treatment (56).

Patients may experience substantial morbidity due to IRIS reactions even though the prognosis for survival is favorable. The CDC/ATS/IDSA guidelines suggest delaying HAART initiation until after 4-8 weeks of TB therapy (50). A practical strategy for dually infected patients who are not already on HAART prior to TB diagnosis may be to give TB treatment alone until clinical improvement plateaus. This will also minimize overlapping toxicities, reduce pill burden and make both treatments more tolerable.

Paradoxical worsening can manifest in a wide variety of sites, including cervical or mediastinal lymphadenopathy, worsening infiltrates on chest x-ray, or enlarging CNS lesions; fever may or may not be present (55, 57-62). The course of paradoxical worsening is often unpredictable; it can be brief or prolonged, with multiple recurrences and exacerbations. These reactions typically occur within a few weeks of starting antiretroviral therapy (55, 57, 61-63). The diagnosis of paradoxical reactions remains a diagnosis of exclusion and relies on negative culture of clinical samples, decrease in HIV viral load and lack of other etiologies such as relapse of TB, poor adherence to treatment, adverse effects of drugs, worsening of TB due to drug resistance, or other infections (64).

Treatment of paradoxical reactions is not well established. Mild and moderate reactions can be managed by reassuring the patients or by non-steroidal anti-inflammatory agents. Repeated aspirations for decompression of extra-pulmonary sites have been used to avoid surgical drainage. Some have advocated the use of corticosteroids or discontinuation of antiretroviral therapy for severe cases— lymphadenopathy that may compromise respiration and swallowing, or the development of CNS mass lesions. Prednisone at doses ranging from 20 to 50 mg daily tapered over as little as two weeks has been used. The use of corticosteroids for these short periods of time does not seem to adversely affect the outcome of the TB treatment (62). Data on the use of corticosteroids for the treatment of paradoxical reactions in HIV-associated TB are limited; their use should therefore be reserved for severe cases.

DIRECTLY OBSERVED THERAPY (DOT) IN HIV-RELATED TUBERCULOSIS

There is no question that DOT improves treatment outcomes in TB. Since many patients do not take their medicines reliably when left to their own devices, DOT provides a cost-effective way to ensure that patients are taking their medicines. It is impossible to accurately predict who will and who will not adhere to their TB treatment. When TB treatment is complicated by drug-drug interactions between drugs used for TB and those used for HIV infection, the need to ensure that patients adhere to their regimens become even more paramount. Poor adherence among these patients would be doubly dangerous in that it would create both TB and HIV drug resistance, which would be catastrophic. To prevent this from happening, it is highly recommended that all HIV-infected TB patients be treated with DOT. DOT also facilitates intermittent (twice or thrice weekly) dosing of TB drugs, and both rifampin and rifabutin, as well as isoniazid, ethambutol, pyrazinamide, and streptomycin have been shown to be efficacious when given intermittently under DOT.

In addition to the Bureau of TB Control, several New York State-sponsored sites provide DOT to TB patients in the City. DOT can be done either in the clinic or in the field; arrangements are made to accommodate the patients' schedules. All services provided by Bureau of TB Control

are free of charge to the patient. Physicians can call the TB Hotline at (212) 788-4162 to make arrangements for patients' enrollment into DOT programs. For those patients who cannot afford their medication due to lack of health insurance, the Bureau can provide the drugs to the physician free of charge, with the stipulation that the medication be given through its "gratis meds" program with DOT.

TREATMENT OF LATENT TB INFECTION

TB remains a common and preventable opportunistic infection in HIV-infected patients. Test people with HIV infection for latent TB infection (LTBI) as soon as possible after diagnosis of HIV infection and at least once a year thereafter.

See Table 4 for currently recommended LTBI regimens. The 9-month isoniazid regimen may be administered concurrently with any antiretroviral regimen used to treat HIV infection. Isoniazid is prescribed daily if on self-administered therapy and twice a week if given by DOT. Rifampin or rifabutin for 4 months can be used with selected antiretroviral drugs as an alternative (see Table 1-3) (36, 43, 65). Because of reports of severe liver injury associated with its use, a regimen of two months of rifampin and pyrazinamide is not recommended and should generally not be offered to persons with LTBI (66).

HIV-positive persons who have had recent close contact with an active TB patient should have a medical evaluation and chest x-ray. Once active TB is ruled out, they should receive treatment for LTBI regardless of age, results of tests for TB infection, or history of previous treatment for LTBI (4).

HIV-positive individuals with a history of prior untreated or inadequately treated TB disease should be re-evaluated for active disease regardless of age or results of tests for TB infection. If active TB disease is ruled out, patients should still receive treatment for old, healed TB, or for LTBI.

Therapy should not be delayed for women who are HIV-infected on the basis of pregnancy alone. The risk of developing TB is high in HIV-infected individuals and the benefits of LTBI treatment outweigh any potential risks. Therefore, LTBI treatment should be given to HIV-infected pregnant women regardless of stage of pregnancy.

Evaluate liver function in all HIV-positive individuals before starting treatment for LTBI. Obtain baseline CBC with platelets if a rifamycin will be given. Monitor all patients monthly with a directed clinical exam and hepatic enzymes. Many patients started on treatment of LTBI do not complete the prescribed regimen. Adherence should be rigorously promoted for this life saving intervention. Directly observed treatment (DOT) for LTBI is available for all HIV-infected patients with LTBI. Contact the TB hotline (212-788-4162) to arrange DOT for your patient. If interruptions of fewer than three months in treatment occur, patients can be given 2 to 3 additional months to complete the regimen.

Table 1: Summary of Antiretroviral Drug Use with Rifampin and Rifabutin

Generic Name	Brand Name	OK with rifampin?	OK with rifabutin?*
Protease Inhibitors (PIs)			
amprenavir (AMP)	Agenerase®	no	yes
atazanavir (TAZ)	Reyataz®	no	yes
darunavir/ritonavir	Prezista™ & Norvir®	no	yes
fosamprenavir (fos-AMP)	Lexiva®	no	yes
indinavir (IDV)	Crixivan®	no	yes
lopinavir/ritonavir (LPV/r)	Kaletra®	no	yes
nelfinavir (NFV)	Viracept ®	no	yes
ritonavir (RTV)	Norvir®	no	yes
saquinavir (SQV)	Invirase®, Fortovase®	no	no
tipranavir/ritonavir (TPV/r)	Aptivus® & Norvir®	no	yes
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
delavirdine (DLV)	Rescriptor®	no	no
efavirenz (EFV) and efavirenz/emtricitabine/ tenofovir combination	Sustiva® Atripla™	yes	yes
nevirapine (NVP)	Viramune®	yes**	yes
Other Antiretroviral Drugs			
abacavir (ABC)	Ziagen®	yes	yes
didanosine (ddI)	Videx®	yes	yes
emtricitabine (FTC)	Emtriva®	yes	yes
enfuvirtide (T-20)	Fuzeon®	yes	yes
lamivudine (3TC)	Epivir®	yes	yes
stavudine (d4T)	Zerit®	yes	yes
tenofovir (TDF)	Viread®	yes	yes
zalcitabine (ddC)	Hivid®	yes	yes
zidovudine (AZT)	Retrovir®	yes	yes
AZT + 3TC	Combivir®	yes	yes
ABC + AZT + 3TC	Trizivir®	yes	yes
FTC + TDF	Truvada®	yes	yes
ABC + 3TC	Epzicom®	yes	yes

*When antiretrovirals are used with rifabutin, the dosage of the PI, NNRTI, and/or rifabutin may need to be adjusted. Please refer to tables 2 and 3 and the figure for details on drug dosages.
** Limited circumstances; refer to text.

Useful websites:
www.cdc.gov/nchstp/tb/tb_hiv_drugs/toc.htm or **www.AIDSinfo.nih.gov**

Table 2: Interactions between Rifamycins and Protease Inhibitors and Dosing Recommendations.

Drugs Affected	RIFAMPIN (RIF)	RIFABUTIN (RBT)
Amprenavir (AMP)	AMP AUC ↓ 82% RIF unchanged	AMP AUC↓ 15 % RBT AUC↑ 193 %
	Co-administration contraindicated	***Decrease RBT dose to 150 mg daily or 300 mg 2 or 3 times/week*** ***No change in AMP dose.***
Amprenavir/ritonavir	Markedly decreased AMP concentrations predicted	See AMP
	Co-administration contraindicated	***Decrease RBT dose to 150 mg daily or 300 mg 2 or 3 times/week*** ***No change in AMP dose.***
Atazanavir (TAZ)	Markedly decreased TAZ concentrations predicted	RBT AUC ↑ 250% 25-O-desacetyl active metabolite AUC ↑ 22 fold
	Co-administration contraindicated	***Decrease RBT dose to 150 mg 3 times/week*** ***No change in TAZ dose***
Atazanavir/ritonavir	Markedly decreased TAZ concentrations predicted	See TAZ
	Co-administration contraindicated	***Decrease RBT dose to 150 mg 3 times/week*** ***No change in TAZ dose***
Darunavir/ritonavir	Markedly decreased darunavir concentrations predicted	Increases are predicted for RBT and 25-O-desacetyl active metabolite AUC
	Co-administration contraindicated	***Administer RBT at a dose of 150 mg 3 times/week*** ***No change in darunavir/ritonavir dose***
Fosamprenavir (fos-AMP)	See AMP. Markedly decreased fos-amprenavir concentrations predicted	See AMP
	Co-administration contraindicated	***Decrease RBT dose to 150 mg/day or 300 mg 2 or 3 times/week*** ***No change in fos-AMP dose***
Fosamprenavir/ritonavir (fos-AMP/r)	***Co-administration contraindicated***	***Decrease RBT dose to 150 mg 3 times/week*** ***No change in fos-AMP dose***

Indinavir (IDV)	IDV AUC ↓ 89% RIF unchanged	IDV AUC ↓ 32% RBT AUC ↑ 2 fold
	Co-administration contraindicated	***Decrease RBT dose to 150 mg/day, or 300 mg 2 or 3 times/week.*** ***Increase IDV to 1000 mg 3 times/day***
Lopinavir/ritonavir (LPV/r) Kaletra™	LPV AUC↓ 75% RIF unchanged	RBT AUC↑ 3-fold 25-O-desacetyl active metabolite AUC↑ 47.5 fold
	Co-administration contraindicated	***Decrease RBT dose to 150 mg 3 times/week.*** ***No change in LPV/r dose***
Nelfinavir (NFV)	NFV AUC↓ 82% RIF unchanged	NFV AUC ↓ 32% RBT AUC↑ 2-fold
	Co-administration contraindicated	***Decrease RBT dose to 150 mg daily, or 300 mg 2 or 3 times/week.*** ***Increase NFV to 1000 mg 3 times/day or use standard BID dose***
Ritonavir (RTV)	RTV AUC ↓ 35% RIF unchanged	RBT levels ↑ 4-fold 25-O-desacetyl metabolite AUC ↑ 35 fold
	No data on dosing ***With co-administration, increased liver toxicity possible*** ***Possible loss of virologic response if RTV is sole PI in regimen***	***Decrease RBT dose to 150 mg 3 times/week*** ***No change in RTV dose***
Saquinavir* (SQV)	SQV AUC↓ 84% RIF unchanged	SQV AUC ↓ 40%
	Co-administration contraindicated	***Co-administration contraindicated***
Tipranavir/ritonavir (TPV/r)	Unknown	RBT levels ↑ 3-fold; 25-O-desacetyl metabolite AUC ↑ 21-fold
	Co-administration contraindicated	***Decrease RBT dose to 150 mg 3 times/week.*** ***No change in TPV/r dose***

AUC—Area under the time-concentration curve.

*Some of the drugs studies used the hard-gel capsule, Invirase®. May not apply to use with the soft-gel capsule, Fortovase®.

Table adapted from references cited in this document.

Table 3: Drug Interactions between Rifamycins and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs).

Drugs Affected	RIFAMPIN (RIF)	RIFABUTIN (RBT)
Delavirdine (DLV)	DLV AUC ↓ 96%	DLV AUC↓ 80% RBT AUC↑ 100%
	Co-administration contraindicated	Co-administration contraindicated
Efavirenz (EFV) and Efavirenz/emtricitabine/tenofovir combination	EFV AUC↓ 26%	EFV unchanged; RBT AUC↓38%
	EFV: Consider increase to 800 mg instead of 600 mg daily ***RIF: Standard dose***	***Increase RBT dose to 450-60 mg/day*** ***or 600 mg 2 or 3 times/week**** ***EFV: Standard dose***
Nevirapine (NVP)	NVP AUC↓ 37%	NVP AUC↓16% RBT AUC unchanged
	NVP: dose unchanged* ***RIF: Standard dose***	***RBT 300 mg/day or 300 mg 2 or 3 times/week*****

AUC—Area under the time-concentration curve.

*Limited circumstances; refer to text.

**These recommendations apply only to regimens that do not contain PIs, which can substantially increase rifabutin levels.

Table adapted from references cited in this document.

Table 4: Treatment for Latent TB Infection in Adults

Drug and Duration	Dosage		Major Adverse Reactions	Comments
	Daily	**Twice Weekly**		
Isoniazid (INH) 9 months	5 mg/kg (max 300 mg) **Completion Criteria** 270 doses within 12 months	15 mg/kg (max 900 mg) **Completion Criteria** 76 doses within 12 months	**Symptoms include:** unexplained anorexia, nausea, vomiting, dark urine, jaundice, persistent fatigue, weakness, abdominal tenderness (especially right upper quadrant discomfort), easy bruising or bleeding, rash, persistent paresthesias of the hands and feet, and arthalgia. **Potential complications include:** hepatic enzyme elevation, hepatitis, icterus, rash, peripheral neuropathy, increased phenytoin levels, possible interaction with disulfiram (Antabuse®).	**Preferred regimen for most individuals.** Vitamin B6 (25 mg/day) or pyridoxine may decrease peripheral and CNS effects and should be used in all HIV-positive persons Aluminum-containing antacids should be avoided—they reduce absorption.

Table 4 (continued): Treatment for Latent TB Infection in Adults

Drug and Duration	Dosage		Major Adverse Reactions	Comments
	Daily	Twice Weekly		
Rifampin (RIF) 4 months	600 mg [range 8-12 mg/kg] **Completion Criteria** 120 doses within 6 months	600 mg[1] [range 8-12 mg/kg] **Completion Criteria** 34 doses within 6 months	**Symptoms include:** nausea, vomiting, loss of appetite, rash, fever or flu-like symptoms, easy bruising **Potential complications include:** hepatic enzyme elevation, hepatitis, rash, thrombocytopenia. Rifampin reduces levels of many drugs, including methadone, warfarin, oral contraceptives, oral hypoglycemic agents, theophylline, dapsone, ketoconazole, protease inhibitors (PIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs).	**May be used to treat persons who have been exposed to INH-resistant, rifampin-susceptible TB, who have severe toxicity t INH, or who are unlikely be available for monitori and follow-up for more than 4-6 months.** Orange discoloration may occur in contact lenses and body secretions such as urine and tears. Patients receiving methadone will need their methadone dosage increased by an average of 50% to avoid opioid withdrawal. RIF may make glucose control more difficult in diabetics. Patients should be advised to use barrier contraceptives while on RIF.

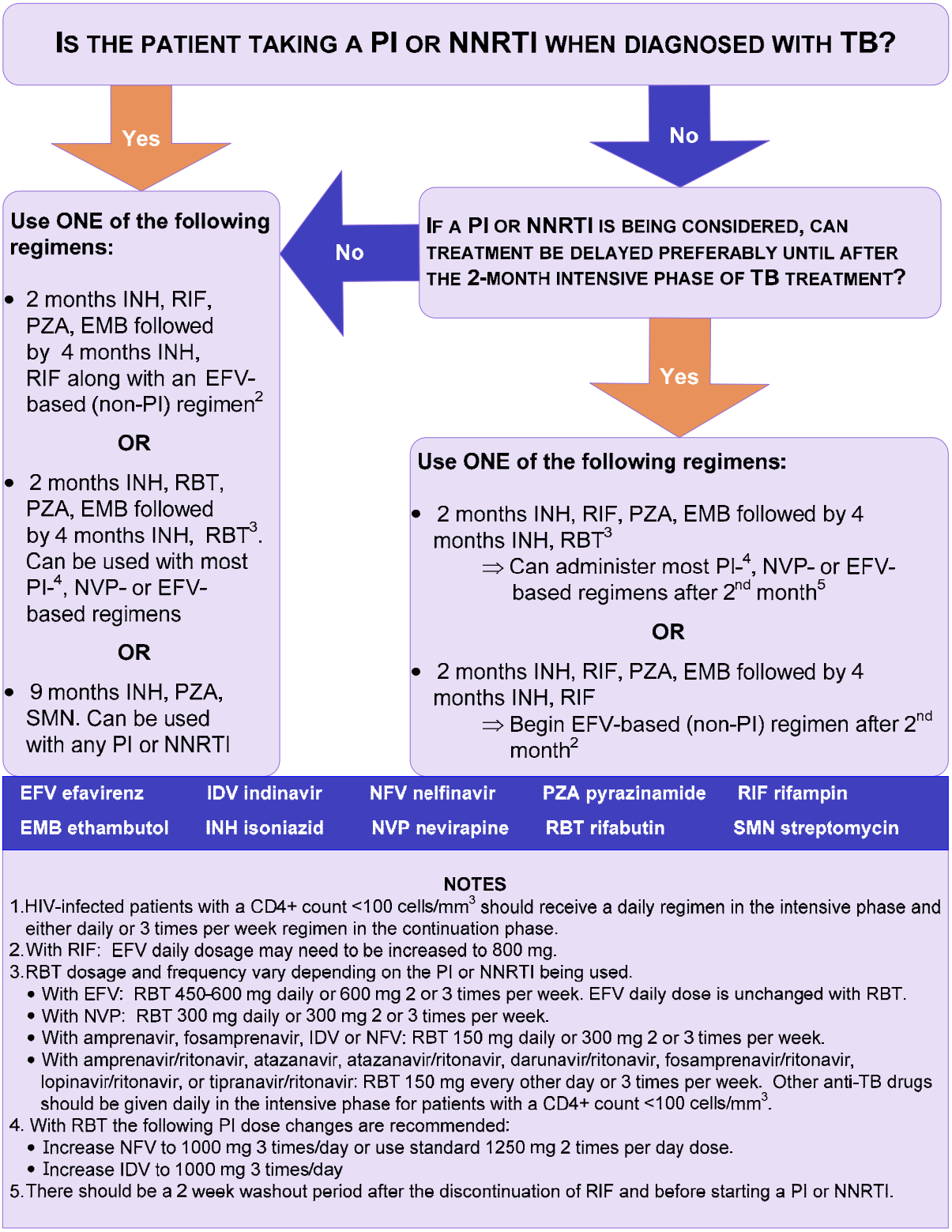
1. There is very little data or clinical experience on the use of intermittent treatment of latent TB infection with rifampin or rifabutin. These regimens should be used with caution.

Table 4 (continued): Treatment for Latent TB Infection in Adults

Drug and Duration	Dosage		Major Adverse Reactions	Comments
	Daily	Twice Weekly		
Rifabutin (RBT) 4 months	5 mg/kg (max 300 mg) **Completion Criteria** 120 doses within 6 months	5 mg/kg (max 300 mg)[1] **Completion Criteria** 34 doses within 6 months	**Symptoms include:** stomach upset, chest pain, nausea, vomiting, headache, rash, muscle aches, redness, and pain of the eye. **Potential complications include:** hepatic enzyme elevation, hepatitis, neutropenia, thrombocytopenia. Reduces levels of many drugs including protease inhibitors, NNRTIs, dapsone, ketoconazole, and oral contraceptives. However, some drugs including protease inhibitors and some NNRTIs increase levels of RBT.	**May be used to treat LTBI in HIV-infected persons who fit the criteria for RIF treatment but for whom RIF is contraindicated, or for patients who need a rifamycin but are intolerant to RIF.** Orange discoloration may occur in contact lenses and body secretions such as urine and tears. For HIV-infected persons, adjust the daily or intermittent dose of RBT and monitor for decreased antiretroviral activity and for RBT toxicity, if taken concurrently with PIs and NNRTIs. Methadone dosage generally does not need to be increased. Patients should be advised to use barrier contraceptives while on RBT.

1. There is very little data or clinical experience on the use of intermittent treatment of latent TB infection with rifampin or rifabutin. These regimens should be used with caution.

Figure 1: Treatment Options for HIV-infected Patients with TB



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