ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2007, p. 958–961 Vol. 51, No. 3
0066-4804/07/$08.00+0 doi:10.1128/AAC.01203-06

Pharmacokinetic Interaction between Darunavir Boosted with Ritonavir and Omeprazole or Ranitidine in Human Immunodeficiency Virus-Negative Healthy Volunteers▽

Vanitha J. Sekar,[1]* Eric Lefebvre,[1] Els De Paepe,[2] Tine De Marez,[1] Martine De Pauw,[2] Wim Parys,[1] and Richard M. W. Hoetelmans[2]

Tibotec Inc., Yardley, Pennsylvania,[1] *and Tibotec BVBA, Mechelen, Belgium*[2]

Received 25 September 2006/Returned for modification 12 November 2006/Accepted 22 December 2006

Darunavir (DRV; TMC114; Prezista) is a human immunodeficiency virus (HIV) protease inhibitor used in combination with low-dose ritonavir (RTV) (DRV/r) as a pharmacokinetic enhancer. Protease inhibitor absorption may be decreased during coadministration of drugs that limit stomach acid secretion and increase gastric pH. This study was conducted to investigate the effect of ranitidine and omeprazole on the plasma pharmacokinetics of DRV and RTV in HIV-negative healthy volunteers. Sixteen volunteers completed the study and received DRV/r, DRV/r plus ranitidine, and DRV/r plus omeprazole, in three separate sessions. Treatment was given for 4 days with an additional morning dose on day 5, and regimens were separated by a washout period of 7 days. Samples were taken over a 12-h period on day 5 for the assessment of DRV and RTV plasma concentrations. Pharmacokinetic parameters assessed included DRV area under the curve, maximum plasma concentration, and trough plasma concentration. The least-squares mean ratios and 90% confidence intervals are reported with treatment of DRV/r alone as a reference. Compared with DRV/r alone, no significant changes in DRV pharmacokinetic parameters were observed during coadministration of DRV/r and either ranitidine or omeprazole. Treatment regimens were generally well tolerated, and no serious adverse events were reported. In conclusion, coadministration of DRV/r and ranitidine or omeprazole was well tolerated by the volunteers. Ranitidine and omeprazole did not have a significant influence on DRV pharmacokinetics. No dose adjustments are required when DRV/r is coadministered with omeprazole or ranitidine.

Darunavir (DRV; TMC114; Prezista) is a new protease inhibitor (PI) administered in combination with low-dose ritonavir (RTV) (DRV/r). DRV has received its first regulatory approvals for the treatment of human immunodeficiency virus (HIV) infection in treatment-experienced adult patients, such as those with HIV type 1 strains resistant to more than one PI (15). DRV binds to the HIV protease and is highly active against both wild-type and resistant strains of the virus (5). The development of new agents to combat HIV infection is imperative, since treatment options for patients with multidrug-resistant HIV strains are currently limited (17).

Clinically relevant interactions may occur between different antiretrovirals and between antiretrovirals and other drug types given for the treatment of coexisting medical conditions (13). Therefore, the potential interactions between any antiretroviral agent and other medications commonly used in HIV therapy should be routinely investigated during drug development.

Since the absorption of some PIs is dependent on an acidic gastric pH (10), the use of anti-acidic drugs may inhibit PI uptake. Gastrointestinal symptoms are common in HIV disease (11, 12) and are frequently treated with anti-acidic drugs, such as H_2-receptor antagonists and proton pump inhibitors (PPIs). It is therefore important that potential interactions between PIs and H_2-receptor antagonists and/or PPIs are investigated.

This multiple-dose pharmacokinetic study was designed to assess the effects of the H_2-receptor antagonist ranitidine and the PPI omeprazole on the plasma pharmacokinetics of DRV and RTV in HIV-negative healthy volunteers.

(These data have been presented at the 6th International Workshop on Clinical Pharmacology of HIV Therapy, abstr. 17, poster 2.10, Montreal, Quebec, Canada, 28 to 30 April 2005, and at the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment, poster WePe3.3C13, Rio de Janeiro, Brazil, 24 to 27 July 2005.)

MATERIALS AND METHODS

Study design. The present trial was a phase I, open-label, randomized, three-way crossover pharmacokinetic interaction study (study no. TMC114-C122). Healthy men and women between 18 and 55 years of age were eligible for enrollment. HIV-infected individuals, those suffering from a clinically significant medical condition, and those with a known history of alcohol and/or drug abuse were excluded from the study. Concomitant therapy was not permitted with the exception of acetaminophen (paracetamol). The study protocol was reviewed and approved by the appropriate institutional ethics committee and health authorities and was conducted in accordance with the Declaration of Helsinki. All volunteers gave written informed consent prior to study commencement.

In three separate sessions volunteers received DRV/r, DRV/r plus ranitidine, and DRV/r plus omeprazole, each for a period of 4 days plus a single dose on the morning of day 5. Volunteers were consecutively assigned to a randomization group on enrollment; each of six randomization groups received the three treatments in a different sequence. The following dose and frequency of each drug were used: 400 mg DRV twice a day (b.i.d.); 100 mg RTV b.i.d.; 150 mg ranitidine b.i.d.; and 20 mg omeprazole once a day (q.d.). Pharmacokinetic sampling was performed on the morning of day 5, and regimens were separated by a 7-day washout period. Individuals remained at the trial facility for the

* Corresponding author. Mailing address: Tibotec Inc., 1020 Stony Hill Road, Suite 300, Yardley, PA 19067. Phone: (609) 730-7500. Fax: (609) 730-7501. E-mail: VSekar@tibus.jnj.com.

▽ Published ahead of print on 8 January 2007.

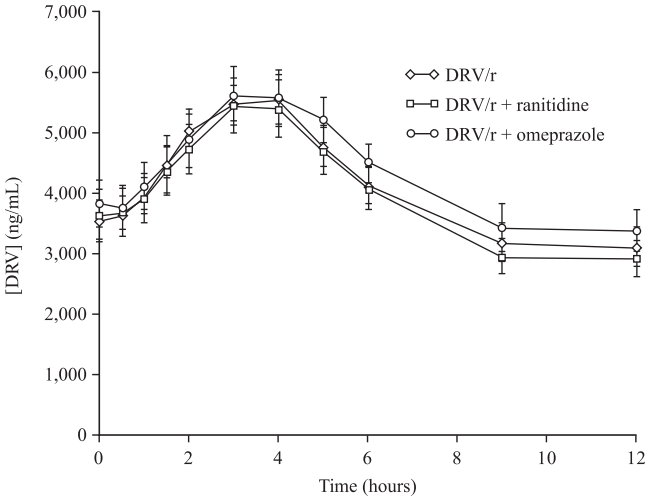

FIG. 1. Mean DRV plasma concentration-time curves on day 5 of each evaluated regimen. The three regimens were DRV/r 400/100 mg b.i.d., DRV/r 400/100 mg b.i.d. plus ranitidine 150 mg b.i.d., and DRV/r 400/100 mg b.i.d. plus omeprazole 20 mg q.d.

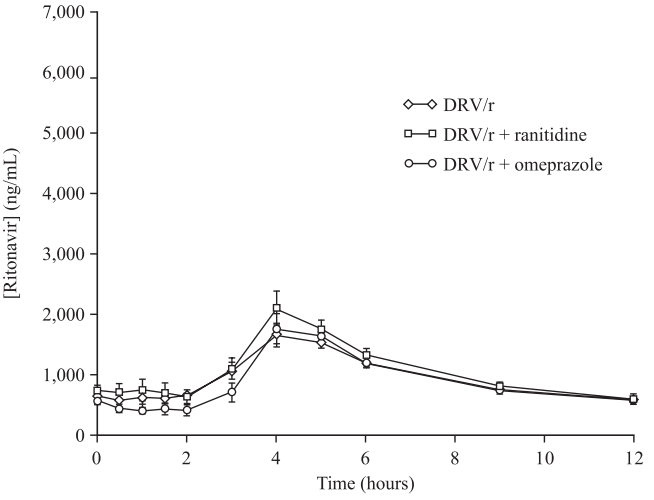

FIG. 2. Mean RTV plasma concentration-time curves on day 5 of each evaluated regimen. The three regimens were DRV/r 400/100 mg b.i.d., DRV/r 400/100 mg b.i.d. plus ranitidine 150 mg b.i.d., and DRV/r 400/100 mg b.i.d. plus omeprazole 20 mg q.d.

duration of treatment (day −1 to day 5), and drug intake was directly observed and timed. Ranitidine and omeprazole were administered within 15 min before food and DRV/r within 15 min after food. Blood samples were taken predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, and 12 h postdose on day 5 for all three regimens.

Bioanalysis. DRV and RTV plasma concentrations were determined using a validated liquid chromatography mass spectrometry/mass spectrometry method. The internal standards were deuterated (d6)-ritonavir and (d4)-darunavir for RTV and DRV, respectively. The mass transition was from 721.3 to 296.0 for RTV and from 548.2 to 392.0 for DRV, respectively. The precision and accuracy for the DRV and RTV quality control (QC) samples in plasma were less than 12% and met the predefined criteria of less than 20% for the low QC and 15% for the medium and high QC samples. The lower limits of quantification were 10.0 and 5.0 ng/ml for DRV and RTV, respectively (3). Omeprazole and ranitidine did not interfere with the quantification of DRV or RTV.

Safety evaluations. Laboratory safety tests were performed at screening, on days 1 and day 5, and at follow-up to assess safety and tolerability of study therapy. All clinical adverse events and laboratory abnormalities were graded according to the AIDS Clinical Trials Group severity grading scale. Clinical adverse events, whether related to study medications or not, and cardiovascular parameters were monitored and recorded over the study period.

Statistical methods. The intent-to-treat population was defined as those volunteers who received at least one dose of trial medication and was the primary population for the safety analyses. No formal sample size calculation was performed for this explorative, crossover, phase I study. A total of between 14 and 18 volunteers was considered sufficient to allow relevant conclusions to be drawn.

Pharmacokinetic parameters were determined by noncompartmental methods and included the following: minimum (C_{min}) and maximum (C_{max}) plasma concentrations; area under the curve from 0 to 12 h (AUC_{0-12}); and time to maximum plasma concentration (T_{max}). Descriptive statistics for the plasma concentrations of DRV and RTV were calculated using WinNonlin Professional (version 3.3; Pharsight Corporation, Mountain View, CA) and Microsoft Excel (version 2000; Microsoft, Redmond, WA).

The least-squares (LS) means of C_{min}, C_{max}, and AUC_{0-12} for each treatment group were estimated with a linear mixed-effects model, controlling for treatment, sequence, and period as fixed effects and volunteer as a random effect. Period effects were considered significant at the 5% level, and sequence effects were considered significant at the 10% level. If period and sequence effects were not significant, they were removed from the model. The LS mean ratio and 90% confidence intervals (CI) were calculated by comparison of DRV/r plus omeprazole or ranitidine (test) with DRV/r alone (reference). Only paired observations for the compared regimens were included in the statistical analysis. The T_{max} of DRV/r plus omeprazole or ranitidine (test) was compared with that of DRV/r alone (reference) by a nonparametric Koch test, using the crossover design tool of WinNonlin Professional.

RESULTS

Study population. Of 18 volunteers initially randomized, 17 received at least one dose of study medication and one was considered by the investigator to be unsuitable for study entry. Of the 17 evaluable volunteers, median (range) age was 26 years (19 to 53), weight was 69 kg (46 to 101), height was 169 cm (150 to 183), and body mass index was 25 kg/m^2 (18 to 30), and eight (47%) subjects were male. These 17 volunteers comprised the intent-to-treat population, which was used for all analyses. One volunteer discontinued treatment due to an adverse event (grade 2 maculopapular rash) prior to study completion. No major protocol deviations were reported, and there were no major differences in demographic parameters between the randomization groups.

Pharmacokinetic data. Mean plasma concentration-versus-time curves for DRV were similar between the regimens, as shown in Fig. 1. This was also true for RTV, as shown in Fig. 2. The mean pharmacokinetic parameters for DRV and RTV are described in Table 1.

There were no differences in DRV plasma C_{min}, C_{max}, and AUC_{0-12} when DRV/r was coadministered with ranitidine, compared with DRV/r alone. As shown in Table 2, the LS mean ratios (90% CI) for this interaction were as follows: C_{min}, 0.94 (0.90 to 0.99); C_{max}, 0.96 (0.89 to 1.05); and AUC_{0-12}, 0.95 (0.90 to 1.01). Similarly, coadministration of ranitidine had no effect on the T_{max} of DRV.

In the presence of omeprazole, there was a slight increase in DRV C_{min}, C_{max}, and AUC_{0-12} compared with DRV/r alone. The LS mean ratios (90% CI) for this interaction were as follows: C_{min}, 1.08 (0.93 to 1.25); C_{max}, 1.02 (0.95 to 1.09); and AUC_{0-12}, 1.04 (0.96 to 1.13). Coadministration of omeprazole had no effect on the T_{max} of DRV.

No changes in RTV exposure were observed in the presence of ranitidine or omeprazole (Table 2).

Safety and tolerability. Treatments were generally well tolerated, and no serious adverse events were reported. The most

TABLE 1. Pharmacokinetics of DRV (coadministered with low-dose ritonavir) on day 5 in the absence or presence of ranitidine or omeprazole

Parameter[a]	Reference (treatment A)[b]	Test		Ratio[e] (90% CI)	
		Treatment B[c]	Treatment C[d]	B:A	C:A
n	16	16	17		
T_{max} (h)	4.0 (1.5–4.0)	3.5 (3.0–5.0)	4.0 (2.0–5.0)		
C_{min} (ng/ml)	2,851 ± 1,172	2,696 ± 1,151	3,121 ± 1,416	0.94 (0.90–0.99)	1.08 (0.93–1.25)
C_{max} (ng/ml)	5,834 ± 1,415	5,743 ± 1,878	6,009 ± 1,844	0.96 (0.89–1.05)	1.02 (0.95–1.09)
$AUC_{0–12}$ (ng · h/ml)	48,905 ± 14,352	47,258 ± 16,340	51,505 ± 18,930	0.95 (0.90–1.01)	1.04 (0.96–1.13)

[a] T_{max} shown as median (range), others parameters shown as means ± standard deviations. *n*, number of subjects with data.
[b] DRV/r 400/100 mg b.i.d.
[c] DRV/r 400/100 mg b.i.d. plus ranitidine 150 mg b.i.d.
[d] DRV/r 400/100 mg b.i.d. plus omeprazole 20 mg q.d.
[e] Ratios based on LS means.

commonly reported adverse events were headache and loose stools, reported in nine and four volunteers, respectively. All adverse events were of grade 1 or 2 severity, with the exception of one volunteer who showed grade 3 increases in lipase and amylase during the follow-up period. Of the 16 individuals who reported one or more adverse event during treatment, six (38%) received DRV/r, eight (50%) received DRV/r plus ranitidine, and nine (53%) received DRV/r plus omeprazole. As requested by protocol, one volunteer withdrew from the trial following the occurrence of a grade 2 maculopapular rash on day 3 of the washout period after receiving treatment C (DRV/r plus omeprazole). No clinically relevant changes in laboratory or cardiovascular variables were reported during the study, and no treatment-emergent grade 3 or 4 laboratory abnormalities were observed.

DISCUSSION

We report here the steady-state pharmacokinetics, safety, and tolerability of the coadministration of DRV/r and ranitidine or omeprazole. No significant change in DRV plasma exposure was observed during coadministration of DRV/r and ranitidine or omeprazole, compared with DRV/r alone. DRV/r with or without ranitidine or omeprazole was well tolerated. The most frequently reported adverse events were headache and loose stools. No grade 3 or 4 adverse events or laboratory abnormalities were observed during treatment.

Ranitidine and omeprazole have the potential to reduce the absorption of pH-sensitive PIs by increasing gastric pH. Both ranitidine and omeprazole reduce gastric acid secretion but achieve this by different mechanisms. Ranitidine specifically binds and antagonizes H_2 receptors in the stomach, while omeprazole irreversibly inhibits the proton pump in actively secreting gastric parietal cells (8). PI elimination could be reduced by drugs that inhibit hepatic metabolism and result in an increased plasma PI concentration. Ranitidine does not interact with hepatic drug-metabolizing enzymes, but omeprazole has been shown to inhibit the hepatic enzyme cytochrome P450 2C19 both in vitro and in vivo (9); however, no relevant increase in DRV exposure was observed in the presence of omeprazole in this study.

The solubility of the PI atazanavir (ATV) decreases as pH increases, causing ATV absorption to be significantly reduced when given with drugs that increase gastric pH (4). Significant decreases in ATV exposure were seen after coadministration with omeprazole or ranitidine in healthy volunteers (2). Similarly, coadministration of the H_2-receptor antagonist famotidine with ATV (400 mg) or ATV/r (300/100 mg q.d.) considerably reduced plasma ATV AUC, compared with ATV alone (1). For volunteers who received 400 mg ATV, the 41% reduction in ATV AUC was almost abolished by giving ATV 10 h after one dose of famotidine and 2 h before the next. Volunteers who received ATV/r with famotidine showed a reduction in ATV AUC of only 18%, which was corrected by increasing the dose of ATV to 400 mg. ATV should not be used in patients receiving PPIs (4, 6).

Decreases in amprenavir (APV) exposure were seen following coadministration of fosamprenavir (FPV) with ranitidine in healthy volunteers; thus, caution is recommended when these

TABLE 2. Pharmacokinetics of ritonavir (coadministered with DRV) on day 5 in the absence or presence of ranitidine or omeprazole

Parameter[a]	Reference (treatment A)[b]	Test		Ratio[e] (90% CI)	
		Treatment B[c]	Treatment C[d]	B:A	C:A
n	16	16	17		
T_{max} (h)	4.0 (1.0–5.0)	4.0 (0.0–6.0)	4.0 (4.0–6.0)		
C_{min} (ng/ml)	437 ± 184	442 ± 209	351 ± 199	0.98 (0.86–1.13)	0.74 (0.61–0.90)
C_{max} (ng/ml)	1,906 ± 560	2,395 ± 1,040	2,031 ± 987	1.19 (1.03–1.39)	1.03 (0.88–1.20)
$AUC_{0–12}$ (ng · h/ml)	11,670 ± 3,039	12,922 ± 4,439	10,945 ± 4,009	1.06 (0.99–1.13)	0.92 (0.83–1.02)

[a] T_{max} shown as median (range), others parameters shown as means ± standard deviations. *n*, number of subjects with data.
[b] DRV/r 400/100 mg b.i.d.
[c] DRV/r 400/100 mg b.i.d. plus ranitidine 150 mg b.i.d.
[d] DRV/r 400/100 mg b.i.d. plus omeprazole 20 mg q.d.
[e] Ratios based on LS means.

drugs are coadministered (7). Conversely, significant increases in saquinavir exposure were observed (82% increase in AUC) when omeprazole and saquinavir boosted with RTV were coadministered, although no short-term toxicities were observed (16). Coadministration of esomeprazole with FPV or FPV/r had no effect on steady-state APV pharmacokinetics, although the impact of staggered administration of PPIs on plasma APV exposure is as yet unknown (14).

Unlike ATV, and to a lesser extent APV, coadministration of DRV/r with either ranitidine or omeprazole had no significant impact on the pharmacokinetics of DRV in our study. Moreover, the DRV T_{max}s were similar when DRV/r was administered alone or in conjunction with either ranitidine or omeprazole, suggesting that coadministration of these drugs did not delay absorption of DRV. The RTV C_{min} was reduced when DRV/r was coadministered with omeprazole, which may be caused by changes in solubility due to increased gastric pH. Importantly, however, this did not alter the pharmacokinetics of DRV. Since no impact on DRV pharmacokinetics occurred in this study evaluating the DRV/r 400/100 mg b.i.d. dose, none is expected with the approved 600/100 mg b.i.d. dose (15).

This study provides clinically relevant information to physicians and patients regarding the appropriate coadministration of DRV/r and ranitidine or omeprazole. No significant interaction was observed between DRV/r and either ranitidine or omeprazole; therefore, no dose adjustments are required when these agents are coadministered.

ACKNOWLEDGMENTS

Medical writing services were provided by Joanne Williams of Gardiner-Caldwell Communications (GCC), Macclesfield, United Kingdom.

Tibotec provided funding for this study.

REFERENCES

1. **Agarwala, S., T. Eley, M. Child, Y. Wang, E. Hughes, E. Chung, R. Wang, and D. Grasela.** 2005. Pharmacokinetic effect of famotidine on atazanavir with and without ritonavir in healthy subjects, abstr. 11. Sixth Int. Workshop Clin. Pharmacol. HIV Ther., Montreal, Quebec, Canada, 28 to 30 April 2005.
2. **Agarwala, S., K. Gray, Y. Wang, and D. Grasela.** 2005. Pharmacokinetic effect of omeprazole on atazanavir co-administered with ritonavir in healthy subjects, abstr. 658. Twelfth Conf. Retrovir. Opportun. Infect., Boston, MA, 22 to 25 February 2005.
3. **Bouche, M. P., L. Michielsen, M. Piot, and P. Timmerman.** 2006. Swift and simultaneous determination of darunavir (TMC114) and ritonavir in human plasma using LC-MS/MS, abstr. TuP-042. Seventeenth Int. Mass Spectrom. Conf., Prague, Czech Republic, 27 August to 1 September 2006.
4. **Bristol-Myers Squibb.** 2004. Reyataz (atazanavir). Prescribing information. Bristol-Myers Squibb, Princeton, NJ.
5. **De Meyer, S., H. Azijn, D. Surleraux, D. Jochmans, A. Tahri, R. Pauwels, P. Wigerinck, and M. P. de Bethune.** 2005. TMC114, a novel human immunodeficiency virus type 1 protease inhibitor active against protease inhibitor-resistant viruses, including a broad range of clinical isolates. Antimicrob. Agents Chemother. **49:**2314–2321.
6. **Eley, T., S. Agarwala, R. Wang, K. Gray, E. Chung, Y. Wang, and R. Bertz.** 2006. Analysis of intra-gastric pH and atazanavir bioavailability in healthy subjects, abstr. 40. Seventh Int. Workshop Clin. Pharmacol. HIV Ther., Lisbon, Portugal, 20 to 22 April 2006.
7. **Ford, S. L., M. B. Wire, Y. Lou, K. L. Baker, and D. S. Stein.** 2005. Effect of antacids and ranitidine on the single-dose pharmacokinetics of fosamprenavir. Antimicrob. Agents Chemother. **49:**467–469.
8. **Hatlebakk, J. G., and A. Berstad.** 1996. Pharmacokinetic optimisation in the treatment of gastro-oesophageal reflux disease. Clin. Pharmacokinet. **31:** 386–406.
9. **Li, X. Q., T. B. Andersson, M. Ahlstrom, and L. Weidolf.** 2004. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. Drug Metab. Dispos. **32:**821–827.
10. **Luber, A. D.** 2005. Use of acid-reducing agents in protease inhibitor-based HAART and the potential for negative treatment outcomes. AIDS Read. **15:**692–700.
11. **Luber, A. D., V. Garg, and S. Gharakhanian.** 2004. Survey of medications used by HIV-infected patients that affect gastrointestinal (GI) acidity and potential for negative drug interactions with HAART, abstr. P294. Seventh Int. Congr. Drug Ther. HIV Infect., Glasgow, United Kingdom, 14 to 17 November 2004.
12. **Mathews, W. C., J. A. McCutchan, S. Asch, B. J. Turner, A. L. Gifford, K. Kuromiya, J. Brown, M. F. Shapiro, and S. A. Bozzette.** 2000. National estimates of HIV-related symptom prevalence from the HIV Cost and Services Utilization Study. Med. Care **38:**750–762.
13. **Piscitelli, S. C., and K. D. Gallicano.** 2001. Interactions among drugs for HIV and opportunistic infections. N. Engl. J. Med. **344:**984–996.
14. **Shelton, M. J., S. L. Ford, J. Borland, Y. Lou, M. B. Wire, S. S. Min, Z. G. Xue, and G. Yuen.** 2006. Coadministration of esomeprazole with fosamprenavir has no impact on steady-state plasma amprenavir pharmacokinetics. J. Acquir. Immune. Defic. Syndr. **42:**61–67.
15. **Tibotec Inc.** 2006. Prezista (darunavir). U.S. prescribing information. Tibotec Inc., Yardley, PA.
16. **Winston, A., D. Back, C. Fletcher, L. Robinson, J. Unsworth, I. Tolowinska, M. Schutz, A. L. Pozniak, B. Gazzard, and M. Boffito.** 2006. Effect of omeprazole on the pharmacokinetics of saquinavir-500 mg formulation with ritonavir in healthy male and female volunteers. AIDS **20:**1401–1406.
17. **Yeni, P. G., S. M. Hammer, M. S. Hirsch, M. S. Saag, M. Schechter, C. C. Carpenter, M. A. Fischl, J. M. Gatell, B. G. Gazzard, D. M. Jacobsen, D. A. Katzenstein, J. S. Montaner, D. D. Richman, R. T. Schooley, M. A. Thompson, S. Vella, and P. A. Volberding.** 2004. Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society-USA Panel. JAMA **292:** 251–265.