

Diagnosing Primary HIV Infection

TO THE EDITOR: Daar and colleagues' (1) primary conclusion—that symptoms do not allow focused screening for primary HIV infection—may not be justified since “compatible symptoms” in part determined inclusion in their study and performance of their gold standard test. Furthermore, the statement that clinicians may be confident that “more than 90%” of patients with primary HIV infection will be identified by a standard HIV p24 antigen test alone is potentially misleading for several reasons. First, the study's sensitivity estimate of 88.7% for the p24 antigen test is relatively imprecise, with a 95% CI whose lower boundary was 77%. Second, the sensitivity of the p24 antigen assay depends on the time between onset of symptoms of primary HIV infection and screening, since antigenemia disappears during primary HIV infection (2). Significant delay before diagnosis of primary HIV infection may be typical in areas other than those served by well-connected clinics in urban centers.

The **Figure** illustrates our experience screening potential patients from the rural southeastern United States for a primary HIV infection treatment trial. Only 8 of 21 patients with confirmed primary HIV infection (38%) had positive results on p24 antigen assay. Primary HIV infection was defined as positivity for HIV RNA or DNA and negative results on enzyme-linked immunosorbent assay or an evolving Western blot within 30 days. The median time from onset of symptoms to screening in our cohort was 26 days (range, 5 to 70 days); this interval was greater than 21 days for most p24-negative persons (11 of 13). Since most of the published literature on treatment of primary HIV infection (3) includes patients with evolving Western blot who had onset of symptoms several weeks previously, these 11 patients should be considered to have true primary HIV infection. Last, the cost-effectiveness of an approach using p24 antigen testing cannot be adequately addressed by the data provided by Daar and colleagues. Formal cost-effectiveness studies, which consider, for instance, the potential adverse impact of false-negative results on sexual transmission rates (4) and therefore public health, are warranted.

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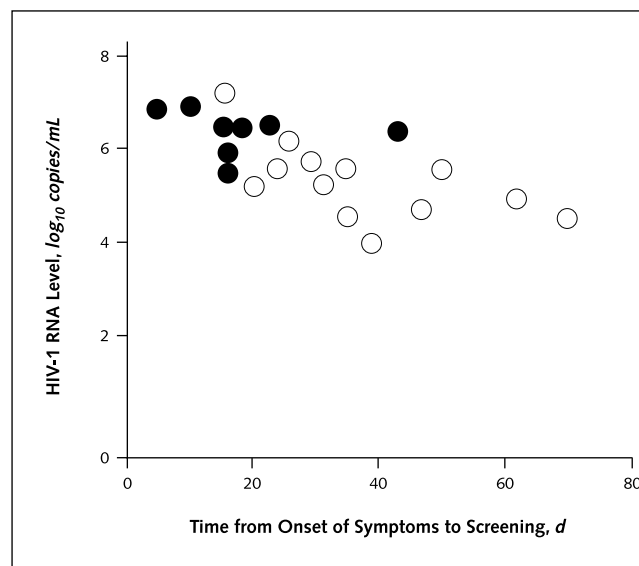
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Figure. Measurements of HIV-1 RNA plasma viral load in 21 patients with confirmed primary HIV infection who had positive (black circles) or negative (white circles) results on p24 antigen assay.



The Roche Amplicor Ultradirect Assay (Roche Diagnostics, Branchburg, New Jersey) was used to measure HIV-1 RNA in blood plasma (lower limit, 50 copies/mL); p24 antigenemia was measured in stored serum specimens (HIVAG-1 Monoclonal, Abbott Laboratories, Abbott Park, Illinois).

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IN RESPONSE: Our study was designed to distinguish between symptomatic patients who had primary HIV infection and those who did not. Since primary HIV infection can present with a broad range of clinical manifestations (1), all referred patients, regardless of symptom complex, were screened. Thus, on the basis of our analysis, which is consistent with that of others (2), we stand by our conclusions that screening should not be limited to patients with select symptoms.

We agree that our estimate of p24 antigen sensitivity could be misinterpreted. Nevertheless, our study demonstrates that this assay can be used to diagnose primary HIV infection in symptomatic, seronegative persons. Clinicians should be aware that sensitivity decreases over time and may vary according to the assay used. As noted in our article, regardless of the virologic test used, all at-risk persons should be counseled about the need for follow-up testing.

Pilcher and colleagues take issue with our focus on patients who were negative for HIV antibody, arguing that studies of primary

HIV infection often include the weeks or months from seroconversion. The objective of our study was to define the utility of virologic tests in diagnosing primary HIV infection during the seronegative window. After all, this is the setting in which the diagnosis is missed if virologic testing is not performed (3, 4). Moreover, patients with positive results on enzyme immunosorbent assay do not need a virologic test to establish their HIV status. Thus, we clearly state in our article the importance of assessing the sensitivity of virologic tests in the context of the clinical setting and the serologic status of the patient. The absence of serologic results in the data provided by Pilcher and colleagues only strengthens this point. Their Figure suggests that they have screened very few patients within the first weeks of infection, when a virologic test is likely to be necessary. Furthermore, the few patients that they have tested during the first weeks appear to be positive on p24 antigen assay, consistent with our observations.

We agree that a formal analysis of cost-effectiveness needs to incorporate the impact of false-negative results. However, such an analysis must also include the significant adverse psychological and financial effects of false-positive results. By defining the characteristics of each assay, our study allows clinicians to make informed decisions about the optimal screening strategy for specific patients in select clinical settings.

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Regression and Progression of Valvulopathy Associated with Fenfluramine and Phentermine

TO THE EDITOR: We read the reports by Mast and colleagues (1) and Weissman and coworkers (2) with interest. Because the combination of fenfluramine and phentermine ("fen-phen") was used extensively in our area, we have asked all patients presenting at our

institution for echocardiography in the past 3.5 years about use of these drugs. Data from our registry have been reported elsewhere (3).

One hundred twenty patients in our registry had follow-up echocardiography at least twice after cessation of fenfluramine-phentermine use. The mean age of these patients was 49 years, and the mean duration between echocardiograms was 10.6 months. Ninety-nine patients met U.S. Food and Drug Administration (FDA) criteria for valvulopathy (mild or greater aortic insufficiency or moderate or greater mitral regurgitation) on first echocardiography. On second echocardiography, 57 of these 99 patients showed no change in valvulopathy (57.6% [95% CI, 47.8% to 67.3%]), 33 showed improvement in valvulopathy (33.3% [CI, 24.1% to 42.6%]), and 9 showed deterioration in valvulopathy (9.1% [CI, 3.4% to 14.8%]). Nine patients no longer met FDA criteria for valvulopathy. Of the 21 patients without valvulopathy on first echocardiography, none met FDA criteria for valvulopathy on second echocardiography.

At our institution, the condition of most patients who developed valvulopathy after use of fenfluramine-phentermine remained unchanged after approximately 1 year. Valvulopathy improved in a substantial number of patients but worsened in a small but still significant number. We can be hopeful that some of our patients will eventually improve, and we are certainly encouraged that no patients developed new valvulopathy. However, because approximately two thirds of the patients in our registry have not improved, we believe that physicians must continue to be vigilant with patients who developed valvulopathy after fenfluramine-phentermine use.

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Appropriate Use of Antibiotics: Pharyngitis

TO THE EDITOR: In March 2001, Snow and colleagues (1) and Cooper and associates (2) proposed a practice guideline for management of acute pharyngitis in adults. This guideline is a major departure from the current recommendations of expert panels of the Infectious Diseases Society of America (3), the American Heart Association (4), and the American Academy of Pediatrics (5) regard-

ing diagnosis of pharyngitis caused by group A streptococci. We believe that certain aspects of the proposed practice guideline, such as eschewing the throat culture as a standard of diagnosis for acute streptococcal pharyngitis in adults, are debatable. Even more troubling is the endorsement of the use of clinical criteria alone, without even confirmation by a rapid antigen test, for management of acute pharyngitis. The guideline recommends that the four-factor algorithm proposed by Centor and coworkers (6) be used when deciding whether to treat with antibiotics. This algorithm can be useful in clinical decision making, particularly in identifying patients whose risk for streptococcal infection is too low to justify microbiological tests. Centor and coworkers did not, however, propose that the algorithm replace such tests.

Although Snow and Cooper and their colleagues allow options for using rapid antigen tests, it is extremely unlikely that clinicians will elect to perform such tests when a guideline endorsed by the American College of Physicians–American Society of Internal Medicine allows decision making on clinical grounds alone. The authors state that a major goal of their guideline is “dramatically decreasing excess antibiotic use” (1). Will their proposal to avoid diagnostic tests and limit antibiotic therapy to patients with three or four Centor criteria actually accomplish this objective?

In the Centor study, only 10% of “adult” patients (patients >15 years of age) presenting to an urban emergency department with pharyngitis had all four predictive factors; in this group, the probability of a positive throat culture for group A streptococci was 56%. In the 20% of patients who had three factors, the probability of a positive culture was only between 30% and 34%. According to these data, if the proposed guideline’s strategy of clinical management alone were followed, 60% of patients for whom antibiotics were prescribed would have had negative results on microbiological tests (throat culture or rapid antigen test).

We must conclude, therefore, that the proposed algorithm-based strategy would result in antimicrobial treatment of an unacceptably large number of adults with nonstreptococcal pharyngitis. This is particularly unfortunate in an age group with low prevalence of streptococcal pharyngitis and exceedingly low current risk (in developed countries) for acute rheumatic fever. It should be noted that the Infectious Diseases Society of America did not endorse the proposed clinical practice guideline. The authors themselves suggest that “prospective studies should be conducted to compare these strategies in terms of relevant patient outcomes and cost” (2). Should not such studies be completed before established methods of diagnosis and treatment of streptococcal pharyngitis in adults are abandoned?

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Sleep Apnea and Gastroesophageal Reflux Disease

TO THE EDITOR: Obstructive sleep apnea is a common condition and is associated with increased risk for hypertension, myocardial infarction, stroke, cardiac arrhythmia, headache, and traffic and industrial accidents (1). The condition may be simple to recognize. An overweight, middle-aged man who presents with a chief complaint of falling asleep during the day, who snores loudly, and who has been observed by his bed partner to stop breathing in his sleep poses no diagnostic challenge. A patient may, however, present with a complication of obstructive sleep apnea; in this case, suspicion of sleep apnea may lead to effective therapy. We report the case of a physician whose severe symptoms of gastroesophageal reflux disease (GERD) were substantially relieved by treatment of his sleep apnea.

A 65-year-old physician had been treated for 8 years for severe GERD. He would awaken every night choking and coughing from reflux of acidic gastric fluid. Omeprazole was beneficial, but the patient was concerned about taking this drug for long periods. He took approximately 15 calcium carbonate tablets per day for symptom relief. An interest in sleep medicine and a concern about his snoring and his tendency to fall asleep at the theater led him to have polysomnography. The test showed severe sleep apnea, with a supine respiratory disturbance index of 80 per hour and oxygen desaturation during sleep to 88%. Nasal continuous positive airway pressure, at a pressure of 10 cm of H₂O, eliminated all apneas. Within a day of beginning this therapy, nocturnal awakenings due to reflux stopped completely and have not returned in 2 years of follow-up. Daytime symptoms of GERD were markedly improved, and consumption of calcium carbonate tablets decreased from approximately 15 per day to 3 per day.

Gastroesophageal reflux disease is a common illness that not

only causes pain and discomfort but also has important complications, including asthma, Barrett esophagus, and esophageal cancer (2). Symptoms of GERD are common during sleep. Regurgitation of acidic gastric fluid may cause discomfort, choking, aspiration, and disturbed sleep with multiple awakenings. A major text of sleep disorders (3) states that esophageal reflux is a frequently observed symptom among patients with obstructive sleep apnea. Continuous positive airway pressure is the most effective therapy for obstructive sleep apnea and may reduce the severity of gastrointestinal reflux in patients with both conditions. We urge physicians to inquire about symptoms of sleep apnea in patients with GERD.

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A Rollover Epidemic in North Dakota from 1994 to 1997

TO THE EDITOR: During the past few years, I felt that reports of vehicle rollovers in the news media were increasing. Also, in 1996, a patient who replaced roofs of sport utility vehicles (SUVs) told me something that stuck in my mind: He could never find enough accident-damaged SUVs with intact roofs to repair SUVs that had only roof damage. Since I have a teenager who is of driving age, I decided to study the issue.

I obtained copies of *North Dakota Vehicular Crash Facts* for 1994 through 1997 (1–4). These publications detailed all aspects of

Table. North Dakota Crash Statistics

| Variable | Rates per 100 Million Vehicle Miles Traveled | | | |
|--------------------|--|---------|---------|--------|
| | 1994 | 1995 | 1996 | 1997 |
| Total crashes | 219.670 | 215.370 | 235.950 | 242.00 |
| Rollover crashes | 16.900 | 20.550 | 24.550 | 30.950 |
| All crash injuries | 88.660 | 86.650 | 88.910 | 85.690 |
| Rollover injuries | 7.280 | 8.177 | 10.080 | 11.460 |
| All crash deaths | 1.378 | 1.116 | 1.256 | 1.525 |
| Rollover deaths | 0.2970 | 0.3319 | 0.4138 | 0.4790 |

fatal and nonfatal vehicle crashes during these years, including but not limited to alcohol or drug use, speeding, seat belt use, type of driver violation, road surface, weather conditions, type of roadway (urban vs. rural), age and sex of the driver, and speed limits. I carefully analyzed the exact nature of the first harmful event in all crashes, as abstracted from standardized crash reports (Table).

On the basis of my analysis, I concluded that our vehicles are suffering from “rolloveritis.” Nearly 5000 rollover crashes, 2500 rollover injuries, and more than 100 rollover deaths occurred in North Dakota alone from 1994 to 1997. These numbers are probably related to a basic change in what we are driving. Pickups and SUVs, which have high centers of gravity and have become more popular for highway driving during the past decade, are the likely culprits in this epidemic. Buyer beware!

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