

Tolerance and Pharmacokinetic Interactions of Rifabutin and Azithromycin

RICHARD HAFNER,^{1*} JAMES BETHEL,² HAROLD C. STANDIFORD,³ STEPHEN FOLLANSBEE,⁴
DAVID L. COHN,⁵ RONALD E. POLK,⁶ LARRY MOLE,⁷ RALPH RAASCH,⁸ PRINCY KUMAR,⁹
DAVID MUSHATT,¹⁰ AND GEORGE DRUSANO¹¹ FOR THE DATRI 001B STUDY GROUP†

Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda,¹ Westat, Rockville,² and University of Maryland School of Medicine, Institute of Human Virology, and the Veterans Administration Medical Center, Baltimore,³ Maryland; Davies Medical Center, San Francisco, California⁴; Denver Public Health and University of Colorado Health Sciences Center, Denver, Colorado⁵; Virginia Commonwealth University/Medical College of Virginia Campus, Richmond, Virginia⁶; AIDS Research Center, Veterans Administration Palo Alto Health Care System, Palo Alto, California⁷; University of North Carolina at Chapel Hill, North Carolina⁸; Georgetown University, Washington, D.C.⁹; Tulane University School of Medicine, New Orleans, Louisiana¹⁰; and Albany Medical College, Albany, New York¹¹

Received 17 April 2000/Returned for modification 8 October 2000/Accepted 8 February 2001

This multicenter study evaluated the tolerance and potential pharmacokinetic interactions between azithromycin and rifabutin in volunteers with or without human immunodeficiency virus infection. Daily dosing with the combination of azithromycin and rifabutin was poorly tolerated, primarily because of gastrointestinal symptoms and neutropenia. No significant pharmacokinetic interactions were found between these drugs.

Mycobacterium avium complex (MAC) disease causes significant morbidity and mortality in patients with late-stage human immunodeficiency virus (HIV) infection (2, 4, 9). Azithromycin (8, 13) and rifabutin (12) are used alone for the prevention of disseminated MAC (DMAC) infection and in combinations for treatment of DMAC (10, 17). Currently recommended doses for use in combination treatment of DMAC are azithromycin at 500 mg daily and rifabutin at 300 mg daily (18). Rifabutin is an inducer of hepatic microsomal cytochrome P-450 enzymes and is known to have significant pharmacokinetic interactions with several therapeutic agents, including clarithromycin (7, 16). Pharmacokinetic interactions between these two drugs could have important implications for the safety and effectiveness of DMAC therapy. The current study was designed to evaluate the tolerance of combination therapy with azithromycin and rifabutin and the potential pharmacokinetic interactions.

All subjects were at least 18 years old and provided written informed consent before enrollment according to the institutional requirements of the participating centers. Subjects were ineligible if they had significant renal or hepatic impairment or were receiving drugs likely to have pharmacokinetic interactions with the study drugs. Drugs likely to interact with the

study agents were to be avoided during the study, if possible. The study initially evaluated high-dose regimens (azithromycin at 1,200 mg daily and rifabutin at 600 mg daily) and enrolled only HIV-infected persons. However, because of a high rate of intolerance and slow enrollment, the protocol was modified to evaluate low-dose regimens (azithromycin at 600 mg daily and rifabutin at 300 mg daily) and to allow the enrollment of HIV-seronegative volunteers to increase the accrual rate. Subjects were initially randomized equally to one of two high-dose regimens (A or B) and later to one of two low-dose regimens (C or D). Regimen A and C subjects received azithromycin on days 1 to 14 and the combination of azithromycin and rifabutin on days 15 to 42. Regimen B and D subjects received rifabutin on days 1 to 14 and the combination of rifabutin and azithromycin on days 15 to 42. Subjects were instructed to take azithromycin 1 h before or 2 h after a meal (alone or in combination) and to take both drugs at the same time. All HIV-infected patients had CD4⁺ cell counts of <200 cells/mm³ and were receiving stable antiretroviral therapy. Clinical evaluations and hematologic and biochemical profiles were repeated every 2 weeks through day 56. Subjects experiencing a possible drug-related adverse event greater than or equal to grade 3, as defined by the Division of AIDS Table for Grading Severity of Adult Adverse Experiences, permanently discontinued the study drug, as did subjects who developed lower-grade adverse events, at the investigator's discretion or the subject's request. Only data for subjects who completed the study evaluations have been included in the pharmacokinetic analyses.

Pharmacokinetic sampling was performed on days 14, 15, and 42. Subjects fasted for 12 h before and 2 h after study drug administration. Samples for pharmacokinetic analysis were obtained predose and at 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 16, and 24 h (also at 1.5, but not 0.75, h when receiving rifabutin only) after dosing and also at 36, 48, 72, and 96 h on days 42 to 46. All

* Corresponding author. Mailing address: Division of AIDS, NIAID, 6700-B Rockledge Dr.—MSC 7624, Bethesda, MD 20892-7624. Phone: (301) 402-2304. Fax: (301) 402-3171. E-mail: RHafner@niaid.nih.gov.

† The DATRI 001B Study Group also includes Maureen Power and Karen Oseekey (DAIDS, NIAID, Bethesda, Md.); Stephanie LaCaruba (Davies Medical Center, San Francisco, Calif.); Beverly Barber (Denver Public Health, Denver, Colo.); Mark Holodniy (Veterans Administration Medical Center, Palo Alto, Calif.); Charles van der Horst (University of North Carolina, Chapel Hill, N.C.); Mary Banach, Marcia Scott, and Suzanne Beckner (Westat, Rockville, Md.); Bernard Landry, Theresa Straut, and Mary Enama (Social & Scientific Systems, Rockville, Md.); and John Pelosi (McKesson, Rockville, Md.).

TABLE 1. Baseline characteristics of subjects assigned to receive the high- and low-dose regimens

Characteristic	High dose		Low dose	
	Enrolled (n = 19) ^a	Completed (n = 9)	Enrolled (n = 31) ^b	Completed (n = 17) ^c
Sex (n)				
Male	19	9	19	13
Female	0	0	12	4
Race (n)				
White	17	7	28	15
Black	1	1	1	1
Other	1	1	2	1
Mean age, yr (SD)	38.7 (10.6)	38.7 (12.4)	36.4 (11.7)	35.1 (13.6)
Mean wt, kg (SD)	70.0 (10.3)	69.9 (7.7)	73.4 (15.6)	77.3 (15.6)
Mean ANC, ^d cells/mm ³ (SD)	1,854 (578)	2,088 (467)	3,775 (1,518)	3,389 (1,629)

^a All subjects were HIV seropositive.

^b Six subjects were HIV seropositive.

^c Five subjects were HIV seropositive.

^d ANC, absolute neutrophil count.

plasma concentrations were determined using validated high-performance liquid chromatography techniques (11, 15) by Pfizer Central Research for azithromycin (between-day standard deviations were <4%; linear range, 10 to 2,000 ng/ml) and Harris Laboratories for rifabutin and 25-*O*-desacetyl-rifabutin (between-day coefficients of variation were ≤10% for both and linear ranges were 5 to 500 and 2.5 to 250 ng/ml, respectively). Values exceeding the linear range were diluted and reassayed with validation for lack of dilution effect by inclusion of appropriate standards.

Based on coefficients of variation provided by the drug manufacturers, a sample size of 14 evaluable subjects receiving each regimen was projected to provide 85% power ($\alpha = 0.05$) for detecting a ≥50% change in the area under the plasma concentration-time curve from time zero to 24 h (AUC_{0-24}). LAGRAN software was used to compute AUC_{0-24} at steady state (14). Maximum drug concentration (C_{max}) and time to C_{max} (T_{max}) were determined by inspecting interpolated curves. For drugs introduced on day 15, $AUC_{0-\infty}$ (AUC from time zero to infinity) was calculated as $AUC_{0-C_n} + C_n/\lambda_z$, where C_n is the concentration at the last measurable time point. The terminal elimination rate constant, λ_z , was determined by fitting a log linear regression to the last four time points of the terminal phase, but in cases of a delayed T_{max} , three points were used. The means of the percent changes in pharmacokinetic parameters for each subject in each arm were compared using two-sample *t* tests.

Subjects were enrolled at seven study sites between March 1993 and October 1994. The baseline characteristics of subjects randomized to the high- and low-dose regimens are shown in Table 1. No significant differences in baseline characteristics were found between the pairs of randomization groups receiving either the high- or low-dose regimens (all *P* values of >0.20). Of the 19 subjects (all HIV seropositive) in the high-dose regimen, 9 completed the study evaluations. Four subjects experienced adverse events requiring study drug termination, five discontinued therapy for lower grade adverse events, and one developed *Pneumocystis carinii* pneumonia. Of 31 subjects

including the low-dose regimen, 17 (receiving 5 of the 6 HIV-positive subjects) completed the study evaluations. One subject never returned after the first visit, eight developed adverse events requiring treatment termination, and five discontinued study drugs for less-serious adverse events. Seven subjects, all receiving the high-dose regimens, received antifungal azoles at some time during the study, but only three of these subjects completed the pharmacokinetic evaluations.

The most frequent adverse events occurring in the high-dose and low-dose groups are listed in Table 2. All subjects prematurely discontinuing the study drug did so during combination therapy, except for one who developed grade 3 neutropenia while receiving high-dose rifabutin alone. Neutropenia (absolute count, <1,500 cells/mm³) was the most frequently reported adverse event, occurring among 33 of 50 subjects (66%). These episodes included seven grade 3 (500 to 750 cells/mm³) and one grade 4 (<500 cells/mm³) neutropenia

TABLE 2. Number of subjects (n) experiencing the most frequent adverse events

Adverse event	High-dose regimens ^a (n = 19)		Low-dose regimens ^b (n = 31)	
	Grade 1 or 2 ^c (n [%])	Grade 3 or 4 ^c (n [%])	Grade 1 or 2 ^c (n [%])	Grade 3 or 4 ^c (n [%])
Neutropenia	9 (47)	5 (26)	16 (55)	3 (10)
Nausea	15 (79)	0 (0)	17 (59)	1 (3)
Diarrhea	13 (68)	0 (0)	13 (45)	0 (0)
Fever	4 (21)	0 (0)	7 (24)	2 (7)
Fatigue	13 (68)	1 (5)	18 (62)	2 (7)
Headache	12 (63)	1 (5)	15 (52)	2 (7)
Peripheral neuropathy	6 (32)	0 (0)	3 (10)	0 (0)
Allergic reaction	5 (26)	0 (0)	5 (17)	0 (0)
Myalgia	1 (5)	0 (0)	6 (21)	3 (10)
Skin rash	5 (26)	0 (0)	6 (21)	1 (3)

^a Azithromycin at 1,200 mg daily and rifabutin at 600 mg daily.

^b Azithromycin at 600 mg daily and rifabutin at 300 mg daily.

^c General toxicity grade definitions: grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life-threatening.

TABLE 3. Pharmacokinetic parameters of azithromycin, rifabutin, and 25-*O*-desacetyl-rifabutin for subjects completing regimens A, B, C, and D^a

Regimen and drug	Mean AUC ₀₋₂₄ (μg · h/ml) ± SD		Mean C _{max} (μg/ml) ± SD		Mean % change in AUC ₀₋₂₄ from days 14 to 42 (P)		Mean T _{max} (h) ± SD		Mean % change in T _{max} from days 14 to 42 (P)				
	Day 14	Day 15	Day 14	Day 15	Day 14	Day 15	Day 14	Day 15	Day 14	Day 15			
High-dose regimen A (n = 4)													
Azithromycin	10.6 ± 2.6	14.3 ± 5.1	11.1 ± 5.6	1.5 ± 0.3	1.2 ± 0.6	1.5 ± 0.3	1.1 ± 0.3	1.98 ± 0.98	2.79 ± 0.98	2 ± 29 (0.91)	1.98 ± 0.05	3.07 ± 0.83	13 ± 27 (0.39)
Rifabutin		7.1 ± 4.2 ^b	6.2 ± 3.7	0.8 ± 0.4		0.8 ± 0.4	0.6 ± 0.2				4.18 ± 3.05	3.07 ± 1.14	
25- <i>O</i> -desacetyl-rifabutin		1.2 ± 1.1 ^b	0.7 ± 0.5	0.1 ± 0.1		0.1 ± 0.1	0.07 ± 0.04				4.71 ± 3.17	3.59 ± 1.92	
High-dose regimen B (n = 5)													
Azithromycin		7.1 ± 1.6 ^b	13.4 ± 7.3	1.6 ± 0.3		1.6 ± 0.3	1.1 ± 0.7				1.62 ± 1.14	4.17 ± 4.32	
Rifabutin	5.9 ± 3.2	7.2 ± 2.8	8.3 ± 6.1	0.8 ± 0.3	0.5 ± 0.3	0.8 ± 0.3	0.7 ± 0.6	4.65 ± 4.54	4.82 ± 4.97	176 ± 297 (0.26)	2.71 ± 1.19	3.97 ± 4.73	27 ± 165 (0.73)
25- <i>O</i> -desacetyl-rifabutin	0.9 ± 1.0	0.9 ± 0.7	1.3 ± 1.4	0.1 ± 0.07	0.07 ± 0.07	0.1 ± 0.07	0.09 ± 0.09	4.82 ± 4.97	4.82 ± 4.97	338 ± 699 (0.40)	2.39 ± 1.06	4.59 ± 5.22	53 ± 179 (0.59)
Low-dose regimen C (n = 9)													
Azithromycin	6.6 ± 2.1	8.1 ± 2.5	8.0 ± 3.3	1.0 ± 0.5	0.7 ± 0.2	1.0 ± 0.5	0.8 ± 0.3	2.9 ± 1.5	2.9 ± 1.5	25 ± 61 (0.24)	2.4 ± 1.6	2.7 ± 1.5	-2 ± 41 (0.87)
Rifabutin		3.0 ± 0.9 ^b	2.7 ± 1.4	0.4 ± 0.1		0.4 ± 0.1	0.3 ± 0.1				3.4 ± 1.7	2.6 ± 1.3	
25- <i>O</i> -desacetyl-rifabutin		0.5 ± 0.3 ^b	0.3 ± 0.2	0.05 ± 0.02		0.05 ± 0.02	0.03 ± 0.02				4.0 ± 3.1	2.7 ± 1.3	
Low-dose regimen D (n = 8)													
Azithromycin		3.6 ± 1.1 ^b	7.6 ± 3.1	0.7 ± 0.2		0.7 ± 0.2	0.9 ± 0.5				1.9 ± 0.8	1.6 ± 0.5	
Rifabutin	3.4 ± 2.0	3.9 ± 1.7	3.1 ± 1.8	0.5 ± 0.2	0.4 ± 0.2	0.5 ± 0.2	0.3 ± 0.1	2.5 ± 1.0	2.5 ± 1.0	5 ± 62 (0.83)	1.8 ± 0.6	2.7 ± 1.6	11 ± 48 (0.56)
25- <i>O</i> -desacetyl-rifabutin ^c	0.3 ± 0.3	0.3 ± 0.2	0.3 ± 0.3	0.03 ± 0.02	0.03 ± 0.02	0.04 ± 0.02	0.03 ± 0.01	2.6 ± 0.9	2.6 ± 0.9	14 ± 48 (0.47)	2.2 ± 0.6	2.9 ± 1.6	6 ± 37 (0.69)

^a Regimen A = azithromycin at 1,200 mg daily (days 1 to 14), followed by azithromycin with rifabutin at 600 mg daily (days 15 to 42); regimen B = rifabutin at 600 mg daily (days 1 to 14), followed by rifabutin with azithromycin at 1,200 mg daily (days 15 to 42); regimen C = azithromycin at 600 mg daily (days 1 to 14), followed by rifabutin with azithromycin at 600 mg daily (days 15 to 42); regimen D = rifabutin at 300 mg daily (days 1 to 14), followed by rifabutin with rifabutin at 300 mg daily (days 15 to 42).

^b AUC reported represents AUC₀₋₂₄.

^c n = 7 for 25-*O*-desacetyl-rifabutin.

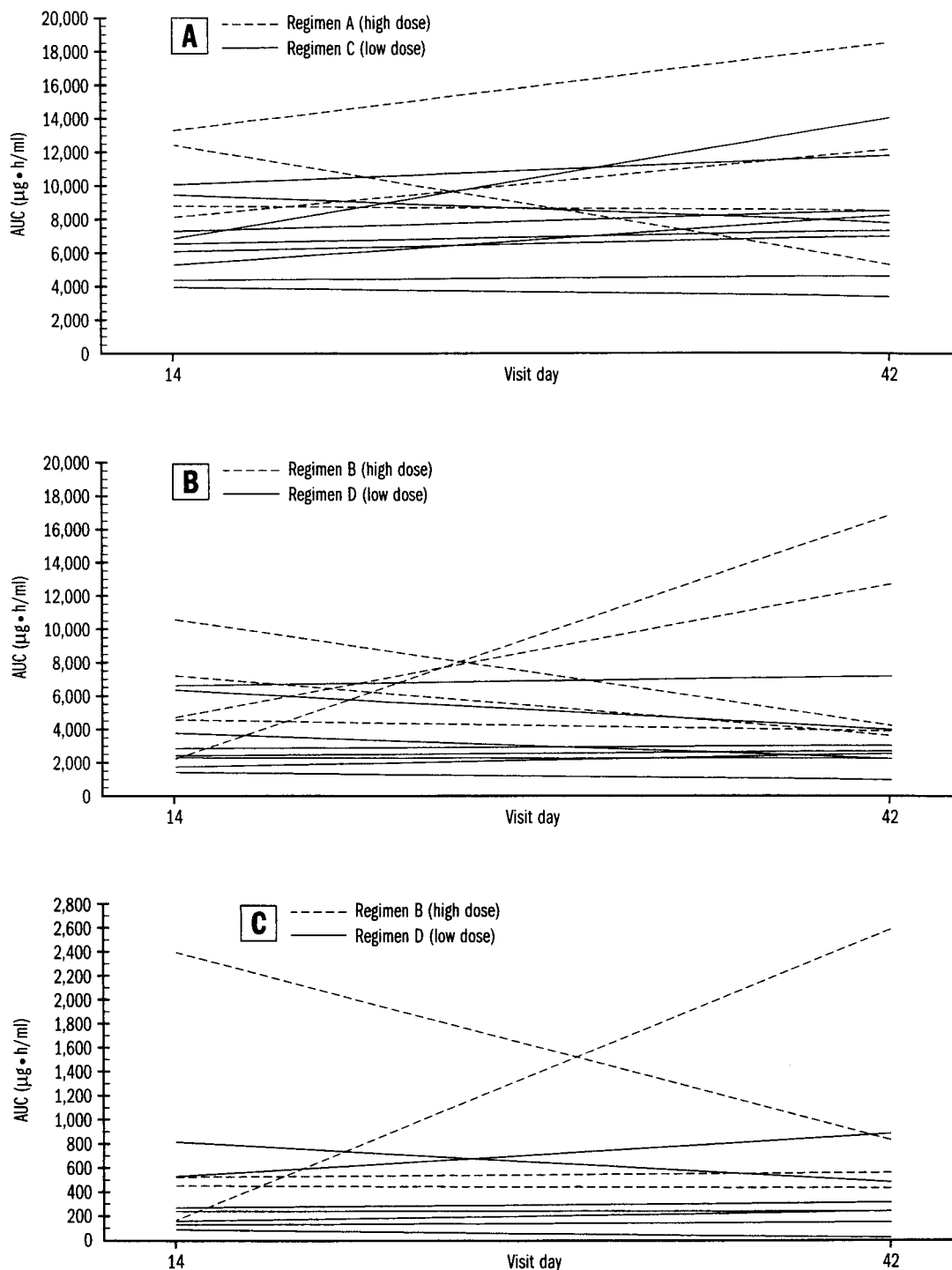


FIG. 1. Changes in the AUC₀₋₂₄ of azithromycin (A), rifabutin (B), and 25-O-desethyl-rifabutin (C) for individual subjects between days 14 and 42.

events. In the low-dose groups, eight subjects had decreases of $>1,000$ cells/ mm^3 (four of these had decreases of $>2,000$ cells/ mm^3), and significant mean decreases in neutrophils occurred during the initial 14 days of monotherapy with either azithromycin (989 cells/ mm^3 , $P = 0.02$) or rifabutin (1,389 cells/ mm^3 , $P < 0.01$). Low-grade nausea, diarrhea, fatigue, and headache

were also common, and most subjects had more than one type of event. The type and frequency of adverse events were similar in the high- and low-dose regimens and in HIV-positive and -negative subjects and occurred primarily during the combination phase. There were no statistically significant differences in the baseline characteristics of subjects who completed

the study compared to those who did not complete the study within the high- and low-dose groups.

Large reversible decreases in leukocyte counts have been observed in non-HIV-infected patients with pulmonary MAC disease treated with combinations including rifabutin (6). Apseloff et al. (1) observed severe neutropenia (<1,000 cells/mm³) in 9 of 18 healthy volunteers receiving 300 mg daily of rifabutin alone (1 of 6) or in combination with azithromycin at 250 mg daily (4 of 6) or clarithromycin at 500 mg twice daily (4 of 6) after 10 to 14 days. Significant decreases in neutrophils occurred during the 14 days of monotherapy with either rifabutin or azithromycin among both HIV-seropositive and -seronegative subjects in the current study. While neutropenia is a known side effect of rifabutin, the large decreases in neutrophils associated with azithromycin monotherapy in this study have not been previously reported. The magnitude of neutrophil decline after 14 days of azithromycin or rifabutin monotherapy was not statistically associated with measurements of systemic exposure for either study drug.

The mean AUC₀₋₂₄, C_{max}, and T_{max} values for azithromycin, rifabutin, and 25-*O*-desacetyl-rifabutin on study days 14, 15, and 42 are presented in Table 3. None of the mean percent changes in the pharmacokinetic parameters for azithromycin, rifabutin, or 25-*O*-desacetyl rifabutin occurring between days 14 and 42 were significant (all *P* values were ≥0.13). For low-dose regimen C, the mean percent change in azithromycin AUC₀₋₂₄ between days 14 and 42 was +21% (*P* = 0.13), and none of the nine individual azithromycin AUC₀₋₂₄ estimates decreased by >25% between days 14 and 42 (Fig. 1). For regimen D, the mean percent change in rifabutin AUC₀₋₂₄ between days 14 and 42 (-5%) was not significant, and only one of the eight individual rifabutin AUC₀₋₂₄ estimates increased by >25% (45%) between days 14 and 42. The mean percent change in the AUC₀₋₂₄ values of 25-*O*-desacetyl-rifabutin observed between days 14 and 42 was also not significant. Among the mean percent changes in pharmacokinetic parameters between days 14 and 42 for either the high- or low-dose regimens, only those for rifabutin and 25-*O*-desacetyl rifabutin in high-dose regimen B exceeded 25%. Since all the *P* values for these changes were >0.20, these differences most likely reflected the wide variation in individual values among the small sample (*n* = 5).

The observed pharmacokinetic parameters are consistent with those reported in previous studies of rifabutin (7, 16) and azithromycin (5). The current pharmacokinetic analysis indicates that neither rifabutin nor azithromycin had a significant effect on the steady-state levels of the other drug. The data for the low-dose regimens strongly support the absence of any clinically relevant pharmacokinetic interactions between these drugs at the highest dosages currently used in clinical practice. Based on the actual number of evaluable subjects and observed standard deviations in the low-dose groups, mean changes of ≥35% in azithromycin AUC₀₋₂₄ and ≥29% in rifabutin AUC₀₋₂₄ could be detected with 80% power. However, the possibility of selection bias caused by the high rate of intolerance must be recognized. Subjects not completing day 42 study evaluations were not included in the pharmacokinetic analyses, and intolerance to the combination study regimens could have been related to pharmacokinetic interactions resulting in increased drug concentrations. These results indicating the ab-

sence of significant pharmacokinetic interactions between azithromycin and rifabutin are consistent with other reported findings. In a study of groups of six volunteers assigned to receive azithromycin at 250 mg daily, rifabutin at 300 mg daily, or both drugs for 14 days, the mean azithromycin and rifabutin concentrations in serum at day 10 did not differ significantly between the groups receiving one of these drugs alone and the group receiving the combination (1). However, pharmacokinetic analyses could not be completed. Also, among HIV-seronegative patients receiving azithromycin to treat mycobacterial lung disease, azithromycin concentrations in serum measured during monotherapy were apparently comparable to concentrations observed after the addition of rifabutin (3). In summary, neither azithromycin nor rifabutin appears to have a significant effect on the pharmacokinetics of the other. However, this combination should not be a first-choice option for treatment or prevention of MAC infections because of poor tolerance.

This study, designated DATRI 001B, was supported by the Division of AIDS Treatment Research Initiative (DATRI) Program, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md., contract no. NO1-AI-15123, and the Division of Acquisition Management, Program Support Center, HHS contract no. 282-97-0015, task order number 21.

Azithromycin was provided as 300-mg tablets by Pfizer, Inc. (New York, N.Y.), and rifabutin was provided as 150-mg capsules by Adria Laboratories (currently Pharmacia & Upjohn, Kalamazoo, Mich.). We thank volunteers who participated in this study, P. K. Narang (Pharmacia & Upjohn) and Michael Dunne (Pfizer Central Research) for helpful review and comments during the conduct and analysis of the study, and statistical programmer David Chang (Westat).

REFERENCES

1. Apseloff, G., G. Foulds, L. LaBoy-Goral, S. Willavize, and J. Vincent. 1998. Comparison of azithromycin and clarithromycin in their interactions with rifabutin in healthy volunteers. *J. Clin. Pharmacol.* **38**:830-835.
2. Benson, C. 1994. Disseminated *Mycobacterium avium* complex disease in patients with AIDS. *AIDS Res. Hum. Retrovir.* **10**:913-916.
3. Brown, B. A., D. E. Griffith, W. Girard, J. Levin, and R. J. Wallace, Jr. 1997. Relationship of adverse events to serum drug levels in patients receiving high-dose azithromycin for mycobacterial lung disease. *Clin. Infect. Dis.* **24**:958-964.
4. Chin, D. P., A. L. Reingold, E. N. Stone, E. Vittinghoff, C. R. Horsburgh, Jr., E. M. Simon, D. M. Yajko, W. K. Hadley, S. M. Ostroff, and P. C. Hopewell. 1994. The impact of *Mycobacterium avium* complex bacteremia and its treatment on survival of AIDS patients—a prospective study. *J. Infect. Dis.* **170**:578-584.
5. Foulds, G., R. M. Shepard, and R. B. Johnson. 1990. The pharmacokinetics of azithromycin in human serum and tissues. *J. Antimicrob. Chemother.* **25**(Suppl. A):73-82.
6. Griffith, D. E., B. A. Brown, and R. J. Wallace, Jr. 1996. Varying dosages of rifabutin affect white blood cell and platelet counts in human immunodeficiency virus-negative patients who are receiving multidrug regimens for pulmonary *Mycobacterium avium* complex disease. *Clin. Infect. Dis.* **23**:1321-1322.
7. Hafner, R., J. Bethel, M. Power, B. Landry, M. Banach, L. Mole, H. C. Standiford, S. Follansbee, P. Kumar, R. Raasch, D. Cohn, D. Mushatt, and G. Drusano. 1998. Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob. Agents Chemother.* **42**:631-639.
8. Havlir, D. V., M. P. Dube, F. R. Sattler, D. N. Forthal, C. A. Kemper, M. W. Dunne, D. M. Parenti, J. P. Lavelle, A. C. White, Jr., M. D. Witt, S. A. Bozzette, and J. A. McCutchan. 1996. Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. *N. Engl. J. Med.* **335**:392-398.
9. Horsburgh, C. R., Jr., J. A. Havlik, D. A. Ellis, E. Kennedy, S. A. Fann, R. E. Dubois, and S. E. Thompson. 1991. Survival of patients with acquired immune deficiency syndrome and disseminated *Mycobacterium avium* complex infection with and without antimycobacterial chemotherapy. *Am. Rev. Respir. Dis.* **144**:557-559.
10. Koletar, S. L., A. Berry, M. Cynamon, J. Jacobson, J. Currier, R. MacGregor, M. Dunne, and D. Williams. 1999. Azithromycin as treatment for

- disseminated *Mycobacterium avium* complex in AIDS patients. *Antimicrob. Agents Chemother.* **43**:2869–2872.
11. Lewis, R. C., N. Z. Hatfield, and P. K. Narang. 1991. A sensitive method for quantitation of rifabutin and its desacetyl metabolite in human biological fluids by high-performance liquid chromatography (HPLC). *Pharm. Res.* **8**:1434–1440.
 12. Nightingale, S. D., D. W. Cameron, F. M. Gordin, P. M. Sullam, D. L. Cohn, R. E. Chaisson, L. J. Eron, P. D. Sparti, B. Bihari, D. L. Kaufman, et al. 1993. Two controlled trials of rifabutin prophylaxis against *Mycobacterium avium* complex infection in AIDS. *N. Engl. J. Med.* **329**(12):828–833.
 13. Oldfield, E. C., III, W. J. Fessel, M. W. Dunne, G. Dickinson, M. R. Wallace, W. Byrne, R. Chung, K. F. Wagner, S. F. Paparello, D. B. Craig, G. Melcher, M. Zajdowicz, R. F. Williams, J. W. Kelly, M. Zelasky, L. B. Heifets, and J. D. Berman. 1998. Once weekly azithromycin therapy for prevention of *Mycobacterium avium* complex infection in patients with AIDS: a randomized, double-blind, placebo-controlled multicenter trial. *Clin. Infect. Dis.* **26**:611–619.
 14. Rocci, M. L., Jr., and W. J. Jusko. 1983. LAGRAN program for area and moments in pharmacokinetic analysis. *Comput. Programs Biomed.* **16**:203–216.
 15. Shepard, R. M., G. S. Duthu, R. A. Ferraina, and M. A. Mullins. 1991. High-performance liquid chromatographic assay with electrochemical detection for azithromycin in serum and tissues. *J. Chromatogr.* **565**:321–337.
 16. Skinner, M. H., M. Hsieh, J. Torseth, D. Pauloin, G. Bhatia, S. Harkonen, T. C. Merigan, and T. F. Blaschke. 1989. Pharmacokinetics of rifabutin. *Antimicrob. Agents Chemother.* **33**:1237–1241.
 17. Sullam, P. M., F. M. Gordin, and B. A. Wynne. 1994. Efficacy of rifabutin in the treatment of disseminated infection due to *Mycobacterium avium* complex. *Clin. Infect. Dis.* **19**:84–86.
 18. U.S. Public Health Service/Infectious Diseases Society of America Prevention of Opportunistic Infections Working Group. 1999. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Morb. Mortal. Wkly. Rep.* **48**:1–66.