of symptomatic primary HIV-1 infection may be as high as 50 to 70 percent. We have recently identified five additional cases of symptomatic primary infection, and Möst et al. describe three others. It is thus likely that many hundreds or thousands of patients present to primary care physicians annually with symptomatic primary HIV-1 infection but are not identified, either because the diagnosis is not suspected or because they test negative for HIV-1 antibody.

We agree with Busch et al. that "the absence of symptoms after high-risk exposures to [to HIV-1] does not obviate serologic evaluation and behavioral precautions." However, we also believe that symptomatic primary HIV-1 infection is not uncommon, and we believe strongly that tests for p24 antigen should be readily available to primary care physicians. The identification of persons with such infection would provide an opportunity for counseling and public health intervention, for comparison of the natural history of infection in patients with mild as compared with severe initial symptoms, for definition of the relative roles of different arms of the host immune system in limiting viral replication, and for antiviral treatment protocols to determine whether certain patients may benefit from therapy during early HIV-1 infection. A carefully designed prospective epidemiologic study of primary infection in persons at high risk that uses sensitive tests for early HIV-1 infection (e.g., p24 antigen and third-generation antibody tests) is needed to lay the groundwork for these studies.

Levy et al. provide information supporting a role for CD8+ lymphocytes in controlling HIV-1 replication in vitro and in vivo. However, it remains to be determined which components of the human immune response, including cytotoxic T lymphocytes, other T or natural-killer lymphocytes, virus-neutralizing antibodies, antibodies mediating antibody-dependent cell-mediated cytotoxicity, or other humoral factors, are primarily responsible for the dramatic down-regulation of viral replication and resolution of clinical symptoms during primary infection. Studies of patients with acute HIV-1 infection provide a unique opportunity to characterize the clinically important components of the host immune response to HIV-1 and to examine the molecular virologic properties leading to viral persistence.

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INHALED PENTAMIDINE AND PREVENTION OF PNEUMOCYSTIS PNEUMONIA

To the Editor: In the report of the recent European controlled trial of inhaled pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia (PCP), Hirschel and colleagues (April 18 issue)[1] state that it appears that prophylaxis against PCP may be less expensive than treating this disease. On the basis of data from the United States, there are several reasons why inhaled pentamidine is unlikely to reduce costs in this country. First, its cost is $100 to $129 per 300-mg vial (the lowest wholesale cost to the hospital), four times the cost in Europe.[2,3] In addition, according to data from the Multicenter AIDS Cohort Study, the probability that PCP would develop during the first year was 18.4 percent,[4] a figure considerably lower than the 27.1 percent in the study by Hirschel et al. The widespread use of zidovudine would be expected to reduce this risk even further.

We have recently completed a formal cost-effectiveness analysis evaluating the effect of primary prophylaxis for PCP in persons infected with HIV whose CD4 counts were below 200 per cubic millimeter.[5] We found that the projected annual costs of prophylaxis with dapsone (50 mg twice a day), trimethoprim–sulfamethoxazole (160 mg of the former and 800 mg of the latter twice a day), or inhaled pentamidine (300 mg monthly) were $440, $700, and $1,680, respectively. These costs included those of medication, monitoring, treating toxic reactions, and crossover to a second agent if needed. When the effects of these treatments were projected for three years under the assumption that all would be 90 percent effective if tolerated, none were cost-saving. However, dapsone and trimethoprim–sulfamethoxazole were reasonably cost effective; the incremental cost-effectiveness ratios were $13,400 and $14,000, respectively, per additional year of life, as compared with the absence of prophylaxis. Because the projected life expectancies were similar, and the cost of inhaled pentamidine was much higher, pentamidine was substantially less cost effective than dapsone or trimethoprim–sulfamethoxazole, unless reserved for persons who could not tolerate oral therapy.

As more data on the efficacy of low doses (administration two or three times a week) of dapsone and trimethoprim–sulfamethoxazole become available, these treatments may prove to be even more cost effective than inhaled pentamidine. Comparison of the efficacy, toxicity, cost, and effect on the quality of life of these different effective strategies will delineate the most cost-effective approach to this problem.

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To the Editor: Hirschel et al. note that 78 percent of patients in both the pentamidine and placebo groups were taking zidovudine before they were recruited. However, there is no mention of the numbers who took the drug during the trial. Zidovudine has been

shown to double the efficacy of pentamidine in secondary prophylaxis,[1] but appears to have little effect on its own in preventing the recurrence of PCP.[2,3] It is of considerable interest, therefore, to know whether most of the patients continued to take zidovudine during the trial. Otherwise, the independent efficacy of pentamidine remains unclear, and one can conclude only that the results demonstrate the efficacy of a combination of pentamidine and zidovudine.

It may be argued that because combination therapy is becoming commonplace, it is only of academic concern to learn of the relative efficacies of pentamidine and zidovudine alone. It must not be forgotten, however, that these drugs exact a cost, both in terms of money and adverse side effects. It is important to know whether one drug is as effective as combined therapy if attempts are to be made to minimize these costs.

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To the Editor: The recent article by Hirschel et al. may mislead some practitioners when it suggests that aerosolized pentamidine is the drug of choice for preventing PCP in patients infected with HIV. Personal experience, discussion with other colleagues who treat these patients, and critical evaluation of the literature suggest that trimethoprim–sulfamethoxazole is the preferred agent for preventing PCP in HIV infection. I have prescribed prophylactic trimethoprim–sulfamethoxazole for over 100 patients and have seen only two episodes of PCP (one episode a week after treatment with the drug was started, and the other two weeks after the patient decided to stop taking the drug). Published data support my anecdotal experience.[1,2] Ruskin and LaRiviere observed no episodes of PCP among 116 patients given one double-strength tablet of trimethoprim–sulfamethoxazole three times a week.[1] Raviglione et al. observed only one episode among 53 patients given one double-strength tablet twice daily for three consecutive days a week.[2]

Oral trimethoprim–sulfamethoxazole is more efficacious, less expensive, and easier to administer, and its systemic distribution may prevent the occurrence of extrapulmonary pneumocystis infection and reactivation of *Toxoplasma gondii*. It does have a higher rate of adverse reactions, but these are rarely severe, are much less frequent than those initially observed with higher doses,[3,4] and do not preclude a switch to an alternative agent. In patients taking aerosolized pentamidine, extrapulmonary pneumocystis infections[5] and atypical presentations of PCP with pneumothoraxes and cystic disease of the upper lobes[6] are not uncommon.

To put this matter to rest, I heartily endorse the randomized trial comparing pentamidine with oral agents that was proposed by Hirschel et al., but for now I will continue to use oral trimethoprim–sulfamethoxazole as the first-line agent to prevent PCP. In fact, I currently consider aerosolized pentamidine to be a third-line agent; in patients who cannot tolerate trimethoprim–sulfamethoxazole, treatment can be changed to oral dapsone (100 mg three times weekly).[7,8]

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To the Editor: The goal of treatment with aerosolized pentamidine is to deposit the medication effectively in all areas of the lungs. In their Methods section, Hirschel et al. describe its administration to patients in a semirecumbent position. The efficacy of the treatment does not lie only in the type of equipment used. An effective nebulizer (which produces particles of <4 μm) may maximize the amount of the drug that reaches the alveoli, but it does not ensure distribution to all lobes of the lungs.[1] Some evidence indicates that the upper lobes are especially prone to infection, even when a patient receives prophylaxis.[2,3] It seems advisable to administer the medication with the patient alternating between sitting upright and lying on either side. This increases the chances of bilateral distribution in the upper lobes, thereby decreasing the potential for infection with PCP in this area.

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The above letters were referred to the authors of the article in question, who offer the following reply:

To the Editor: The cost analysis by Freedberg et al. shows that under conditions prevailing in the United States, dapsone and cotrimoxazole (trimethoprim–sulfamethoxazole in a ratio of 1:5) are considerably cheaper than pentamidine for preventing PCP. Their conclusions are influenced by the prices of the drugs, and the differences between countries are indeed enormous. For instance, the wholesale cost of a vial of 300 mg of pentamidine in Switzerland is currently $29 (at an exchange rate of 1.5 Swiss francs to the dollar), or less than 25 percent of the average price in the United States cited by Freedberg et al.

Husain inquires about zidovudine treatment. As he surmises, most patients continued to take zidovudine during the trial. Of course, zidovudine has no known effect on *P. carinii*, but it might influence the incidence of PCP by reducing immunosuppression. The effect of zidovudine alone on the recurrence of PCP was investigated in 1987[1]; the level of protection was about 50 percent during the first few months. On the other hand, no such effect was evident in a more recent study.[2] The effect of pentamidine in the absence of zidovudine has not been assessed in relation to primary prophylaxis for PCP. As stated by Husain, the issue is moot, because good medical practice now demands that immunodeficient patients with HIV infection receive both drugs.

We are impressed, as is Bender, with the many noncomparative studies showing excellent efficacy and acceptable tolerance of oral

co-trimoxazole, and have no argument with those who use this drug as their first choice. As was revealed by a show of hands at the Seventh International Conference on AIDS in Florence, Italy (June 20, 1991), these advocates are less numerous than physicians who use pentamidine.

We did not observe PCP affecting the upper lobes in any of the patients in our trial. Among the patients given pentamidine who had pneumonia, most fell ill very soon (suggesting that PCP was subclinically present at the time of enrollment) or, if they had late-onset pneumonia, they were noncompliant or did not tolerate inhalation of pentamidine. Therefore, we do not think that we could have improved the results by adopting different protocols for inhalation, as suggested by Slote.

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FAILURE OF PROPHYLAXIS WITH DAPSONE IN PATIENTS TAKING DIDEOXYINOSINE

To the Editor: Both dapsone (25 mg by mouth four times a day) and trimethoprim–sulfamethoxazole (160 mg of the former and 800 mg of the latter by mouth twice a day) are highly effective in preventing PCP in patients with HIV infection[1] (and Metroka CE, et al.: unpublished data). In a previous report, only 2 of 162 patients had PCP while taking dapsone during a mean follow-up period of 9.6 months (range, 2 to 43) (Metroka CE, et al.: unpublished data). From December 7, 1989, to February 21, 1991, 66 patients were enrolled in the Videx (dideoxyinosine) treatment investigational-new-drug and open-label studies of dideoxyinosine, sponsored by Bristol-Myers. Nine patients could not be evaluated because of noncompliance or the development of adverse reactions to dideoxyinosine in the first 30 days. All the 57 patients who could be evaluated had less than 200 CD4+ cells per cubic millimeter at the initiation of therapy with dideoxyinosine and were receiving prophylaxis for PCP. PCP developed in 11 of the 28 patients receiving dapsone, in none of the 17 receiving trimethoprim–sulfamethoxazole, and in 1 of the 12 receiving 300 mg of aerosolized pentamidine monthly. Of the 12 patients in whom prophylaxis failed, 4 of those receiving dapsone and the 1 receiving pentamidine died of respiratory failure. The mean time from the beginning of dideoxyinosine treatment to the development of pneumocystis infection was 66 days (range, 10 to 130). Seventeen other patients have been receiving dideoxyinosine and dapsone for up to 14 months, without the development of PCP.

The most likely mechanism for the failure of dapsone prophylaxis is the citrate–phosphate buffer contained in the packet of dideoxyinosine to facilitate absorption of the drug at a pH of 7 to 8. Previous studies in human subjects have shown that dapsone is very insoluble at neutral pH but will dissolve fully in 100 ml of acidic gastric fluid. The mean absorption half-time of dapsone is 1.1 hours, with a median of 50 minutes and a range of 38 minutes to 2.7 hours.[2]

The absorption characteristics of other drugs that depend on the presence of gastric acidity, such as ketoconazole, pyrimethamine, trimethoprim, and itraconazole, may also be affected by the formulation of dideoxyinosine. Administering ketoconazole two hours before administering dideoxyinosine will allow normal absorption of the ketoconazole (Knupp C: personal communication). These observations suggest that dapsone administration should be separated from dideoxyinosine administration by at least two hours.

It is also possible that the combination of dideoxyinosine and dapsone may alter the hepatic metabolism or renal excretion of dapsone, resulting in decreased serum levels; this possibility appears less likely because of the molecular similarity of zidovudine and dideoxyinosine.

Pharmacokinetic studies to investigate further the interaction of dapsone and dideoxyinosine are in progress.

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HELICOBACTER PYLORI AND PEPTIC ULCER DISEASE

To the Editor: In his review on *Helicobacter pylori* (April 11 issue),[1] Peterson states that "the gold standard for the detection of *H. pylori* in tissue is a combination of culture and histologic staining of mucosal-biospy specimens obtained by endoscopy." We think these aspects deserve further consideration.

Because of the potentially patchy distribution of *H. pylori* on gastric mucosa, multiple mucosal-biopsy specimens should be obtained. Two to four have been suggested,[2] but the appropriate number is not known. Because there is little correlation between the presence of endoscopically observed mucosal features and the presence of histologic gastritis, the macroscopic appearance of the mucosa on endoscopic examination cannot ensure adequate biopsy specimens.[3] Although Warthin–Starry silver stain is said to be best for the histologic detection of *H. pylori*, Giemsa stain provides the best combination of simplicity and accuracy.[4] The optimal procedure for transporting specimens has not been established, but they can be held in 0.5 ml of sterile 20 percent glucose or in sterile 0.85 percent saline at 4°C for up to five hours without loss of viability.[5]

Detection of *H. pylori* by culture is less accurate than by other methods. This may be so in part because of the ingestion of topical anesthetic, the use of simethicone during endoscopy, the recent use of antibiotics, or the contamination of biopsy forceps with glutaraldehyde or with other microorganisms. Grinding biopsy specimens before inoculating culture mediums has been reported to increase the number of colonies recovered.[5] Although several different mediums have been used to recover *H. pylori*, chocolate agar without supplementation appears to work best.[4] The inoculated plates should be incubated at 37°C in an environment containing 5 percent oxygen, 10 percent carbon dioxide, and 85 percent nitrogen for seven days.

Culture is the most time-consuming and expensive method, and it is less sensitive than histologic staining. Thus, culture alone cannot be used to exclude *H. pylori* infection, and it adds little to the information obtained by histologic staining. Only by study of mucosal histologic features can we detect both the causative agent, *H. pylori*, and the disease, histologic gastritis. Nevertheless, culture is necessary to monitor the susceptibility of *H. pylori* to antimicrobial agents in cases of potential resistance.

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