Partnership of HIV-Infected Women and Health Status

To the Editor:

Social and psychological characteristics of partners may influence a person's health status[1,2] or even survival.[3] According to a recently published paper on HIV-infected persons,[4] lack of a stable partnership may be considered an important determinant of clinical progression.

In a study we conducted on women with HIV infection enrolled in the Italian Cohort Naive to Antiretrovirals (ICONA Study), we found that having a current partner who was an intravenous drug user (IDU) was associated with significantly lower levels of psychological well-being even when adjusted for several confounders.

ICONA is an Italian multicenter observational study on the natural history of HIV disease among adults who are naive to antiretrovirals at the time of enrollment. Within the ICONA cohort, the Behavioural Epidemiology (BEHEPI) Study investigates behavioral profile and health status of the enrolled HIV-infected persons. Participants were asked to complete a self-administered questionnaire including items on psychological well-being, personal behavior (self-reported HIV acquisition modality, lifetime number of sex partners, sexual intercourse in the previous 2 weeks, having a current IDU partner) as well as demographic characteristics.[5] Psychological well-being was measured through a 5-item scale with 5-point responses (BEHEPI Psychologic Well-Being scale or B-PWBS). Answers to the scale were summed and the result was linearly transformed in a 0–100 score. The scale included the most frequently used items for measuring the psychological well-being and was designed after a focus discussion with HIV experts and people living with HIV infection. We aimed to create a very brief tool for the screening of impaired psychological well-being.

From March 1998 to March 2000, 746 women participated in the BEHEPI Study. Mean age of women enrolled was 32 years (interquartile range [IQR] 28–36), 33% were unemployed, 37% were IDUs, 8% had Centers for Disease Control–defined AIDS: mean of CD4 was 460 (IQR 300–633), and median log of plasma HIV RNA was 4.1 (IQR 3.4–4.7). At enrollment, no woman was receiving antiretroviral therapy. Fifty-five of 746 women (9.7%) reported a current IDU partner. Women with a current IDU partner has a 17-fold probability (95% CI 7.6–38.8; $P < 0.0001$) of being currently IDU themselves compared with women who did not report a current IDU partner. Fifty-three percent of women had not sexual intercourse in the 2 weeks before the survey.

Missing data for the B-PWB Scale ranged from 4.6% to 5.5% among the 5 items and 7.4% for the whole scale. The validity of the B-PWB scale, evaluated through internal consistency, was good (Cronbach α: 0.81). Median of the B-PWB Scale was 55 (IQR 35–70); 0.5% of patients scored 0 (minimum) and 1.1% scored 100 (maximum).

A multiple linear regression analysis was performed to identify variables independently associated with the B-PWB Scale scores (Table 1). Having a current IDU partner was associated with lowest values on the psychological well-being scale. The multivariate analysis suggested that this association was independent of past or current use of drugs. Results were similar when we considered as IDU only current IDU women (n = 37) (data not shown).

Our results suggest that a focused analysis of familiar and social characteristics of women may be helpful in identifying determinants of health status because even a stable partnership may be associated with a mental health impairment if the partner is a current IDU. Particularly, we suggest that a gender-oriented approach should be used when analyzing social and psychological factors that may influence health outcomes. We did not analyze the potential association of type of partner with clinical course of HIV infection. However, several published papers have demonstrated that depression and mental health impairment are associated with a suboptimal adherence to drugs[6] and thus with worse outcomes of therapy.

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TABLE 1. Variables Associated with the B-PWB Scale Scores: Multiple Linear Regression Analysis

	Coefficient (β)	Standard Error	95% CI	*P*
General and clinical characteristics				
HIV disease stage: CDC group C	−14.02	4.00	−21.88; −6.16	<0.001
Injection drug use	−2.72	2.00	−6.64; 1.20	0.17
$CD4^+$ cell count	0.04	0.003	−0.003; 0.01	0.26
Log HIV RNA	−0.84	1.12	−3.05; 1.37	0.46
Behavioral Characteristics				
Having had sexual intercourse during the 2 weeks before the survey	5.20	1.95	1.36; 9.05	0.008
Current IDU partner	−14.35	3.28	−20.81; −7.90	<0.001
Socioeconomic Characteristics				
Unemployment	−6.49	2.07	−10.55; −2.43	0.002
Having children	−2.68	1.97	−6.55; 1.19	0.17

CDC indicates Centers for Disease Control.

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Co-Administration of Atazanavir With Proton-Pump Inhibitors and H_2 Blockers

To the Editor:

Drug–drug interactions are one of the challenging issues in the treatment of HIV-infected patients. Concern has been expressed about the coadministration of the new protease inhibitor, atazanavir (ATV; Reyataz, Bristol-Myers Squibb) with proton-pump inhibitors (PPIs) and H_2 receptor blockers (H_2RBs), because of inadequate absorption of ATV from a nonacidic environment. This interaction poses a significant problem clinically as many HIV-positive patients have requirements for PPIs and H_2RBs and are currently being treated with them. The likelihood that boosting ATV with ritonavir may possibly overcome this problem is uncertain, as the problem is one of absorption and not metabolism.

TABLE 1. Characteristics of Subjects in the PPI and H_2RB Groups

	PPI n = 15	H_2RB n = 19
Mean CD4, cells/mm^3	267	400
Range	8–877	108–806
Mean HIV RNA copies/mL ($\log_{10}$)	12935 (4.11)	69722 (4.84)
Range	<50–67,900	<50–750,000
	1.68–4.83	1.68–5.88
Patients with <400 copies/mL (%)	8/15 (53)	10/19 (53)
Patients <50 copies/mL (%)	2/15 (13)	3/19 (16)
Mean ATV TC, μg/mL	0.65	1.12
Range	<0.05–1.85	<0.05–3.17
Patients with low ATV TC (%)	6/15 (40)	4/20 (20)
	5/6 boosted	2/4 boosted

We surveyed the electronic medical record at 10 HIV clinics in Los Angeles to identify patients treated with ATV and PPIs or H_2RBs and recommended an intervention: either stopping PPIs/H_2RBs or switching their protease inhibitor. Fifty patients were identified. The trough concentrations (TCs) were analyzed using a centralized laboratory with validated techniques (Consolidated Laboratory Services, Van Nuys, CA). The results of ATV TCs (reference: TC = 0.27 μg/mL) were available in 34 patients before intervention: 15 on PPIs and 19 on H_2RBs. Table 1 summarizes these findings.

The mean TC of ATV in the PPI group was significantly lower than in the H_2RB group (0.65 vs. 1.12 μg/mL). Six of 15 patients (40%) on PPIs had levels <0.27 μg/mL, even though 5 of the 6 were receiving boosted ATV. Four of 19 patients (21%) on H_2RBs (2 of the 4 being on boosted ATV) also had inadequate levels. However, from those, 4 of 6 still had an HIV RNA level <400 in the PPI group as did 2 of 4 in the H_2RB group.

Gastroesophageal reflux disease and related symptoms are very common among HIV-infected patients. In one survey, 56% of patients used nonprescription antiacid drugs.[1] This poses a major concern in the use of agents such as ATV and their efficacy in suppressing HIV RNA levels. Another consideration is that the single drug level measurement in a patient may not be useful given the multiple factors involved and also the fact that a few patients with low ATV TC levels were still suppressed. Clinicians should use their best clinical judgment in interpreting such single data.

In conclusion, our findings suggest that PPIs and H_2RBs do interact negatively when used with standard ATV dosing and that boosting with ritonavir probably does not result in adequate levels. We suggest that the use of ATV, even boosted with low-dose ritonavir with either PPIs or H_2RBs, should be avoided until further data are available.

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Statins and HIV: Beyond the Metabolic and Cardiovascular Benefit

To the Editor:

Recommendations for the management of dyslipidemia and other cardiovascular risk factors in HIV-infected patients have been recently discussed in this and other important medical journals.[1,2] In the recent article by Hulgan et al,[3] the authors evaluated the use of protease inhibitors (PIs) and statins in these patients in terms of recommendations to avoid important pharmacologic interactions between these 2 groups of drugs; at the same time, they showed that the proportion of patients on PI-based

Presented in part at the 7th International Congress on Drug Therapy in HIV Infection, November 14–18, 2004, Glasgow, UK.

therapy who were concomitantly prescribed statins has sharply increased in recent years.

We note that significant "immunologic interactions" may also be possible with the use of statins in the HIV-infected population and should receive consideration. Thus, some evidence suggests that statins may exert significant modulator effects in the balance of the cytokine network in human beings. Shimada et al[4] reported that in patients with unstable angina who received statins as part of their treatment, the T helper 1 (T_H1)/T helper 2 (T_H2) ratio (estimated by the ratio of $CD4^+$ [interferon (IFN)-γ^+] [interleukin (IL)-4^-] cells/$CD4^+$[IFN-γ^-] [IL-4^+] cells) significantly decreased at 16 weeks when compared with those patients who did not receive this lipid-lowering therapy, and C-reactive protein (CRP) levels were positively correlated with changes in this ratio. This observation is also supported by basic studies[5] and is in concordance with the beneficial effect of statins in coronary artery disease and its related inflammatory markers seen in large clinical trials.[6] It is because of these immunomodulatory properties that statins are being evaluated in the treatment of diseases beyond classic cardiovascular conditions, such as multiple sclerosis[7] and refractory chronic graft-versus-host disease.[8] Conversely, during the course of HIV-1 infection, secretion of T_H1 type cytokines, such as IL-2 and antiviral IFN-γ, is generally decreased, whereas production of T_H2 type cytokines, such as IL-4, IL-10, proinflammatory cytokines (IL-1, IL-6, and IL-8), and tumor necrosis factor-α (TNFα), is increased.[9] Also, cross-modulation and cross-regulation between T_H1 and T_H2 cytokines seem to be necessary in the maintenance of adequate anti-HIV CD8 T-cell responses in HIV-infected chronic nonprogressors.[10] Moreover, eliciting adequate antiviral $CD8^+$ T-cell responses to control the level of HIV replication in vivo in an attempt to induce cellular immune responses that are qualitatively better, if not also quantitatively larger, than those otherwise generated during natural HIV infection is an important concept in the development of a possible HIV vaccine,[11] and cytokine balance should also play an important role in this process. Interestingly, small studies have suggested that the use of statins is associated with lower absolute CD4 T-cell responses after 6, 12, and 18 months of treatment in HIV-infected patients on PI-based highly active antiretroviral therapy (HAART).[12]

Whether these observations translate into significant clinical interactions is uncertain, and no doubt exists about the beneficial effects of statins in the management of dyslipidemia and atherosclerotic disease, but we believe that possible long-term immunologic effects should remain a consideration when statins are used in HIV-infected individuals on HAART, especially because the measurement of immune recovery in these patients is based on a quantitative test (CD4 count) that may not necessarily reflect the functionality of their immune system. This group of patients deserves particularly close evaluation in the future.

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Epoetin Alfa Once Weekly Improves Anemia in HIV/Hepatitis C Virus–Coinfected Patients Treated With Interferon/Ribavirin: A Randomized Controlled Trial

To the Editor:

Guidelines for HIV/hepatitis C virus (HCV)–coinfected patients recommend HCV treatment with pegylated interferon-α (PEG-IFN) plus ribavirin (RBV).[1] The adverse effects of IFN/RBV, particularly anemia, may be more common among HIV/HCV-coinfected than HCV-monoinfected patients[2] and are often associated with decreased health-related quality of life (HRQOL)[3] as well as with discontinuation or dose reduction of RBV.[4] This study evaluated the effectiveness of once-weekly (QW) epoetin alfa (epoetin alfa) compared with standard of care (SOC) in correcting anemia, improving HRQOL, and minimizing RBV dose reductions in HIV/HCV-coinfected patients receiving IFN/RBV therapy.

This was a 16-week, open-label, randomized, parallel-group, multicenter study in anemic patients with HIV/HCV coinfection receiving IFN/RBV therapy for an anticipated period of $\geq$16 additional weeks. Key inclusion criteria in-

cluded patient age of 18 to 75 years and hemoglobin (Hb) ≤12 g/dL or a ≥2-g/dL decrease in Hb after IFN/RBV initiation. Key exclusion criteria included a history of uncontrolled hypertension or seizure disorder, anemia attributable to another cause, and exposure to any epoetin within 3 months.

Patients were randomized (1:1 ratio) to receive up to 16 weeks of epoetin alfa (PROCRIT™; Ortho Biotech Products, LP, Bridgewater, NJ) at a dose of 40,000 U subcutaneously QW or SOC (no epoetin alfa). Epoetin alfa dosage was increased to 60,000 U QW after 4 weeks of therapy if Hb had not returned to pre-IFN/RBV levels. Epoetin alfa was discontinued after an additional 4 weeks at 60,000 U QW if Hb had not increased ≥1.0 g/dL from the nadir Hb value. If Hb exceeded 14 g/dL in women or 16 g/dL in men, epoetin alfa was withheld temporarily.

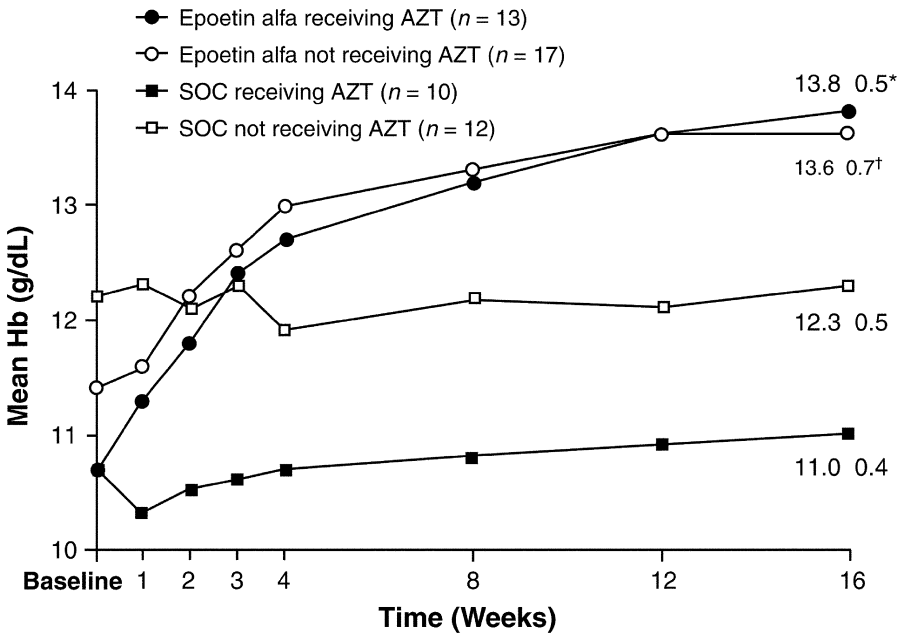

FIGURE 1. Hemoglobin (Hb) levels by treatment group stratified by zidovudine (AZT) treatment status (modified-intention-to-treat [MITT] population). *P = 0.001 versus standard of care (SOC) receiving AZT (analysis of covariance [ANCOVA]). †P < 0.001 versus SOC not receiving AZT (ANCOVA).

The primary end point was to compare the mean change in Hb from baseline (ie, first dose of study drug in epoetin alfa group, day 1 in SOC group) to week 16 in the epoetin alfa group with that in the SOC group. Secondary end points were mean change in RBV dosage, HRQOL scores (measured by modified Short Form-12 [SF-12] Health Survey–Acute; Physical and Mental Health Components [PCS, MCS]),[5] and transfusion. Patients were required to complete HRQOL assessments before each visit. Safety assessments included monitoring vital signs, adverse events, alanine aminotransferase (ALT) levels, $CD4^+$ counts, and HIV and HCV viral loads.

Efficacy analyses were based on a modified intent-to-treat (MITT) population defined as all patients who had baseline Hb measured and had at least 1 follow-up Hb assessment and, for the epoetin alfa group, received at least 1 dose of epoetin alfa. Safety analysis considered all patients. Missing values were imputed for the efficacy analyses using the last-value-carried-forward technique. Changes in Hb and SF-12 PCS and MCS scores were analyzed within each treatment group using paired t tests and were compared between groups using an analysis of covariance (ANCOVA) model with treatment group as a factor and baseline values as a covariate. RBV dosage changes were assessed by on-treatment analysis and were analyzed using a Wilcoxon signed-rank test to compare between groups. A post hoc analysis of changes in Hb stratified by zidovudine (AZT) status was performed. The incidence of adverse events between groups was compared using the Fisher exact test.

Sixty-six patients were randomized (34 to epoetin alfa group and 32 to SOC group). Baseline characteristics were comparable between the 2 groups. Immediately after randomization (day 1/week 0), 14 patients (4 epoetin alfa and 10 SOC) dropped out of the study without baseline or follow-up assessments. Compared with SOC patients included in the MITT analysis, early SOC dropout patients had lower Hb levels at study entry (10.3 vs. 11.5 g/dL; P = 0.03). Thirty epoetin alfa patients and 22 SOC patients were included in the MITT analysis. Twenty (63%) SOC patients and 11 (32%) epoetin alfa patients dropped out during the 16-week study period. The median time between initiation of IFN/RBV and baseline was 50 days (range: 16–306 days) in the epoetin alfa group and 60 days (range: 22–171 days) in the SOC group.

Supported by Ortho Biotech Clinical Affairs, LLC.Mark S. Sulkowski has received research grants and/or research support and is a member of the speakers' bureaus for Schering-Plough Corporation, Roche Laboratories, and Ortho Biotech Products, LP. Douglas T. Dieterich has received honoraria from and has served on the speakers' bureaus of Ortho Biotech Products, LP, GlaxoSmithKline, Gilead Sciences, Inc., Schering-Plough Corporation, and Roche Laboratories. Edmund J. Bini has received research funding from Ortho Biotech Products, LP. Norbert Bräu has received research grants from and has served on the advisory board for Ortho Biotech Products, LP. Daniel Alvarez is a member of the speakers' bureaus at Ortho Biotech Products, LP and GlaxoSmithKline; he also has received research support from GlaxoSmithKline and Ortho Biotech Products, LP. Edwin DeJesus has received grant and research support from Roche Laboratories, Inc.; he is also a consultant to and/or serves on the advisory boards of Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Gilead Sciences, Inc. (regional consultant), GlaxoSmithKline, Merck & Company, Inc. (national ID consultant), Ortho Biotech Products, LP, and Roche Laboratories, Inc. In addition, he is a member of the speakers' bureaus at Boehringer Ingelheim Pharmaceuticals, Inc. (visiting professor program), Bristol-Myers Squibb Company, Gilead Sciences, Inc., GlaxoSmithKline, Ortho Biotech Products, LP, and Roche Laboratories, Inc. Gerhard J. Leitz is an employee of Ortho Biotech Clinical Affairs, LLC and a stockholder of Johnson and Johnson.

Mean baseline Hb (±SE) was 11.1 ± 0.3 g/dL in the epoetin alfa group and 11.5 ± 0.3 g/dL in the SOC group ($P = 0.33$), and mean increases in Hb from baseline to week 16 were 2.6 ± 0.3 g/dL and 0.2 ± 0.3 g/dL, respectively ($P < 0.001$). No patient had epoetin alfa withheld because of reaching the upper limit of Hb. Patients receiving epoetin alfa and AZT had a greater mean increase in Hb from baseline to week 16 than those not receiving AZT (3.2 ± 0.4 g/dL [n = 13] vs. 2.1 ± 0.4 g/dL [n = 17]; Fig. 1). For SOC patients, the mean change in Hb was similar in AZT users and nonusers. No transfusions occurred.

Mean RBV doses at initiation of IFN/RBV and at baseline, respectively, were 1047 and 973 mg/d in the epoetin alfa group and 1027 and 982 mg/d in the SOC group. At week 16, 67% of epoetin alfa patients and 45% of SOC patients were receiving RBV doses ≥10.6 mg/kg/d ($P = 0.09$).

The SF-12 PCS score (mean ± SE) increased significantly from baseline to week 16 in the epoetin alfa group (6.0 ± 1.8 points; $P = 0.004$), whereas the mean increase in the SOC group was not significant (2.2 ± 1.2 points; $P = 0.09$). The mean increase in the SF-12 MCS scale score was 2.3 ± 2.0 points in the epoetin alfa group and 0.1 ± 1.5 points in the SOC group (P = nonsignificant vs. baseline for both groups). There were no significant differences between groups for mean change from baseline to week 16 in the SF-12 PCS or SF-12 MCS scale score.

Epoetin alfa was well tolerated, with most adverse events mild to moderate in severity. Patients treated with epoetin alfa had significantly less fatigue (n = 3 [10%]) compared with those in the SOC arm (n = 9 [38%]) ($P = 0.02$); there was no other significant difference between groups in the incidence of common adverse events. Four serious adverse events were reported: 1 in the epoetin alfa group (constipation, which was considered unrelated to epoetin alfa) and 3 in the SOC group (chest pain, myocardial infarction, and psychosis). There were no reports of thrombovascular events or antierythropoietin antibodies related to epoetin alfa.

In this randomized study, epoetin alfa effectively corrected anemia in HIV/HCV-coinfected patients treated with IFN/RBV, including those taking AZT. The magnitude of Hb increase (mean = 2.6 g/dL) in coinfected patients was similar to that previously observed in IFN/RBV-related anemia in patients with HCV monoinfection.[6,7] In contrast to studies in patients with HCV alone, no effect of epoetin on RBV dose was observed.[6,7] A significant number of SOC patients dropped out after randomization (10 patients) and before week 16 (20 patients), however, substantially limiting our ability to assess the secondary end point of RBV dose, because patients and investigators may have selectively discontinued study participation in those SOC patients with worse outcomes. Improvements in HRQOL scores were greater in patients receiving epoetin alfa, but the small sample size precluded definitive conclusions. Significantly fewer patients treated with epoetin alfa than SOC reported fatigue as an adverse event. In conclusion, epoetin alfa was effective in correcting anemia and was well tolerated in HIV/HCV-coinfected patients receiving IFN/RBV therapy compared with SOC. Larger, double-blind, placebo-controlled studies as well as studies evaluating alternative criteria for the use of epoetin alfa are warranted to further assess the effects of epoetin alfa on HRQOL, maintenance of RBV dose, and HCV response.

ACKNOWLEDGMENTS

Coinvestigators include the following individuals: Philip Keiser, MD, University of Texas, Dallas, TX; David Bernstein, MD, North Shore University Hospital, Manhasset, NY; Christine Zurawski, MD, Office of Joel Rosenstock, MD, Atlanta, GA; Coleman Smith, MD, Minnesota Clinical Research Center, St. Paul, MN; Vilma Vega, MD, Infectious Diseases Associates, Sarasota, FL; Daniel Wolde-Rufael, MD, Chase Brexton Health Services, Baltimore, MD; Joseph Jemsek, MD, Jemsek Clinic, Huntersville, NC; Sangik Oh, MD, Beth Israel Deaconess Medical Center, Boston, MA; and Gerald Pierone, MD, Treasure Coast Infectious Disease Consultants, Vero Beach, FL.

The authors acknowledge the contributions of Kimberly Marino, Bann-Mo Day, Nicole Slacik, Kevin Smith, and Angela Klopfer of Ortho Biotech Clinical Affairs, LLC.

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