Rifamycin Use in HIV-Infected Patients with Tuberculosis

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1. Introduction

One-third of the world’s population is latently infected with mycobacterium tuberculosis (MTb). (Raviglione et al., 1995; 2010c) Of those infected a 5% to 10% chance exists during that person’s lifetime for the disease to become active. (Corbett et al., 2003) Patients who are immunocompromised have a much greater risk of experiencing active tuberculosis. Patients who have contracted human immunodeficiency virus (HIV) have a 10% chance yearly of developing active disease. Tuberculosis (TB) is the most common opportunistic infection in patients with HIV. (2010a) A person with HIV is 20-30 times more likely to develop active tuberculosis than a person without the virus. (2010b) The World Health Organization (WHO) states that tuberculosis is the leading infectious killer in HIV-positive patients worldwide, killing one out of every four patients.

Guidelines recommend treating both infections concurrently as this has shown an increased probability of survival versus sequential therapy. (2010a; Abdool Karim et al., 2010) Unfortunately, several problems arise when combining therapy. Both disease states require multidrug regimens for long durations of time. TB is generally treated for nine or more months in patients with dual disease states, while HIV is treated for a lifetime. Not only does the combination of regimens lead to multi-way drug interactions, but to overlapping side effects, the immune reconstitution inflammatory syndrome (IRIS), and subsequently an increased difficulty on the part of the patient to adhere to the complicated regimens, which ultimately may result in viral or bacterial resistance.

The current recommendations for treating tuberculosis in HIV patients are the same as treatment in patients without HIV: an initial two month phase of isoniazid, pyrazinamide, ethambutol and rifampin or rifabutin followed by an extended four month phase of isoniazid and one of the rifamycins. In HIV patients the duration may be substantially longer. While each of the rifamycins have significant Cytochrome P450 (CYP450) interactions, rifabutin is considered to have the least among the three and therefore the best choice to be used in treating tuberculosis in HIV patients. (Piscitelli and Gallicano, 2001) Rifabutin is not available in many parts of the world which need it most, specifically low-resource countries (e.g., many sub-Saharan Africa nations). Also, many of the antiretrovirals which are necessary to treat AIDS are not available.

With multiple drug interactions, overlapping toxicities, and an unknown pharmacokinetic response in individual patients, clinicians are often at a disadvantage in making treatment decisions. Monitoring of serum concentrations could help elucidate sub- or supra-
therapeutic concentrations of not only the rifamycins but co-administered HIV medications, leading to a more optimal dosing of medications, reduced toxicities, and a decreased likelihood of drug resistance. In this chapter we will discuss the co-pathophysiology of HIV and TB, the interactions among the rifamycins and HIV medications, and how therapeutic drug management (TDM), also known as therapeutic drug monitoring, may aid the clinician in making informed clinical decisions.

2. Interrelated pathophysiology

The specific pathways by which TB and HIV impact each other have yet to be fully elucidated. (Patel et al., 2007) CD4+ T-helper cells in the body activate macrophages which engulf MTb. In an immunocompetent patient alveolar macrophages undergo apoptosis to destroy MTb. With HIV infection macrophages are prevented from initiating apoptosis. Alternatively, TB-infected macrophages express tumor necrosis factor-alpha (TNF-α) which leads to an increase in HIV replication. As HIV replication increases, TB is no longer well contained. The clinical course of TB accelerates which may lead to extrapulmonary involvement. In short, the combination of the two disease states begins a vicious cycle which ultimately leads to an increased risk of mortality.

3. The rifamycins

The first rifamycins were isolated in 1957 from the bacterium Streptomyces mediterranei (now Amycolatopsis rifamycinica). (Margalith, 1960) Since their discovery they have been used in the treatment of numerous diseases including: methicillin-resistant Staphylococcus aureus (MRSA), leprosy, Legionnaires’ disease, and, of course, TB. The rifamycins currently available for treatment of TB are rifampin, rifabutin, and rifapentine. They are considered the most important drugs for the treatment of TB due to their potent sterilizing effect on MTb. Briefly, the sterilizing effect is the ability of a TB drug to prevent post-treatment relapses. Regimens without a rifamycin or not using a rifamycin for at least six months have increased rates of treatment failure. (Okwera et al., 1994; Jindani et al., 2004) A meta-analysis by Khan et al. reported that patients using regimens with a rifamycin for only two months were much more likely to experience relapse than those patients on a regimen consisting of a rifamycin for at least eight months. (Khan et al., 2010) The rifamycins act by inhibiting the DNA dependent RNA polymerase encoded by the rpoB gene. The rifamycin binds to the β-subunit and blocks the synthesis of the RNA chain. Importantly, the drugs do not inhibit the mammalian enzyme. In regards to the rifamycin family, rifampin is the fastest absorbed with the highest bioavailability, while rifapentine has the slowest absorption and a half-life Intermediate (~13.19h) (1998) between the short half-life of rifampin (~2.46h) (2004 Jan) and the long terminal elimination half-life of rifabutin (~45h)(2010 Jan).

3.1 Rifampin

Rifampin has been used in the treatment of TB for nearly half a century. Along with isoniazid, rifampin is considered the cornerstone for successful treatment. However, rifampin’s potent inductive effects on many hepatic and intestinal enzymes as well as the drug transporter, P-glycoprotein, generate many drug interactions. With regards to HIV treatment, rifampin interacts with the non-nucleoside reverse transcriptase inhibitors (NNRTIs), the protease inhibitors (PIs), the integrase inhibitors (e.g., raltegravir), and the
entry inhibitors (e.g., maraviroc). Ideally, rifabutin is substituted for rifampin in HIV patients. Unfortunately, rifabutin is not available in most resource-poor countries who cannot afford the newer rifamycin. Also, unlike rifampin, rifabutin is not available in a multidrug capsule (e.g., Rifater®: rifampin, isoniazid, pyrazinamide) which aids adherence. Thus, drug interactions between rifampin and HIV medications must be managed. In this chapter we will limit our discussion to rifampin’s interactions with the NNRTIs and the PIs as these are the most commonly used medications for HIV treatment.

3.1.1 Rifampin & the PIs
Due to its inhibitory effects on CYP enzymes, ritonavir is generally prescribed at a low dose with a second PI (also known as ritonavir “boosting”). (King et al., 2004; Burger et al., 2006b) As rifampin’s inductive effects are especially strong with the PIs, only two formulations approach therapeutic concentrations when given concomitantly with rifampin: lopinavir and saquinavir, both of which must be administered with substantial doses of ritonavir. (Maartens et al., 2009)
The standard dose of lopinavir-ritonavir is 400/100 mg given twice daily. When administered with the standard 600 mg dose of rifampin, Bertz et al. noted a substantial reduction in $C_{\text{max}}$ (45%), AUC (75%) and $C_{\text{min}}$ (99%). (Bertz R, 2001) Building upon this observation, La Porte et al. performed a study with 32 healthy volunteers to compare the pharmacokinetics of the standard lopinavir-ritonavir dose given without rifampin with two dose-adjusted regimens: 800/200 mg twice daily and 400/400 mg twice daily of lopinavir/ritonavir with rifampin. (La Porte et al., 2004) Lopinavir concentrations were markedly higher in the adjusted regimens, when compared to the reported data for standard doses. However, the authors could not demonstrate that the adjusted regimens were equivalent to lopinavir-ritonavir without rifampin. This may be due to rifampin’s inductive effects, or limitations of the study (e.g., small sample size). Regardless, the study indicates that super-boosted lopinavir-ritonavir may be an option for co-infected patients when alternative regimens are unavailable. The $C_{\text{max}}$, $AUC_{0-12}$, and $C_{\text{min}}$ for lopinavir during therapy composed by lopinavir-ritonavir 400/400 mg after 10 and 24 days, respectively, were: 12.3 and 11.5 mg/liter; 102.9 and 100.7 mg*h/liter; 5.2 and 5.9 mg/liter. The lopinavir $C_{\text{max}}$, $AUC_{0-12}$ and $C_{\text{min}}$ for the lopinavir-ritonavir 800/200 mg regimen after days 10 and 24 were: 12.9 and 13.8 mg/liter; 111.8 and 104.5 mg*h/liter and 6.5 and 5.1 mg/liter, respectively. Of note, the authors point out that 31% of the patients stopped treatment with the adjusted regimens due to side effects, primarily elevated liver function tests (LFTs). In patients co-infected with HIV and TB who must receive the medications for a greater amount of time and/or additional potential hepatotoxic drugs these side effects may be exacerbated.

In a study of ten healthy volunteers, rifampin reduced the concentration of atazanavir significantly for both 300 and 400 mg doses given BID. (Acosta et al., 2007) A larger study with 71 healthy volunteers revealed that ritonavir was not able to overcome rifampin’s induction. The following proportions of atazanavir-ritonavir were analyzed: 300/100 mg, 300/200 mg and 400/200 mg, in combination with 600 mg of rifampin. (Burger et al., 2006b) These dosage regimens were compared with the administration of just atazanavir 400 mg or with the combination atazanavir-ritonavir 300/100 mg. The comparisons showed significant reductions in $C_{\text{max}}$ and AUC. However, the reductions in $C_{\text{min}}$ were the most significant: around 60% for the regimens when compared with just atazanavir 400 mg and greater than 90% for the three regimens when compared to the combination atazanavir-ritonavir 300/100 mg. The obtained atazanavir $C_{\text{min}}$ were: 15.9 ng/mL (300/100/600 mg-atazanavir/
ritonavir/rifampin), 40.6 ng/mL (300/200/600 mg-atazanavir/ritonavir/rifampin) and 74.4 ng/mL (400/200/600 mg-atazanavir/ritonavir/rifampin). Another study from Mallolas and collaborators confirmed these results. (Mallolas et al., 2007) The researchers performed a study in patients with HIV to verify the feasibility of a regimen with 600 mg of rifampin combined with 300/100 of atazanavir-ritonavir. The study had to be interrupted because of very low concentrations of atazanavir. The median reductions in $C_{\text{max}}$, AUC, and $C_{\text{min}}$ for the three patients that completed the treatment were 48, 64, and 100%, respectively.

In a study of 22 patients co-infected with TB and HIV, Ribera et al. found that saquinavir was reduced substantially in the presence of rifampin. (Ribera et al., 2007) Patients were treated with the standard TB regimen of rifampin, isoniazid, pyrazinamide, and with or without ethambutol for two months. Ethambutol and pyrazinamide were then dropped from the regimen and once-daily antiretroviral (ART) added. ART consisted of 1600 mg saquinavir, and 200 mg ritonavir along with didanosine and lamivudine. The saquinavir pharmacokinetic parameters $C_{\text{max}}$, $AUC_{0-24}$, and $C_{\text{min}}$ were reduced by 35%, 40% and 49%, respectively. The obtained saquinavir $C_{\text{max}}$, $AUC_{0-24}$, $C_{\text{min}}$ were 2.1 μg/mL, 13.6 μg*h/mL and 0.06 μg/mL, respectively. The authors concluded that twice-daily administration of saquinavir or higher doses might result in therapeutic concentrations, but it is unknown what doses would be necessary. A study of 30 co-infected HIV/TB patients given 400 mg saquinavir and 400 mg ritonavir plus two NRTIs suggests that these doses are able to maintain therapeutic concentrations of rifampin and the PIs; however, the study had a substantial attrition rate with ten patients dropping out during TB therapy and another fifteen patients dropping when ART was added. (Rolla et al., 2006)

Hepatotoxicity is one of the primary concerns facing clinicians when using a saquinavir-containing regimen with the rifamycins. A 2009 two-period crossover study consisting of 28 healthy volunteers received either 600 mg rifampin once daily or 1000/100 mg saquinavir-ritonavir twice daily for two weeks. (Schmitt et al., 2009) Volunteers then received all three drugs for two weeks. All patients in the arm who initially received rifampin and subsequently received saquinavir-ritonavir experienced elevations in their alanine aminotransferases (ALTs) from 11 to 70 times the upper limit of normal, prompting an early termination of the study.

In a study of six HIV patients, ritonavir (100mg - BID) was not able to overcome the induction caused by rifampin (300 mg – half of the normal dose) in indinavir (800 mg - BID) metabolism. An 87% reduction in the indinavir concentration and a 94% reduction in ritonavir concentration was verified 12 hours after the last dose. (Justesen et al., 2004) This study detected a $C_{\text{max}}$ of 10,116 ng/mL and $C_{\text{min}}$ of 112 ng/mL (both quantified 4 days after rifampin administration). The AUC was not calculated.

In short, ritonavir’s effect on overcoming the induction caused by rifampin is variable according to the co-administered PI and the dosage schemes have to be carefully chosen in order to achieve therapeutic drug concentrations. Also, it is important to consider the possible hepatotoxicity which may occur with increased dosing.

3.1.2 Rifampin & the NNRTIs

Efavirenz is primarily metabolized by CYP2B6 and to a lesser extent by CYP3A4 and CYP2A6 to inactive metabolites. (Kwara et al., 2010; Rakhmanina and van den Anker, 2010) As rifampin is a potent inducer of CYP2B6, concern exists regarding efavirenz concentrations when the two are given concurrently, considering that subtherapeutic efavirenz concentrations could lead to treatment failure and resistance. This hypothesis was
based on previous studies where reduced efavirenz concentrations caused treatment failure. In a study performed by Marzolini and collaborators virological failure was associated with low plasma concentrations in 50% of the patients on efavirenz ($C_{\text{min}} < 1000 \mu g/L$) while CNS toxicity was three times more frequent in patients with high efavirenz concentrations ($C_{\text{min}} > 4000 \mu g/L$). (Marzolini et al., 2001) The drug concentrations were determined between 8 and 20 hours post dose and the concentrations varied from 125 to 15,230 $\mu g/L$. The drug is administered at bedtime because of its side effects, therefore it is difficult to determine the real $C_{\text{min}}$. Efavirenz CNS toxicity occurs in approximately 20-40% (Gazzard, 1999) of patients, manifesting as light-headedness, feeling faint, dizzy, “out of control,” or restless.

Attempting to avoid sub-therapeutic concentrations, an increase in the efavirenz dosage from 600 mg to 800 mg has been recommended when concomitant treatment with rifampin is necessary (2004). A trial with 24 patients showed a reduction of efavirenz (600 mg) $C_{\text{max}}, AUC$ and $C_{\text{min}}$ of around 24, 22, and 25%, respectively, in the presence of rifampin. (Lopez-Cortes et al., 2002) The obtained $C_{\text{max}}, AUC$ and $C_{\text{min}}$ for efavirenz 600 mg in presence of rifampin, were 2.32 mg/L, 28.3 mg*h/L and 0.63 mg/L, respectively. However, the concentrations achieved with the combination of rifampin and efavirenz 800 mg are equivalent to values obtained with efavirenz 600 mg without rifampin. No improvement in virological efficacy with concomitant administration of rifampin and efavirenz 800 mg in relation to efavirenz $C_{\text{min}}$ and virological efficacy has been proven. (Manosuthi et al., 2005; Lopez-Cortes et al., 2006; Manosuthi et al., 2006)

Moreover, the use of a higher dose may increase the risk for experiencing side effects, especially in patients from specific ethnic groups. African-Americans, Hispanics and Asians tend to have higher efavirenz concentrations than Caucasians. (Burger et al., 2006a; Ramachandran et al., 2009; Kwara et al., 2010)

It is not clear if body weight is related to efavirenz plasma concentration or clearance, considering that studies have found contradictory results. Additional studies are needed regarding the impact of body weight, especially in patients weighing more than 60 kg. (Manosuthi et al., 2009b) What effect sex may play is contradictory as well. While some studies have found that females have higher plasma concentrations than males, other studies show no difference. (Gounden et al., 2010)

Pharmacogenomics studies have been performed to elucidate the source of variability on efavirenz plasma concentrations. The effect of CYP2B6 polymorphisms on efavirenz concentrations was investigated in several studies. The polymorphism CYP2B6 516 G>T (CYP2B6*6) has the most data. The 516 T/T genotype was associated with lower efavirenz clearance, a longer half-life (~48 hours), and CNS toxicity. (Tsuijya et al., 2004; Arab-Alameddine et al., 2009) Thus, while efavirenz may be affected only mildly by the rifamycins the effects of certain covariates, specifically the role of pharmacogenetics, needs to be resolved.

The concomitant administration of nevirapine with rifampin is known to reduce the exposure of nevirapine, affecting pharmacokinetic parameters such as $C_{\text{max}}, AUC$, and $C_{\text{min}}$. Despite this reduction various studies show drug concentrations to be within therapeutic range. (Ribera et al., 2001; Autar et al., 2005; Matteelli et al., 2009) However, a small study by Ramachandran et al. noted that 8 out of 13 patients had blood concentrations under the $C_{\text{min}}$ (3 $\mu g/mL$). (Ramachandran et al., 2009) They proposed the use of a higher dose (300 mg) for providing therapeutic drug concentrations to those patients; however, the study was composed of a small number of patients and conducted in a short period of time. The effect of rifampin on
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nevirapine’s concentrations seems to decrease over time when nevirapine is used chronically with anti-TB drugs. Matteelli et al. conducted a study with 16 co-infected patients receiving HIV and TB treatment. (Mattelli et al., 2004) A reduction in the AUC of nevirapine by 25.6% was detected after four weeks of TB treatment while patients experienced a reduction of only 7.5% after 10 weeks. The $C_{\text{max}}$, AUC, and $C_{\text{min}}$ of nevirapine after 4 weeks were 4.8 μg/mL, 43.7 μg*h/mL and 3.2 μg/mL, respectively.

Manosuthi and collaborators conducted a study comparing the use of efavirenz or nevirapine with rifampin. (Manosuthi et al., 2009a) They found that the levels ($C_{\text{min}}$) of efavirenz (600 mg) are less affected by rifampin than the levels of nevirapine (400 mg). The mean $C_{\text{min}}$ for week six were 4.27 mg/L (efavirenz) and 5.59 mg/L (nevirapine), and for week twelve: 3.54 mg/L (efavirenz) and 5.6 mg/L (nevirapine).

3.2 Rifabutin
Several medium-sized studies suggest that rifabutin may be as effective as rifampin for TB treatment. (Felten, 1987; Gonzalez-Montaner et al., 1994; McGregor et al., 1996) Schwander et al. first compared rifabutin to rifampin in co-infected HIV patients and found rifabutin to be as effective in the treatment of TB. Additionally, rifabutin treated patients in the study experienced earlier sputum conversion than their rifampin counterparts. Two issues arise with the use of rifabutin in AIDS patients. The first involves intermittent dosing and the second is in regards to drug interactions. In the pharmacokinetic sub-study of Tuberculosis Trials Consortium (TBTC) Study 23, patients were treated with twice-weekly rifabutin and isoniazid. (Weiner et al., 2005) Eight of the 102 patients involved in the study developed rifamycin resistance with seven of these experiencing low serum concentrations of rifabutin. As with rifampin, due to the possibility of MTb developing resistance, highly intermittent dosing is not recommended in this patient population.

As previously mentioned, rifabutin has less of an inductive effect on enzymes than rifampin (~40% less). (Burman et al., 1999) For this reason rifabutin is the preferred rifamycin for use in HIV patients when available. While less potent than rifampin and rifapentine, rifabutin still has several significant interactions with medications used to treat HIV or concomitant infections. Further complicating treatment with rifabutin is the fact that it is a CYP3A4 substrate itself, leading to interactions with CYP inducers and inhibitors. For HIV patients requiring either a PI- or NNRTI-based therapy this poses substantial difficulty in finding a good therapeutic regimen.

3.2.1 Rifabutin & the PIs
Due to the potential of lopinavir-ritonavir to increase the serum concentrations of rifabutin the current recommendation by the CDC is to lower the dose of rifabutin from 300 mg thrice weekly to 150 mg thrice weekly or every other day when given together. There is recent evidence to suggest that this recommendation should be reconsidered.

A pharmacokinetic study by Boulanger et al. measured the drug concentrations of rifabutin and lopinavir-ritonavir as well as the rifabutin metabolite, 25-desacetyl rifabutin, in HIV positive patients with active tuberculosis. (Boulanger et al., 2009) When rifabutin was administered at 150 mg thrice weekly in combination with lopinavir-ritonavir a majority of the patients had $C_{\text{max}}$ values below the normal range (0.3 to 0.9 μg/mL). PK-PD simulations by the authors suggested that when the two medications are administered together, rifabutin should be given daily, and that doses as high as 450 mg daily would be needed to
achieve free drug plasma concentrations at or above the minimum inhibitory concentration (MIC) for part of the dosing interval. The obtained rifabutin $C_{\text{max}}$ and AUC$_{0-24}$ were 0.23 μg/mL and 2.97 μg*h/mL, respectively. It should be noted that one patient developed rifamycin resistance during the study.

A second study by Khachi et al. reported similar results. (Khachi et al., 2009) The authors monitored concentrations of an antiretroviral regimen containing lopinavir-ritonavir (400/100 mg) in combination with rifabutin 150 mg. Of the five patients studied, rifabutin levels were below target in all five patients (0.10 to 0.37 μg/ml). Two patients were reported to “deteriorate clinically” and had their rifabutin increased to 300 mg three times a week. Additionally, lopinavir-ritonavir concentrations were below targeted concentrations in two patients. While both studies are limited in scope due to small sample sizes, ten and five patients respectively, they indicate the need for a larger study to determine appropriate dosing.

Darunavir and tipranavir result in increased rifabutin concentrations while rifabutin decreases their concentrations. (2004) The CDC recommends decreasing the dose of rifabutin by 75% to 150 mg every other day or 150 mg thrice weekly. However, these daily primarily reflect data from healthy volunteers, who tend to have more profound increases in rifabutin and 25-desacetyl-rifabutin concentrations than HIV-infected patients. As noted above, daily rifabutin doses, perhaps starting with 150 mg, may be preferred. This requires additional study. The remaining PIs (amprenavir, fosamprenavir, atazanavir, and indinavir) increase the AUC of rifabutin from 200 to 250% (again, primarily in healthy volunteers), while rifabutin does not appreciably alter any of their pharmacokinetics with the exception of indinavir. Indinavir is recommended to be increased to 1000 mg every 8 hours while rifabutin should be decreased to 150 mg daily or 300 mg three times per week.

Finally, saquinavir is contraindicated with rifabutin use unless boosted by ritonavir. When rifabutin is used with unboosted saquinavir there is an approximate 40% increase in rifabutin AUC and a subsequent 40% decrease in saquinavir AUC. (2007 Jul.) Dosing is then recommended at 150 mg every other day or thrice weekly. All of these recommendations reflect mean changes, mostly from healthy volunteers, and results in individual HIV-infected patients may be substantially different. (Gallicano et al., 2001)

### 3.2.2 Rifabutin & the NNRTIs

All of the NNRTIs are reported to interact with rifabutin to some degree. Delavirdine is contraindicated with rifabutin use due to an increase in rifabutin’s AUC (over 200%) and a decrease in delavirdine’s (80%)(2004). When rifabutin is prescribed with a PI boosted regimen, etravirine should be avoided because of the reduction in its concentration. (2008 Jan) This leaves efavirenz and nevirapine as the two NNRTIs which work best with rifabutin.

When efavirenz is given the AUC of rifabutin is decreased substantially, necessitating a dose of 450 to 600 mg. Studies explored three times weekly dosing regimens; daily dosing with rifabutin 450 to 600 mg also would be acceptable with efavirenz (2004). The same is true of nevirapine regarding cell counts, but with a dose of 300 mg daily or thrice weekly for rifabutin. Again, three times weekly rifabutin may not be sufficient in all or even most patients, given the demonstrated risk of acquired rifamycin resistance in HIV-infected patients receiving intermittent rifabutin regimens.
3.3 Rifapentine
Rifapentine is the latest rifamycin to be developed. A cyclopentyl derivative of rifampin, rifapentine has a longer half-life than rifampin and a 2 to 4-fold lower MIC. (Birmingham et al., 1978; Vital Durand et al., 1986) Unfortunately, rifapentine also inherited rifampin’s strong enzyme-inducing properties. Thanks to its extended half-life, rifapentine has been tested for intermittent dosing in the hopes of increasing patient compliance. Use of rifapentine is primarily reserved for the four month continuation phase of TB treatment, but is being studied for possible initial therapy. As with rifampin and rifabutin problems arose with highly intermittent dosing. TBTC Study 22 compared once-weekly rifapentine and isoniazid with twice-weekly rifampin and isoniazid in co-infected HIV/TB patients. (Vernon et al., 1999) HIV positive patients in the once-weekly rifapentine arm had higher rates of relapse than HIV positive patients in the twice-weekly rifampin arm. Four of the five patients who relapsed had acquired rifamycin monoresistance.

4. Immune Reconstitution Inflammatory Syndrome (IRIS)
In addition to drug interactions another common problem associated with co-infected patients which bears mentioning is the immune reconstitution inflammatory syndrome, otherwise known simply as IRIS. (Jevtovic et al., 2005; Tappuni, 2011) IRIS most commonly occurs when ART is added to a patient’s regimen already being treated for TB. IRIS may occur anywhere from days to months following addition of ART. Symptoms are broad and may range from a mild fever to renal failure. Respiratory distress, expanding intracranial lesions and meningitis, lymphadenopathy, and skin lesions may develop also.

The exact mechanism of IRIS is not completely known. Researchers believe that when ART begins to reduce HIV’s viral load the body’s immune system gradually recovers. This recovery leads to the immune system’s “awareness” of TB. The body overreacts to MTb antigens, releasing inflammatory cytokines and causing the aforementioned symptoms. Risk factors identified include: extrapulmonary TB, African-American race (one study), and early initiation of ART following TB therapy. (Breen et al., 2004; Burman et al., 2007)

Steroids are most often used as initial treatment of IRIS. Some clinicians recommend prednisone 1 mg/kg/day or dexamethasone 8 to 16 mg/kg/day divided twice daily. (Sexton, 2011) Clinicians should initiate steroids on a case-by-case basis and be cautious about their use. Studies are mixed in regards to the mortality benefit of steroids and one study reported an increased incidence of Kaposi’s Sarcoma. (Hakim et al., 2000; Elliott et al., 2004; Sharma et al., 2008) Other drug treatments which have been tried, but have little information regarding their use are: the non-steroidal anti-inflammatories (NSAIDs), the TNF-α inhibitor, pentoxifylline, and thalidomide. (Marais et al., 2009) However, information regarding their efficacy is scarce.

5. Pediatrics
A relatively small amount of literature exists regarding rifamycin pharmacokinetics for young patients with HIV and TB. Schaaf et al. examined 54 pediatric patients, aged three months to 13 years, receiving rifampin, 21 of which had HIV. (Schaaf et al., 2009) In the study a majority of HIV positive and HIV negative patients experienced concentrations below what is considered the normal two hours $C_{\text{max}}$ range (8-24 ug/ml). While there was a trend for HIV positive patients toward a lower rifampin $C_{\text{max}}$ no significant difference existed between the two groups.
Ren et al performed a study with 30 children aged seven months to four years and divided them in two groups. (Ren Y, 2008) One group composed of 15 HIV positive children without TB received lopinavir and ritonavir in a 4:1 ratio without rifampin. The second group of 15 HIV positive children with TB were treated with an increased concentration of ritonavir to achieve 1:1 ratio of lopinavir-ritonavir (“super boosted” lopinavir). There was a reduction of the $C_{\text{max}}$ and $AUC_{0-12}$ in the group that received additional ritonavir. However, there was no difference in the $C_{\text{min}}$ between both groups. The lopinavir $C_{\text{max}}$, $AUC_{0-12}$, and $C_{\text{min}}$ obtained for the regimen with rifampin were: 10.5 mg/L, 80.9 mg*h/L and 3.94 mg/L, respectively.

The same researchers used population pharmacokinetic analysis to characterize the pharmacokinetic interactions and to examine the data from the Ren study. (Elsherbiny et al., 2010) The adjustment of ritonavir to an equal proportion of the PI's (that is, 1:1) was not able to entirely overcome the inductive effect that rifampin has over lopinavir. One of the reasons, as the authors point out, can be the fact that children aged one to four have more pronounced enzymatic activity, eliminating the lopinavir. However, the predicted trough concentrations by the model are over 1 ug/ml, indicating that with the additional ritonavir concentrations of lopinavir will be efficacious. More studies are necessary to verify the safety and efficacy of this combination. Studies also are needed regarding the use of rifabutin and rifapentine in the pediatric setting as data are limited.

### 6. Therapeutic drug management

Due to the extensive drug interactions, the overlapping side effects, and the length of treatment, a patient co-infected with TB and HIV has a more difficult time adhering to his or her regimen than patients with either disease state alone. TDM offers clinicians the ability to make a more informed therapeutic decision. Several studies have shown TDM to be of benefit in the TB patient. (Peloquin, 2002b) TDM for HIV medications has been studied in a series of small trials. Because most such trials have several additional variables, it is difficult to achieve statistical significance in these settings. However, it remains true that PIs are competitive, reversible inhibitors, so their continued presence is required for continued activity. Also, patients with HIV may have other opportunistic infections and experience malabsorption which can affect the concentration of TB drugs. (Kotler DP et al., 1984; Gillin JS et al., 1985; Peloquin, 2002b) TDM could be a useful tool to monitor the concentration in those patients. In a review of eight trials Kredo et al. reported that routine use of TDM is not warranted but TDM use in treatment-naïve patients initiated on a PI containing regimen may improve virological efficacy. (Kredo et al., 2009)

In addition TDM may prove useful in determining which patients are experiencing malabsorption. Few studies have expressly looked at the malabsorption of anti-TB medications in HIV patients, and data are still accumulating, but evidence points toward the disease state negatively affecting concentrations of TB medications. A retrospective study of 21 HIV/TB patients by Holland et al. demonstrates this effect. Out of 21 patients, 18 had two-hour concentrations of at least one drug (either, isoniazid, a rifamycin, or both) below the recommended range. (Holland et al., 2009) Current guidelines list TDM as an option for clinicians but further research in the area is needed. (CDC, 2007)

TDM is recommended by many clinicians when both TB and HIV are treated concomitantly, especially when PIs and NNRTIs are used. However, TDM is not a substitute for clinical evaluation or directly observed treatment, but is useful to verify inadequate dose administration, or help solve drug-drug interaction problems. (Peloquin, 2002a)
7. Conclusion

Patients co-infected with HIV and TB have a difficult time adhering to their medication regimens due to many reasons. Even in those patients who are fortunate enough to receive appropriate treatment adherence is difficult. In addition to overlapping side effects and the possibility of IRIS, the drug regimens are lengthy and involve many drug interactions. Drug interactions between the rifamycins and the PIs and NNRTIs are varied and not easily quantified. Often, concentrations are unique to the individual in whom the interactions take place. One solution to this problem is to either use and/or develop new medications that have fewer interactions. While studies are underway with new (as well as older) anti-TB drugs a set timeline for their arrival is unknown. Additionally, a majority of patients reside in resource-poor settings where economics (or political or military strife) inhibit optimal care.

Until new and improved regimens are developed a reasonable solution is to monitor the concentrations of HIV and anti-TB medications and alter the doses when warranted to achieve therapeutic success, i.e., TDM. TDM has been used in TB patients for many years and is considered a valuable tool by many clinicians in the successful treatment of their patients.

8. References


The collective efforts of HIV/AIDS research scientists from over 16 countries in the world are included in the book. This 27-chapter Open Access book well covers HIV/AIDS translational researches on pathogenesis, diagnosis, treatment, prevention, and also those beyond conventional fields. These are by no means inclusive, but they do offer a good foundation for the development of clinical patient care. The translational model forms the basis for progressing HIV/AIDS clinical research. When linked to the care of the patients, translational researches should result in a direct benefit for HIV/AIDS patients.

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