Think HIV

Why Physicians Should Lower Their Threshold for HIV Testing

Kenneth A. Freedberg, MD, MSc; Jeffrey H. Samet, MD, MA, MPH

More than 1 million people in the United States are estimated to be infected with the human immunodeficiency virus (HIV), a national prevalence of 0.3%. About half of those infected are men who have sex with men and a quarter are injection drug users. The incidence of HIV infection appears to have leveled off among men who have sex with men but continues to rise in injection drug users, women, and persons who have acquired HIV infection through heterosexual contact.

In the past several years, there have been crucial advances made in understanding the biology and treatment of HIV infection. The ability to quantify virus in both plasma and peripheral blood mononuclear cells has confirmed that HIV infection is a dynamic process characterized by rapid daily CD4 lymphocyte turnover. Advances in the understanding of viral replication have provided the rationale for interrupting this process as early and as effectively as possible.

In parallel with the rapid growth of virological and immunological knowledge concerning HIV, options for effective antiretroviral therapies have multiplied. The era of zidovudine and other nucleoside monotherapy ended abruptly, as clear benefit in terms of both morbidity and mortality has been demonstrated for combination regimens. Trials of combination regimens that include protease inhibitors have now demonstrated both immunological and survival benefits. In addition to these therapies, the nonnucleoside reverse transcriptase inhibitors are now available. Clearly, multidrug regimens of antiretroviral medications for HIV infection have become the new standard of care in the United States, providing both hope and evidence of prolonged survival for patients with HIV disease.

These developments in the HIV epidemic necessitate a reassessment of different aspects of our approach to medical care for this disease. In that context, this article has several objectives. First, we review data concerning the timing of presentation to medical care of persons who are infected with HIV, the status of HIV testing in the United States, and the seroprevalence of HIV infection in specific populations. Second, we address the physician role in HIV testing, the US Preventive Services Task Force recommendations for a screening test, and the clinical triggers that might raise a patient above a screening threshold. Third, we consider policy issues related to HIV testing, including cost-effectiveness and resources for additional testing.

CLINICAL PRESENTATION, HIV TESTING, AND SEROPREVALENCE

Human immunodeficiency virus infection is increasingly being viewed as a treatable chronic disease, the diagnosis of which is frequently delayed. It has a natural history in which a median period of 11 years precedes an acquired immune deficiency syndrome (AIDS) diagnosis. There is often a prolonged asymptomatic phase of the disease after acute infection, and diagnosis frequently occurs only after striking symptoms are noted. Twenty-two percent of patients (97/436) between 1991 and 1993 in a London hospital presented with their first AIDS-defining illness at the same time as their first positive HIV test result. Porter et al found that among 3556 patients who had voluntarily reported their AIDS status in England and Wales be-
A 30-year-old African American woman presented to her assigned physician for the first time complaining of cough, fever, and chills for 2 days. Her medical history was unremarkable. She had had 2 male sexual partners in her lifetime; her present relationship had been with a single partner for the previous 5 years. Condom use was intermittent. She had been treated for gonorrhea at age 20 years. She denied any drug or alcohol use. The physical examination was notable for crackles in the left lower lung field. A chest radiographic film revealed a left lower lobe infiltrate. No sputum was obtained. The physician prescribed azithromycin and recommended an HIV test. Her HIV test result was positive. Her subsequent CD4 lymphocyte count was \(0.1 \times 10^9/L\) (100/µL), and the HIV RNA level was 22 000 copies per milliliter.

Between 1989 and 1992, 1742 (49%) had been aware of their infection for 9 months or less before AIDS was diagnosed.

CD4 lymphocyte counts at initial clinical presentation have been used as an approximation of the duration of HIV infection prior to medical care. Samet et al\(^1\) found that many patients who presented for the first time for HIV-related primary care to Boston City Hospital, Boston, Mass, from 1990 to 1992 had advanced immunosuppression: 30% had CD4 lymphocyte counts lower than \(0.2 \times 10^9/L\) (200/µL) and 51% had CD4 lymphocyte counts between 0.2 and \(0.3 \times 10^9/L\). These findings are consistent with the work of Katz et al,\(^1\) according to which 29% of patients beginning medical care at a university AIDS clinic in San Francisco, Calif, between 1989 and 1991 had CD4 lymphocyte counts lower than \(0.2 \times 10^9/L\). More recently, Samet et al\(^1\) found that of patients presenting for HIV care in hospitals in Boston and Providence, RI, from 1994 to 1996, 37% had CD4 lymphocyte counts lower than \(0.2 \times 10^9/L\). Bozzette et al,\(^1\) in a nationally representative sample, estimated that 91% of HIV-infected adults in care in the United States in early 1996 had CD4 lymphocyte counts below \(0.5 \times 10^9/L\). These studies clearly demonstrate that many HIV-infected patients do not learn of their infection and do not receive medical care early in the course of their infection, a period in which therapeutic interventions could provide beneficial effects.\(^4,7,11\)

Unfortunately, studies that have examined factors associated with delayed presentation to medical care facilities have revealed few specific patient characteristics that might provide direction for targeted outreach efforts to those who present for treatment late in the disease course.\(^1,13\)

Entering medical care early in the course of HIV infection requires early HIV testing. According to the 1992 National Health Interview Survey, 32.4% of all adults in the United States have been tested for HIV infection. When testing through blood donation was excluded, 18.1% of US adults had been tested; about half of these tests were voluntary and half were required.\(^18\) More recent data from the Centers for Disease Control and Prevention (CDC) have shown an increase in the frequency of voluntary HIV testing among adults aged 18 to 65 years from 13.8% in 1993 to 23.2% in 1996. However, those at medium to high risk for HIV infection showed more modest increases in the frequency of testing than those at low or no risk.\(^19\) Data from the HIV Cost and Services Utilization Study Consortium\(^16\) suggest that in 1996 an estimated 37% to 64% of HIV-infected adults in the United States were not receiving care, and it was likely that many of them had not been tested.

Several policies recommending aggressive HIV testing have been advocated. All patients in hospitals with 1 per 1000 patient discharges of newly diagnosed AIDS should be advised to undergo HIV testing, according to the CDC; however, there is little evidence that this recommendation has been implemented.\(^20\) In 1995, the CDC recommended that all pregnant women in the United States be offered routine HIV counseling and testing.\(^21\) The case has also been made for rapid HIV testing during labor for women who have not received prenatal care and therefore may not have had the option of HIV testing.\(^22\) A recent report from the Institute of Medicine\(^23\) suggests that HIV testing should become routine for all pregnant women in the United States. In addition to these policy recommendations, anonymous HIV testing sites were developed with the aim of facilitating HIV testing. In a CDC-sponsored study, anonymous testing was shown to be associated with higher initial CD4 lymphocyte counts than confidential testing.\(^24\)

Although concern is often raised regarding false-positive HIV tests, the enzyme-linked immunosorbing assay (ELISA) and confirmatory Western blot analysis for HIV have excellent test characteristics. At Walter Reed Hospital, Washington, DC, the frequency of a false-positive test was 1 in 130 000.\(^25\) Kleinman and colleagues\(^26\) found an overall false-positive prevalence of 1 in 251 000. If diagnosis required the additional finding of detectable HIV RNA, this exceedingly high level of specificity may even be an underestimate.

Currently, a passive approach to HIV testing prevails in many clinical settings. Despite public health policies promoting more aggressive HIV testing, physicians generally view the HIV test as a diagnostic test rather than as a screening test. A diagnostic test paradigm sets the stage for a physician perspective in which ordering the test is appropriate only if test results are positive at some regular frequency, ie, 1 in 4 or perhaps 1 in 10. In a paradigm in which HIV testing is viewed as a screening test, one would expect a positive test result much less frequently. In the case of a screening test, a positive result of 1 in 20 or 1 in 100 would be perfectly acceptable. Physicians do not expect 20% or even 10% of mammogram results to reveal cancer; perhaps physicians should not expect that 10% of the HIV tests they administer will be positive. If HIV testing is used only as a diagnostic tool, too few patients will be encouraged to undergo testing, and many will remain untested for prolonged periods.
The appropriateness of HIV testing in any individual patient depends in part on the particular HIV risk profile. There are more than 800 studies in the literature examining the seroprevalence of HIV in various groups of patients; about half of these studies are from the United States. When these studies are examined, it is striking how much is known about HIV prevalence; equally striking is how much is not known. Seroprevalence based on demographic characteristics and a few clinical characteristics has been the major focus of study (Table 1). Seroprevalence ranges from 0.2% in adolescents across the United States, to 14.6% in men in a New York City emergency department, to 17.9% in young men who have sex with men in San Francisco, to 39.1% among injection drug users in New York City. Other seroprevalence data include the following: 0.4% in the Dallas County Household HIV survey, 0.3% in the 1988-1994 National Health and Nutrition Examination Survey (NHANES III), 0.9% among 21-year-old Job Corps enlistees, and 2.0% in a survey of outpatient clinical laboratories in the United States. Seroprevalence increases to 5.0% and 10.3% among alcoholics in detoxification programs, 5.8% among psychiatric inpatients, and 19.4% among psychiatric patients in a New York City shelter for homeless men.

Data are lacking, however, concerning HIV seroprevalence with specific clinical presentations (Table 2). What is the probability that a given patient with an abnormal Papanicolaou smear, shingles, or the patient described in the boxed “Report of a Case” section with community-acquired pneumonia has HIV infection? It is impossible to say from the medical literature. All of the clinical and historical triggers listed in Table 2 should increase a physician’s suspicion for HIV infection. However, the extent of the increased risk for HIV infection compared with a population without these triggers is uncertain. The absolute risk depends in part on the overall community prevalence. A 30-year-old person in Washington, DC, with community-acquired pneumonia is certainly at higher risk than a 30-year-old person in Des Moines, Iowa, with the same clinical presentation. Data describing HIV seroprevalence in populations with specific clinical presentations would be of great benefit in elucidating the value of HIV testing in particular patients in the clinical arena. In addition, the assessment of an individual’s risk for HIV infection focuses attention on a crucial question: what should be the threshold for recommending HIV testing?

HIV TESTING: PHYSICIAN ROLE, THRESHOLD, AND RISK RECOGNITION

Any physician encounter may provide an opportunity to test an HIV-infected patient earlier in the course of the infection than he or she might otherwise have been tested. An HIV test can be performed in a variety of settings: routine nonclinical care (eg, blood donation, military induction, or obtaining life insurance), anonymous HIV testing centers, nonvoluntary settings (eg, immigration or prison), or physicians’ offices. As previously noted, in 1996, 23.2% of US adults had been tested for HIV voluntarily. The percentage of those tests that occurred as a result of a physician-initiated recommendation is not known. The percentage of patients who pursue HIV testing prior to clinical manifestation of HIV infection is also unknown, but it is undoubtedly not the majority of HIV-infected patients, based on the data described above.

Lack of physician involvement in addressing this important per-
The US Preventive Services Task Force criteria provides some in-
using the US Preventive Services
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initiated by physicians.54
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associations with HIV testing was a
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Among sexually active adolescents in
clinical spheres53 and in influ-
tence to injection drug users is also im-
there is no question that people at
improvement from therapy now available, not test-
ing means not providing effective
health care system for years without being tested.
With highly active antiretrovi-
therapy now available, not testing means not providing effective
therapy to patients who may ben-
effit substantially.4 This brings us back to the question noted above:
“what should be the threshold for recommending HIV testing?” Perhaps a patient in any subgroup with
0.5% or 1.0% seroprevalence should be offered HIV testing. If 1 of 100 people seen in any physician’s prac-
tice had undiagnosed HIV infec-
tion, would it be worth testing all
100 to identify that 1? Primary care
clinicians routinely screen for many
diseases with lower prevalence than
HIV infection, including diseases for
which the benefits of therapy have been less clearly demonstrated. A Pa-
panicolaou smear for cervical can-
er in women aged 20 to 64 years, a
Papanicolaou smear for cervical can-
er in women aged 20 to 64 years, a

Table 2. Clinical and Historical Triggers to Suggest Risk of Human Immunodeficiency Virus Infection

<table>
<thead>
<tr>
<th>Clinical Triggers</th>
<th>Historical Triggers</th>
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<tbody>
<tr>
<td>Sexually transmitted diseases</td>
<td>Psychiatric hospitalization</td>
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<tr>
<td>Herpes simplex virus</td>
<td>Alcohol detoxification or dependence</td>
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<tr>
<td>Gonorrhea</td>
<td>Homelessness</td>
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<tr>
<td>Abnormal Papanicolaou smear</td>
<td>Cocaine or crack use</td>
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<tr>
<td>Trichomonias</td>
<td>Unsafe sex with partner whose human</td>
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<td>Syphilis</td>
<td>immunodeficiency virus serostatus is</td>
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<tr>
<td>Hepatitis B virus</td>
<td>unknown or positive</td>
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<tr>
<td>Chlamydia</td>
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<tr>
<td>Pelvic inflammatory disease</td>
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<tr>
<td>Condylomata acuminata</td>
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<tr>
<td>Other infections</td>
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<tr>
<td>Tuberculosis</td>
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<tr>
<td>Recurrent vaginal candidiasis</td>
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<tr>
<td>Community-acquired pneumonia</td>
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<tr>
<td>Varicella zoster virus</td>
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<tr>
<td>Skin</td>
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<td>Psoriasis</td>
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<tr>
<td>Seborrheic dermatitis</td>
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<tr>
<td>Systemic</td>
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<tr>
<td>Mononucleosis syndrome</td>
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<tr>
<td>Weight loss</td>
<td></td>
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<tr>
<td>Bell palsy</td>
<td></td>
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<tr>
<td>Generalized lymphadenopathy or unexplained focal adenopathy</td>
<td></td>
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<tr>
<td>Pregnancy</td>
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sonal and public health problem is distressing. This inaction has oc-
curred despite evidence that physi-
cians are influential in motivating pa-
tients to change their behavior in
other clinical spheres53 and in influ-
tencing a patient’s willingness to un-
dergo HIV testing specifically.54
Among sexually active adolescents in
Massachusetts, one of the strongest
associations with HIV testing was a
discussion with a physician about this
issue; 85% of the discussions were
initiated by physicians.59
Who should be tested for HIV infec-
tion? Examining the question using the US Preventive Services
Task Force criteria provides some in-
sight.55 Human immunodeficiency virus infection is a disease with sub-
stan
tial morbidity and mortality for
which effective therapy exists that, ide-
ally, should be instituted either
during the acute HIV syndrome or
prior to late symptoms of the dis-

ease.4 The HIV test itself is mini-
mally invasive and has extraordi-
narily high sensitivity and specificity.
These aspects of HIV testing meet the
criteria for its general institution as
a screening test. The overall preva-
lence of HIV infection, its preva-
lence in specific subgroups, and the
cost of screening are important,
changing variables that need to be
more adequately addressed in for-
mal cost-effectiveness analyses.
There is no question that people at
high risk for acquiring HIV infec-
tion, such as injection drug users; men
who have sex with men; sexually ac-
tive men and women with multiple
partners; or people with symptoms
highly suggestive of HIV, such as oral
thrush, should be tested for HIV in-
fec
tion. A detailed history regarding
previous injection drug use or expo-
sure to injection drug users is also im-
portant. However, these screening cri-
ter

HIV testing not being recom-
mended. The sexually transmitted dis-
ese occurred 10 years prior to pre-
sentation. This long time lag may be
correctly construed to be out of
range for HIV transmission. Second,
physicians often find it difficult to ob-
tain detailed sexual histories or dis-
cuss HIV serostatus.56 Finally, al-
though an acute bacterial infection
such as pneumonia is more com-
mon in HIV-infected individuals, the
extent of increased risk for HIV in-
fection is uncertain; thus, it may not
be viewed as an opportunistic in-
fec
tion. If, however, physicians wait for
clear evidence of immune dysfunc-
tion, only patients with advanced dis-
ase will be detected.12-14 Many HIV-
infected patients will interact with the
health care system for years without being tested.
With highly active antiretrovi-

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bates do not incorporate the excellent characteristics of HIV tests and the current availability of HIV RNA testing. Initial evaluation of the exceedingly rare false-positive patient would likely include a normal CD4 lymphocyte count and undetectable HIV RNA, suggesting that a false positive is indeed false.

An HIV test can provoke anxiety, even if the results turn out to be negative. Testing positive for HIV infection has the potential to precipitate bad outcomes, such as the relapse of substance use behavior or even suicide. However, few data describe the prevalence of these outcomes. Individuals might be discriminated against for being HIV positive or even for having been tested for HIV. This raises the question of whether testing should be done anonymously, particularly for those at low risk, for whom a negative result is expected. Alternatively, adopting a much more aggressive physician-initiated HIV testing approach might begin to normalize HIV testing itself.

The potential disadvantages of testing need to be balanced against the advantages. Treatment with effective antiretroviral agents can clearly improve individual health. Potential public health benefits are substantial—infectivity via sexual behavior or needle use and vertical transmission can be decreased. Finally, HIV testing combined with counseling has been shown to decrease high-risk sexual behavior both in the United States and abroad.

What are the triggers that should raise physician concern for HIV infection? As evident from the seroprevalence data listed in Table 1, a number of triggers are historical: alcohol dependence and cocaine abuse, including noninjection use; homelessness; or psychiatric hospitalization. Having unsafe sex with a partner who has any of the historical or clinical risks and whose HIV status is unknown is a trigger indicating that HIV testing is appropriate.

Many more triggers are clinical and can be divided into systemic indications (weight loss and unexplained lymphadenopathy), dermatological diseases (psoriasis or seborrheic dermatitis), any sexually transmitted disease, or other infections that occur more frequently among those with compromised immunity (community-acquired pneumonia, varicella zoster virus, tuberculosis, or recurrent vaginal candidiasis). If there is no recognition of HIV risk at the time of clinical presentation, there may not be another testing opportunity for years. Of course, these clinical syndromes often occur in individuals who are not infected and otherwise healthy. In addition, the reality about patients who are seen in episodic care sites, such as emergency departments and walk-in clinics, is that follow-up may be difficult. As important as it is for HIV testing to occur within the windows of opportunity that physician encounters represent, it remains crucial that testing occur with appropriate counseling and follow-up.

POLICY ISSUES

Cost and cost-effectiveness issues are also important in considering screening a low-prevalence population. Several studies in the literature have addressed this. McCarthy and colleagues suggest that screening a population with a prevalence for HIV infection of more than 0.5% had a cost-effectiveness ratio of less than $41 000 per year of life saved. Owens et al found a ratio of $47 000 per year of life saved at a prevalence of 1.0%. While these ratios are comparable or better than those for screening with Papanicolaou smears and mammograms ($184 500 per year of life saved and $45 700 per year of life saved, respectively). They are based on the use of zidovudine monotherapy. Human immunodeficiency virus care is now clearly both more expensive and more effective; early studies suggest that combination antiretroviral therapy is reasonably cost-effective. No studies have looked at the cost-effectiveness of screening when subsequent treatment includes current therapy; this is an important area for further research.

If we are going to recommend HIV testing for many more patients in primary care, urgent care, emergency departments, and hospitals, new systems are needed to facilitate testing. This may mean developing anonymous and confidential testing capabilities in more health care institutions and providing more support for counselors to see patients on the inpatient floors of hospitals with a higher prevalence of HIV infection. Maintaining the present US standard that informed consent is needed prior to any HIV testing is essential. A substantial effort needs to be made to identify those with undiagnosed HIV infection and to facilitate testing; this will require resources at the national level. Furthermore, it will be of crucial importance to develop systems that facilitate timely linkage to the care of those who test positive for HIV infection. These individuals, many of whom consider themselves at low risk, will need access to medical, nursing, mental health, and social services; these must be readily available at the time the HIV test results are given.

Finally, a cornerstone of the argument for HIV testing is the availability of effective therapy for HIV disease. However, this availability varies widely by state, particularly for those who are uninsured. In March 1999, Nebraska covered only 11 medications in its AIDS Drug Assistance Program while New York covered 218. Any increased testing effort must be accompanied by access to proven effective therapy for those who need it.

CONCLUSIONS AND FUTURE DIRECTIONS

Human immunodeficiency virus infection is a common disease for which highly effective and potent therapy is now available. However, the majority of those identified with HIV infection are tested late in the course of their disease. Many subgroups of patients in the United States have been identified with an HIV seroprevalence above 0.5% or 1.0%. The time has come for a reappraisal of the appropriate clinical threshold for HIV testing. Should HIV testing remain primarily diagnostic, or should HIV testing be construed as a legitimate screening test in a population with low but not negligible risk? In the latter paradigm, any patient with any historical or clinical sign that suggests an increased risk for HIV infec-
tion would be offered testing. As physicians, we must be vigilant to have a substantial impact on this continuing epidemic. The question at hand is, “Should we lower the clinical threshold for HIV testing?” We argue that the answer is yes and that the era of embracing a screening paradigm for HIV testing has arrived.

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Corresponding author: Kenneth A. Freedberg, MD, MSc, Clinical Economics Research Unit, Boston Medical Center, 91 E Concord St, Suite 200, Boston, MA 02118 (e-mail: kfreedbe@bu.edu).

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