

CASE REPORT

Therapeutic Drug Monitoring in Patients Coinfected with Human Immunodeficiency Virus and Disseminated *Mycobacterium avium* Complex

Keith J. Dunn, Pharm.D., Paul R. Skolnik, M.D., Leyla Azis, M.D., and Helene Hardy, Pharm.D.

In patients infected with human immunodeficiency virus (HIV), antiretroviral therapy has decreased the risk of progression to acquired immunodeficiency syndrome or death significantly. However, many individuals still present with an opportunistic infection as the first clinical manifestation of HIV infection. This complicates therapy due to frequent and complex drug interactions between antiretrovirals and the drugs used to treat the opportunistic infection. We describe a 48-year-old man coinfecting with HIV and disseminated *Mycobacterium avium* complex (MAC). His treatment for MAC started about 2 weeks before he started antiretroviral therapy. The MAC regimen consisted of clarithromycin 500 mg/day, ethambutol 1200 mg/day, rifabutin 150 mg every other day, and ciprofloxacin 500 mg twice/day. His antiretroviral therapy consisted of atazanavir 300 mg/day, ritonavir 100 mg/day, and emtricitabine 200 mg–tenofovir 300 mg/day. Approximately 95 days after receiving these concomitant therapies, his rifabutin peak concentration was 0.08 µg/ml (goal peak concentration > 0.45 µg/ml); thus, the dosage of rifabutin was increased to 300 mg every other day. Fourteen days later, his rifabutin peak concentration was 0.43 µg/ml. Drug interactions between antiretrovirals and antimycobacterials are complex and not fully understood in patients with HIV infection. Although the recommended dosage of rifabutin in patients receiving a ritonavir-boosted protease inhibitor, such as atazanavir, is 150 mg every other day, higher dosages may be required to attain optimal rifabutin concentrations in patients receiving these drugs concomitantly.

Key Words: HIV, human immunodeficiency virus, *Mycobacterium avium-intracellulare* infection, *Mycobacterium avium* complex, drug interaction, rifabutin, atazanavir, clarithromycin, lopinavir, ritonavir.
(Pharmacotherapy 2011;31(4):76e–82e)

It is currently estimated that more than 1 million persons in the United States are infected with human immunodeficiency virus (HIV).¹ Despite focused efforts aimed at HIV screening and increased availability of antiretroviral therapy, a substantial number of new HIV diagnoses present “late to care.” The Massachusetts

Department of Public Health defines late to care as patients presenting with acquired immunodeficiency syndrome (AIDS) within 2 months of their initial HIV diagnosis. In a review of epidemiologic data by the Massachusetts Department of Public Health, 31% of patients newly diagnosed with HIV between 2005 and 2007 had a late-to-care concurrent diagnosis of AIDS.² This population with late-to-care diagnoses is susceptible to opportunistic infections, as they often present with severe immunosuppression. The development of opportunistic infections, in addition to their

From the Center for Infectious Diseases, Boston Medical Center, Boston, Massachusetts (all authors).

For reprints, visit <http://www.atypon-link.com/PPI/loi/phco>. For questions or comments, contact Keith J. Dunn, Pharm.D., Boston Medical Center, 850 Harrison Avenue, Boston, MA 02118; e-mail: dunnkeithj@gmail.com.

deleterious effects on morbidity and mortality, can often complicate treatment with antiretroviral therapy due to poorly quantified drug-drug interactions and additive adverse events.

Current treatment guidelines for opportunistic infections suggest that patients with disseminated *Mycobacterium avium* complex (MAC), who are not receiving antiretroviral therapy, should have antiretroviral therapy withheld until after the first 2 weeks of antimycobacterial therapy have been completed to reduce risk for drug interactions, pill burden, and complications associated with the occurrence of immune response inflammatory syndrome.³ Disseminated MAC should be treated with antibacterials that act synergistically; the regimen usually consists of a macrolide, a bacteriostatic antimycobacterial drug (ethambutol) and a rifamycin (rifabutin) for a minimum duration of 1 year, regardless of whether sterile blood cultures are achieved sooner during therapy.³⁻⁶ Clarithromycin is considered to be the preferred macrolide for the treatment of MAC because it is associated with more rapid clearance of MAC in blood cultures compared with azithromycin.^{3,7} However, azithromycin remains an acceptable second-line macrolide for patients who are unable to tolerate clarithromycin or in whom drug interactions preclude its use. Clarithromycin is a known substrate and inhibitor of the cytochrome P450 (CYP) 3A4 isoenzyme and therefore competes for the same metabolic pathways as many antiretrovirals, whereas azithromycin has limited effects on the CYP isoenzyme system.^{8,9} Rifamycins are also known to interact with antiretrovirals due to their ability to induce CYP3A4. Rifampin is considered a strong inducer of CYP3A4 and is rarely used in the treatment of mycobacterial infections if patients are taking a ritonavir-boosted protease inhibitor-containing regimen because of the substantial effects on protease inhibitor drug concentrations. Rifabutin, which is considered to be a more moderate inducer of CYP3A4, is used instead.¹⁰ However, access to rifabutin may be limited in developing nations due to its cost, compared with generically available rifampin.

Previous guidelines for the treatment of MAC in persons with HIV or AIDS have taken drug-drug interactions into account.^{3,4} These guidelines provided the recommended dosage adjustments of various antimycobacterials when given in combination with antiretroviral agents. The strength of these recommendations has been limited because pharmacokinetic studies used to

support these suggested dosage adjustments were conducted mainly in healthy volunteers.¹¹⁻¹³ In 2009, results of a pharmacokinetic evaluation brought into question some of these recommendations, but these findings were limited to interactions between rifabutin and lopinavir-ritonavir (lopinavir boosted with ritonavir).¹⁴ As a result of these findings, treatment guidelines now recommend monitoring rifabutin plasma concentrations in those receiving ritonavir-boosted protease inhibitors.¹⁵ In this case report, we present data that support this recommendation in HIV-positive patients who are receiving rifabutin in combination with another protease inhibitor, atazanavir, boosted with ritonavir.

Case Report

A 48-year-old African-American man came to the emergency department with increased fatigue, yellow sputum production, and a weight loss of about 25 pounds over the previous 3 months. He had been diagnosed with HIV and AIDS approximately 4 years earlier, with a nadir CD4⁺ cell count of 54 cells/mm³ (normal range 800–1200 cells/mm³) and HIV RNA (viral load) of 74,611 copies/ml. He refused antiretroviral therapy after his diagnosis due to ongoing substance abuse, denial, and depression. The patient's other medical history was significant only for hypertension, for which he was receiving hydrochlorothiazide 25 mg/day.

At this visit, the patient was noted to have a CD4⁺ cell count of 53 cells/mm³ and a viral load of 4271 copies/ml. A chest radiograph and computed tomographic scan of his chest showed cavitory lung disease consistent with an infectious process. Sputum samples were obtained for aerobic, anaerobic, and mycobacterial culture; no organisms were observed on staining for acid-fast bacilli. The patient was diagnosed with community-acquired pneumonia and admitted to the hospital for treatment. A 7-day course of antibiotic therapy was administered, consisting of azithromycin 500 mg/day and ceftriaxone 1 g/day for 5 days followed by cefpodoxime 200 mg twice/day for 2 days.

The patient was then discharged, with azithromycin 1200 mg/week started for prophylaxis against MAC. He was referred for antiretroviral therapy initiation at the hospital's outpatient infectious disease clinic. Prophylaxis for other opportunistic infections such as *Pneumocystis jiroveci* pneumonia was not initiated because the patient had documented glucose-6-phosphate

Table 1. Timeline of Patient's Drug Therapy and Drug Concentrations

Day After Hospital Discharge	Drug Regimen	HIV RNA (copies/ml)	Drug Concentration (time measured)
0	Antimycobacterial prophylaxis: azithromycin 1200 mg/wk HCTZ 25 mg/day for hypertension		
20	Antimycobacterial prophylaxis discontinued Antimycobacterial regimen started: clarithromycin 500 mg/day, ethambutol 1200 mg/day, rifabutin 150 mg every other day, ciprofloxacin 500 mg twice/day HCTZ 25 mg/day continued	74,611	
31	Antimycobacterial regimen continued Antiretroviral regimen started: atazanavir 300 mg/day, ritonavir 100 mg/day, tenofovir 300 mg—emtricitabine 200 mg/day HCTZ 25 mg/day continued		
41	No changes	189	Clarithromycin trough 1.0 µg/ml ^a (30 hrs after dose)
126	No changes		Rifabutin peak 0.08 µg/ml ^b (3 hrs after dose)
140	No changes except for rifabutin dosage increased to 300 mg every other day	< 75 ^c	
154	No changes		Rifabutin peak 0.43 µg/ml ^b (2 hrs after dose) Clarithromycin trough 2.7 µg/ml ^a (24 hrs after dose)
203	No changes	< 75 ^c	Atazanavir (random) 2.68 µg/ml ^d (19 hrs after dose)

HIV = human immunodeficiency virus; HCTZ = hydrochlorothiazide.

^aTherapeutic trough concentration for clarithromycin is > 0.7 µg/ml.

^bGoal peak concentration for rifabutin is > 0.45 µg/ml.

^cLower limit of HIV RNA detection.

^dTherapeutic trough concentration for atazanavir is > 0.15 µg/ml.

dehydrogenase deficiency and may have experienced leukopenia while previously receiving atovaquone for prophylaxis.

Thirteen days after discharge, MAC was identified using an RNA probe assay for all blood and sputum samples obtained during the patient's hospital admission. The patient was contacted regarding these positive cultures, and he reported to the clinic 1 week later. An antimycobacterial regimen consisting of clarithromycin 500 mg/day, rifabutin 150 mg every other day, ethambutol 1200 mg/day, and ciprofloxacin 500 mg twice/day was initiated (Table 1). The dosages of the patient's antimycobacterials, specifically rifabutin and clarithromycin, were adjusted from the standard dosages of rifabutin 300 mg/day and clarithromycin 500 mg twice/day according to the recommendations in the Department of Health and Human Services (DHHS) HIV treatment guidelines for patients receiving concomitant therapy with a ritonavir-boosted protease

inhibitor.¹⁵ Clarithromycin was chosen over azithromycin given the severity of the patient's disease, as well as concern for azithromycin resistance after the recent course of azithromycin monotherapy for treatment of pneumonia and MAC prophylaxis. Ciprofloxacin was added as a fourth agent given the patient's high mycobacterial load (disseminated disease), low CD4⁺ cell count, and increased viral load (74,611 copies/ml).

Approximately 11 days after starting MAC therapy, the patient returned to the clinic to start an antiretroviral regimen consisting of atazanavir 300 mg/day, ritonavir 100 mg/day, and emtricitabine 200 mg—tenofovir 300 mg/day.

Due to the known drug interaction between clarithromycin and rifabutin (Table 2), a clarithromycin trough concentration was measured 10 days after the start of antiretroviral therapy (day 21 of MAC therapy). The established therapeutic trough concentration for clarithromycin for the treatment of MAC is 0.7 µg/ml.¹⁶ The

Table

2. Relevant Pharmacokinetic Interactions Among Antimycobacterials, Protease Inhibitors, and Nonnucleoside Reverse Transcriptase Inhibitors

Antimycobacterial Agent	Concomitant Agent	Mechanism of Interaction	Pharmacokinetic Effects	Management Recommendation
Clarithromycin	Atazanavir-ritonavir	CYP3A4 inhibition by atazanavir and ritonavir	Clarithromycin AUC ↑ 94%	Reduce clarithromycin dose by 50% Consider alternative therapy
	Other PIs + ritonavir	CYP3A4 inhibition by PIs and/or ritonavir	Clarithromycin AUC ↑ 19–66%	Monitor for clarithromycin toxicity No dosage adjustment necessary unless $Cl_{cr} < 60$ ml/min
	All NNRTIs	CYP3A4 induction by NNRTIs	Clarithromycin AUC ↓ 31–39%	Consider alternative macrolide such as azithromycin
Rifabutin	Rifabutin	CYP3A4 induction by rifabutin CYP3A4 inhibition	Clarithromycin AUC ↓ 44% and C_{max} ↓ 41% Rifabutin C_{max} ↑ 69%	Monitor effectiveness of clarithromycin Monitor for rifabutin toxicity
	All PIs + ritonavir	CYP3A4 inhibition by PIs and/or ritonavir	Rifabutin AUC ↑ 400% vs rifabutin 300 mg/day alone in healthy, HIV-negative volunteers	Decrease rifabutin dosage to 150 mg every other day
		Possible CYP3A4 induction by ritonavir or decreased absorption in HIV-positive patients	Subtherapeutic rifabutin peak concentrations were observed in HIV-positive patients receiving lopinavir-ritonavir + rifabutin 150 mg 3 times/wk	As of December 2009, rifabutin peak concentration should be monitored when given in combination with a ritonavir-boosted PI
	Nevirapine	Possible competitive CYP3A4 metabolism with rifabutin, but mechanism not yet established	Rifabutin AUC ↑ 17%	No dosage adjustments recommended
		CYP3A4 induction by rifabutin	Nevirapine C_{min} ↓ 16%	No dosage adjustments recommended
	Efavirenz	CYP3A4 induction by efavirenz	Rifabutin C_{min} ↓ 35%	Increase dosage of rifabutin to 450–600 mg/day
	Etravirine	CYP3A4 induction by etravirine CYP3A4 induction by rifabutin	Rifabutin AUC ↓ 17% Etravirine AUC ↓ 37% ^a	Dosage of rifabutin 300 mg/day is recommended

CYP = cytochrome P450; AUC = area under the concentration-time curve; PIs = protease inhibitors; Cl_{cr} = creatinine clearance; NNRTIs = nonnucleoside reverse transcriptase inhibitors; C_{max} = peak concentration; C_{min} = minimum concentration.

^aWhen etravirine is combined with a ritonavir-boosted PI, rifabutin should not be coadministered due to the risk of decreased etravirine concentration and increased risk of rifabutin toxicity secondary to CYP3A4 inhibition by PIs and ritonavir.

Adapted from reference 15.

patient's clarithromycin trough concentration 30 hours after dosing was 1.0 µg/ml, warranting no changes in the clarithromycin dosage. A true trough at 24 hours after dosing was not obtained due to conflicts between the patient's dosing schedule and the clinic's operating hours. The patient's next dose was withheld to accommodate the scheduled visit for clarithromycin concentration measurement.

Over the next 3 months, the patient continued to receive the same antimycobacterial and antiretroviral regimens without experiencing any

adverse effects, and an initial anti-HIV therapeutic response was noted (Table 1). Subsequent blood cultures, obtained 55 days after starting MAC therapy, were negative for mycobacterial growth after 8 weeks of incubation. Given the conflicting data regarding the drug interaction between ritonavir-boosted protease inhibitors and rifabutin, and considering the findings of the 2009 pharmacokinetic evaluation in patients receiving rifabutin and lopinavir-ritonavir¹⁴ along with the release of the updated DHHS guidelines (December 2009),¹⁵ a rifabutin plasma peak

concentration was assessed. On day 126, 95 days after starting combination therapy with antiretroviral therapy (with the dosage of rifabutin at 150 mg every other day), a rifabutin peak concentration was assessed 3 hours after dosing. The results showed a rifabutin concentration of 0.08 µg/ml (goal peak concentration > 0.45 µg/ml). Adherence to both antibiotic therapy and antiretroviral therapy was verified through pill counts and patient self-report.

In response to the patient's suboptimal rifabutin peak concentration, the rifabutin dosage was increased to 300 mg every other day on day 109 of antiretroviral therapy (day 140 of MAC therapy). A new steady-state concentration was established after this dose increase over the next 14 days, and a rifabutin peak concentration was reassessed on day 154 of MAC therapy. Two hours after dosing, the plasma rifabutin and desacetyl-rifabutin concentrations increased to 0.43 µg/ml and 0.37 µg/ml, respectively. Because of this dose increase in rifabutin, a known CYP3A4 inducer, a repeat clarithromycin trough concentration was also measured on day 154 of MAC therapy to ensure that a therapeutic concentration of the macrolide was maintained. The clarithromycin trough concentration measured 24 hours after dosing was 2.7 µg/ml. Again, no change in the clarithromycin dosage was required. The patient continued to deny any adverse effects related to therapy and maintained a virologic response with the increased dose of rifabutin.

Discussion

The pharmacokinetic interactions between antimycobacterial and antiretroviral agents are not fully known because data are relatively scant. Data concerning ritonavir-boosted atazanavir and rifabutin have mainly been obtained in HIV-seronegative volunteers.¹¹ To our knowledge, this is the first case report describing the successful use of therapeutic drug monitoring to adjust the rifabutin dosage in an HIV-infected patient treated for disseminated MAC while taking an atazanavir-ritonavir-containing regimen. Our findings have several important implications.

First, our case report agrees with recent findings suggesting that a rifabutin dosage of 150 mg 3 times/week may produce suboptimal rifabutin concentrations in patients receiving ritonavir-boosted protease inhibitors.^{14, 15} In the pharmacokinetic study discussed earlier,¹⁴ the authors conducted an analysis of 10 HIV-positive

patients receiving rifabutin as part of a four-drug regimen for the treatment of active *Mycobacterium tuberculosis* infection. Patients initially received rifabutin 300 mg 3 times/week. Two to four weeks after starting antimycobacterial therapy, the dosage of rifabutin was decreased to 150 mg 3 times/week, and an antiretroviral regimen that included lopinavir 400 mg–ritonavir 100 mg twice/day was started. The maximum plasma concentration (C_{max}) of rifabutin and desacetyl-rifabutin were measured before and 1–2 weeks after starting lopinavir-ritonavir. The authors found that 8 of the 10 patients did not reach optimal rifabutin peak plasma concentrations (> 0.3 µg/ml). These results conflict with the elevated rifabutin peak plasma concentrations reported in studies involving HIV-negative volunteers receiving ritonavir-boosted protease inhibitors.^{11–13}

Second, our findings and those of a previous pharmacokinetic study¹⁴ are concerning given the pharmacokinetic parameters required to effectively target MAC. The rifabutin minimum inhibitory concentration (MIC) for MAC is typically less than 2 µg/ml; however, this represents a much higher MIC than that of *Mycobacterium tuberculosis*, which is typically sensitive at a rifabutin concentration of 0.06 µg/ml.¹⁷ Previous studies have documented that rifabutin, when used in combination with a macrolide and ethambutol, is not associated with improved clearance of MAC from blood cultures; rather, its use may prevent the development of resistance to macrolides.^{5, 6} The Tuberculosis Trials Consortium documented an increase in the development of rifabutin resistance and relapse of *Mycobacterium tuberculosis* when peak concentrations of rifabutin were less than 0.45 µg/ml.¹⁸ We are not aware of any data that support the development of similar resistance patterns to MAC relative to plasma rifabutin concentrations, nor could we assess this pharmacodynamic parameter because the patient had sterile blood cultures on day 55 of MAC treatment. However, this is a real concern given the higher rifabutin MIC for MAC compared with *Mycobacterium tuberculosis*. In addition, given the variable pharmacokinetic interactions documented between rifabutin and protease inhibitors, and the prolonged treatment duration required, it is important to ensure that the rifabutin concentration is within an acceptable range from a safety perspective.

Finally, our findings are also distinctive in that we documented suboptimal plasma rifabutin

concentrations despite concomitant administration of two known CYP inhibitors, clarithromycin and ritonavir. Previous studies have demonstrated contrary findings—significant increases in rifabutin plasma concentrations—when rifabutin was coadministered with ritonavir or clarithromycin.^{19,20} The mechanisms by which suboptimal rifabutin concentrations may occur in HIV-positive patients taking concomitant ritonavir-boosted atazanavir remain to be well described. Although ritonavir typically inhibits metabolism through CYP isoenzymes, it may also induce metabolism of various CYP substrates. In one study, 12 healthy volunteers received ritonavir 400 mg twice/day in combination with warfarin 5 mg/day. Overall, these patients experienced a 33% decrease in the area under the curve of the R-warfarin isomer, whereas no significant changes in S-warfarin pharmacokinetics were observed.²¹ R-warfarin undergoes metabolism through CYP1A1, CYP1A2, and CYP3A4, whereas S-warfarin is metabolized through CYP2C9, indicating induction of select isoenzymes.²² This effect may persist when ritonavir is used to boost atazanavir concentrations. Atazanavir is a CYP3A inhibitor when given without ritonavir; however, when given in combination with ritonavir, variable effects on other CYP isoenzymes have been observed.²³ In studies involving coadministration of ethinyl estradiol with atazanavir plus ritonavir, decreases in ethinyl estradiol concentrations have been observed, indicating possible induction of CYP3A isoenzymes by atazanavir plus ritonavir.²³ Rifabutin is metabolized extensively by CYP3A4.¹⁰ The activity of ritonavir as a dual inhibitor and inducer of CYP isoenzymes may explain decreases in rifabutin concentrations observed in patients treated with lopinavir-ritonavir and atazanavir plus ritonavir.

Suboptimal rifabutin peak concentrations may also be caused by altered absorption in patients with HIV. In a study comparing drug absorption of various antimycobacterials in healthy patients versus patients with different stages of HIV disease, a trend toward decreased drug absorption was observed as the severity of HIV disease progressed.²⁴ Moreover, single-dose studies showed that healthy volunteers receiving rifabutin 300 mg attained a mean maximum rifabutin concentration of 0.375 µg/ml, whereas HIV-positive patients averaged a 20% decrease in oral bioavailability.¹⁰ It is important to make this distinction between healthy volunteers and HIV-infected patients since the initial drug-drug

interaction studies that led to the recommendation of using a reduced rifabutin dose in patients receiving concomitant protease inhibitors were conducted in healthy volunteers. Healthy volunteers may absorb rifabutin more efficiently than HIV-positive patients, which may explain the conservative dosage recommendations for rifabutin when given with ritonavir-boosted protease inhibitors. The above comparisons describe the mean results observed in larger populations. In these comparative studies, it is typical to see variable results that fall both above and below the mean. Therefore, our results from a single patient with suboptimal rifabutin concentrations could be interpreted as a general deviation from the expected mean rifabutin concentration, and not a true drug-drug interaction.

Regardless of the mechanism, we were able to effectively adjust the rifabutin dosage in our patient to achieve the recommended concentration of rifabutin while continuing atazanavir plus ritonavir. The concentrations of atazanavir and clarithromycin remained greater than 0.15 µg/ml and 0.7 µg/ml, respectively, even in the setting of possible induction by rifabutin. This case report supports the current DHHS treatment guideline recommendations to monitor rifabutin concentrations in patients receiving concomitant therapy with ritonavir-boosted protease inhibitors. Since the half-life of rifabutin is 49 hours, we recommend assessing the rifabutin peak concentration 10–14 days after starting rifabutin to reflect steady-state conditions. As rifabutin achieves maximum concentrations at 3 hours, we recommend assessing rifabutin peak concentration at 2–3 hours after dosing.¹⁰ If further dosage adjustments are required for rifabutin or other CYP inducers or inhibitors, we recommend reassessing the rifabutin peak concentration 10–14 days after the addition of those drugs or a rifabutin dosage change. The current literature does not provide concrete recommendations on increasing the rifabutin dosage for a rifabutin concentration less than 0.45 µg/ml. We followed the recommendations of a 2009 pharmacokinetic evaluation¹⁴ and achieved the desired concentrations of rifabutin by increasing the rifabutin dosage from 150 mg every other day to 300 mg every other day. Future studies of these drug interactions in patients with HIV may yield a better understanding of the pharmacokinetic interactions relative to metabolic induction, inhibition, and absorption in this complex population.

Conclusion

We report suboptimal concentrations of rifabutin when given concomitantly with atazanavir plus ritonavir at the currently recommended dosage of rifabutin 150 mg every other day. These findings are in agreement with similar observations when rifabutin was coadministered with another ritonavir-boosted protease inhibitor, lopinavir. The changes in drug concentrations in our patient are likely explained by induction and inhibition effects of ritonavir on CYP isoenzymes, although suboptimal absorption of rifabutin in HIV-positive patients cannot be excluded. Further studies should be conducted in HIV-infected patients since previous pharmacokinetic studies have been conducted in otherwise healthy patients. Until more data become available, therapeutic drug monitoring remains a crucial tool to ensure adequate therapy when antimycobacterial and antiretroviral agents are coadministered. Clinicians should use caution when increasing the dosage of rifabutin in this patient population given the limited evidence supporting such dosage increases; however, a rifabutin dosage of 300 mg every other day appears to be both safe and effective based on the findings in our patient as well as those of previous studies.

References

- Center for Disease Control and Prevention. HIV prevalence estimates—United States, 2006. *MMWR Morb Mortal Wkly Rep* 2008;57(39):1073–6.
- Massachusetts Department of Public Health Bureau of Infectious Disease Office of HIV/AIDS. Concurrent dilemmas: lateness to HIV/AIDS care as a challenge, December 1, 2009. Available from http://www.mass.gov/Eeohhs2/docs/dph/aids/lateness_to_care.pdf. Accessed July 2, 2010.
- Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. *MMWR Morb Mortal Wkly Rep* 2009;58(4):1–203.
- National Institutes of Health, Department of Health and Human Services, Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, November 3, 2009. Available from <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed November 30, 2009.
- Benson CA, Williams PL, Currier JS, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated *Mycobacterium avium* complex disease in persons with acquired immunodeficiency syndrome. *Clin Infect Dis* 2003;37:1234–43.
- Gordin FM, Sullam PM, Shafran SD, et al. A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with *Mycobacterium avium* complex (MAC). *Clin Infect Dis* 1999;28:1080–5.
- Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for *Mycobacterium avium* complex bacteremia in patients with human immunodeficiency virus infection. *Clin Infect Dis* 1998;27(5):1278–85.
- Abbott Laboratories. Biaxin filmtab (clarithromycin) package insert. North Chicago, IL; 2009.
- Pfizer Inc. Zithromax (azithromycin) package insert. New York, NY; 2009.
- Pfizer Inc. Mycobutin (rifabutin) package insert. New York, NY; 2007.
- Agarwala S, Mummaneni V, Randall D, Gerald M, Stoltz R, O'Mara E. Pharmacokinetic effect of rifabutin on atazanavir with and without ritonavir in healthy subjects [abstract 445-W]. Presented at the 9th conference on retroviruses and opportunistic infections, Seattle, WA, February 24–28, 2002.
- Sekar VJ, Lavreys L, de Paepe E, et al. Pharmacokinetic interaction between darunavir in combination with low-dose ritonavir and rifabutin [abstract H-4053]. Presented at the 48th interscience conference on antimicrobial agents and chemotherapy, Washington, DC, October 25–28, 2008.
- Ng J, Nada A, Freeman S, et al. Pharmacokinetics of rifabutin 150 mg tid plus lopinavir/ritonavir 400/100 mg bid administered in healthy adult subjects [abstract O21]. Presented at the 10th international workshop on clinical pharmacology of HIV therapy, Amsterdam, Netherlands, April 15–17, 2009.
- Boulanger C, Hollender E, Farrell K, et al. Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. *Clin Infect Dis* 2009;49(9):1305–11.
- National Institutes of Health, Department of Health and Human Services, Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, December 1, 2009. Available from <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed June 6, 2010.
- Barradell LB, Plosker GL, McTavish D. Clarithromycin. A review of its pharmacological properties and therapeutic use in *Mycobacterium avium-intracellulare* complex infection in patients with acquired immune deficiency syndrome. *Drugs* 1993;46(2):289–312.
- Kiehn TE, Edwards FF, Brannon P, et al. Infections caused by *Mycobacterium avium* complex in immunocompromised patients: diagnosis by blood culture and fecal examination, antimicrobial susceptibility tests, and morphological and seroagglutination characteristics. *J Clin Microbiol* 1985;21:168–73.
- Weiner M, Benator D, Burman W, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. *Clin Infect Dis* 2005;40(10):1481–91.
- Hafner R, Bethel J, Power M, et al. Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob Agents Chemother* 1998;42(3):631–9.
- Cato A III, Cavanaugh J, Shi H, et al. The effect of multiple doses of ritonavir on the pharmacokinetics of rifabutin. *Clin Pharmacol Ther* 1998;63:414–21.
- Abbott Laboratories. Norvir (ritonavir) package insert. Princeton, NJ; 2010.
- Daly AK, Aithal GP. Genetic regulation of warfarin metabolism and response. *Semin Vasc Med* 2003;3:231–8.
- Bristol Myers Squibb Company. Reyataz (atazanavir) package insert. Princeton, NJ; 2003.
- Sahai J, Gallicano K, Swick L, et al. Reduced plasma concentrations of antituberculosis drugs in patients with HIV infection. *Ann Intern Med* 1997;127(4):289–93.