day of admission was positive (titer, 1:80). The patient was treated with azithromycin, 500 mg q.d., on the first day, and then 250 mg q.d. for 2 additional days. Defervescence occurred within one day of therapy, and she recovered without complications. A second serology could not be performed because the patient did not visit the outpatient clinic after discharge.

Telephone follow-up 1 year after hospital admission indicated that both patients gave birth to healthy babies.

To determine the therapeutic dosage for the first patient, we referred to the treatment of chlamydial infection in pregnant women for which a single, 1.0-g dose of azithromycin was used successfully [5]. However, because the optimal dosage of azithromycin for the treatment of scrub typhus has not been determined, we added 500 mg of azithromycin for 2 additional days experimentally to reduce the risk of relapse or therapeutic failure. Because the result of treatment in the first patient was satisfactory, for the second patient, we reduced the therapeutic dose to 500 mg on the first day, and to 250 mg for 2 additional days. The result of this treatment was also successful.

Although this report of two cases provides only limited information, it suggests that azithromycin can be used in pregnant patients as therapy for scrub typhus. Further study is required to assess the effectiveness of azithromycin in the treatment of scrub typhus and to determine the appropriate dosage.

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Gynecomastia Associated with Indinavir Therapy

The syndrome of peripheral fat wasting (lipodystrophy) with central adiposity, hyperlipidemia, and insulin resistance has been associated with the use of HIV-1 protease inhibitors [1]. To date, the mechanisms of these effects have been only hypothesized [1, 2]. Two cases of breast hypertrophy in association with abdominal swelling and thinning of the thighs in women treated with indinavir have been reported [3, 4]. A proposed hypothesis explains breast hypertrophy in women as being secondary to the default accumulation of fat by more metabolically active breast adipocytes in the presence of estrogen [1]. We describe two HIV-1-infected men with normal testosterone and estrogen levels, in whom gynecomastia developed in association with indinavir therapy.

A 49-year-old patient with AIDS was started on lamivudine, stavudine, and indinavir therapy in November 1996 (case 1). He was also taking doxepin, famotidine, amitriptyline, and acetaminophen with codeine. Two months after the initiation of antiretroviral treatment, he noted redistribution of fatty tissue, and he also noted a nontender left breast lump, not associated with redness. Findings on physical examination included a 4-cm × 5-cm, non-tender, palpable mass in the left breast, increased abdominal girth, and thin limbs; no other abnormalities were noted. His last CD4 cell count was 640 cells/mm^3, and the viral load was undetectable (<500 copies/mL).

A 65-year-old, asymptomatic, HIV-infected man had no history of opportunistic infections and had not received antiretroviral therapy (case 2). His CD4 cell count was 140/mm^3 and he had a viral load of 72,985 RNA copies/mL. Therapy with zidovudine, lamivudine, and indinavir was initiated in standard doses, as well as trimethoprim-sulfamethoxazole three times per week. After 4 weeks, the viral load was undetectable (<500 RNA copies/mL). After 4 months of therapy, his CD4 cell count was 210 cells/mm^3. Six months after the initiation of treatment, he noted bilateral nipple tenderness and painful enlargement of his left breast. Physical examination revealed a 4-cm × 3-cm area of palpable glandular tissue in that breast. The remainder of the physical examination findings were within normal limits.

For both patients, studies for evaluation of gynecomastia included serum prolactin, serum cortisol, human chorionic gonadotropin, testosterone, estradiol, and gonadotropin (luteinizing hormone, follicle stimulating hormone) levels; all were within normal limits. Results of renal, liver, and thyroid function tests were also within normal limits. Cholesterol levels were normal, and triglyceride levels were elevated (933 mg/dL) only for the first patient.

We describe two patients who developed gynecomastia 2 and 6 months after initiation of antiretroviral treatment. No other cause was found. The gynecomastia was not severe enough to warrant discontinuation of antiretroviral therapy, and after 4 months of follow-up the condition had remained unchanged in both patients.

Before the availability of protease inhibitors, gynecomastia in association with HIV infection was described for two patients [5], and in both cases the condition resolved within 6 months; neither of the two patients was receiving any medications. Case 1 (present report) was receiving other medications with which gynecomastia has been associated [6]; however, the patient had been taking those medications for >2 years, and it was after the initiation of antiretroviral therapy that gynecomastia developed. For both of the patients we described, therapy with nucleoside analogues and protease inhibitors was started simultaneously. Despite their exten-

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sive use, none of the nucleoside analogues used to treat our patients (zidovudine, lamivudine, or stavudine) have been associated with gynecomastia, whereas indinavir has already been described as a cause of breast enlargement in women. One of the patients we described and the two previously reported women with indinavir-associated breast enlargement developed redistribution of body fat, a feature of the syndrome of peripheral fat wasting (lipodystrophy), hyperlipidemia, and insulin resistance that has been recently described in patients who received HIV-1 protease inhibitors [1]. One of our patients had associated lipid abnormalities; repeated fasting blood glucose levels have remained within normal limits.

Gynecomastia is a benign glandular enlargement of the male breast. This entity has been associated with the use of various drugs including anabolic steroids; antimicrobials (isoniazid, ketoconazole, metronidazole); cardiovascular, antiulcer, and psychoactive medications; and certain chemotherapeutic agents [6]. Breast enlargement, although uncommon, should be included among the adverse effects associated with use of protease inhibitors in both men and women. The mechanism for this side effect is unknown, but does not appear to be associated with any obvious endocrine abnormalities. Whether this effect is exclusively due to indinavir is a matter of speculation, and it remains to be determined if gynecomastia is another feature of the syndrome of HIV-1 protease inhibitor–associated peripheral lipodystrophy.

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Clostridium difficile Diarrhea After Use of Tacrolimus Following Renal Transplantation

Tacrolimus (FK506; Prograph [Fujisawa Healthcare, Deerfield, IL]) is a relatively new immunosuppressive agent with a macrolide molecular structure, which is indicated for the prophylaxis of organ rejection after allogeneic kidney or liver transplants. We describe a patient with *Clostridium difficile* diarrhea that was associated with the use of tacrolimus after renal transplantation.

A 29-year-old man with end-stage renal disease secondary to hypertensive nephrosclerosis received a cadaveric renal transplant in February 1990. He had had excellent allograft function until mid-1996, when he stopped taking his antirejection medication. He was noted to have a serum creatinine level of 1.4 mg/dL in 1995, and, in November 1996, when he returned for a visit, his creatinine level was 4.2 mg/dL. He was treated with methylprednisolone with no improvement in his creatinine level.

He was subsequently given mycophenolate mofetil (Cell-Cept, Roche Pharmaceuticals, Nutley, NJ) and then tacrolimus in February 1997. His creatinine level continued to rise, and he began receiving hemodialysis with a plan to taper his immunosuppressants. Within 4 weeks of starting tacrolimus, he developed diarrhea, nausea, and malaise. He had no nosocomial exposure to infectious causes and had not been receiving any antibiotics in the preceding 3 months. He was initially treated symptomatically with little benefit. A routine stool test for *C. difficile* toxin was found to be positive. He had no other opportunistic infections, and his symptoms improved with 2 weeks of metronidazole therapy. Tacrolimus was continued at this stage.

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In April 1997, diarrhea and fever recurred. He was admitted to the hospital with severe dehydration. Testing for sepsis was negative except for a positive result for *C. difficile* toxin in his stool. At this point, tacrolimus was discontinued. In addition, he received oral vancomycin solution, with complete resolution of symptoms in the next 2 weeks. A repeat stool test was negative for *C. difficile* toxin. He continues to do well while receiving hemodialysis.

Antibiotic-associated pseudomembranous colitis became a major clinical problem in the 1960s and 1970s, particularly with the use of broad-spectrum agents such as lincomycin and clindamycin, which caused diarrhea in ~10% of patients and pseudomembranous colitis in 1% [1].

In 1978, *C. difficile* was identified as the source of cytotoxin responsible for antibiotic-associated pseudomembranous colitis [2, 3]. It is now established as the most common nosocomial enteric pathogen causing pseudomembranous colitis, antibiotic-associated colitis, and antibiotic-associated diarrhea [4]. Antibiotic treatment, older age, and underlying illness are the major risk factors for the development of symptomatic disease [4]. In the last 3 years, there have been reports of pseudomembranous colitis following treatment with clarithromycin, a newer macrolide antibiotic indicated for eradication of *Helicobacter pylori* in peptic ulcers [5], and with third-generation cephalosporins [6].

Tacrolimus is a newer macrolide used for immunosuppression, and there have been no previous published reports of *C. difficile* diarrhea associated with its short-term use. The manufacturer of Prograph has received isolated reports of *C. difficile*–induced diarrhea in association with Prograph use (personal communication, P. C. Blahunka, Medical Information Department, Fujisawa Healthcare, 1998). This case serves as a warning of the need for attentiveness to the side effects of macrolide molecular structure.

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