CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will discuss the public health implications of diagnosing and treating human immunodeficiency virus infection

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Seek and treat: HIV update 2011

ABSTRACT

Although mortality rates from human immunodeficiency virus (HIV) infection have declined dramatically in the United States, the incidence of new infections has not improved for more than a decade. The case is now strong for routine screening and early treatment of HIV infection to reduce transmission of the infection and to give patients an opportunity to live a reasonably healthy life. Clinicians in all health care settings should routinely and matter-of-factly test their patients for HIV infection, just as they screen for other diseases.

KEY POINTS

Recommendations from the US Centers for Disease Control and Prevention call for routine HIV screening for all people ages 13 to 64 at least once regardless of their risk profile, and annual testing for people with known risk factors for acquiring HIV.

Early treatment of HIV infection may reduce the risk of cancer, cardiovascular disease, neurocognitive disorders, and osteoporotic fractures and improve the rate of survival compared with patients treated late in the course of HIV infection.

Finding and treating patients early in the course of infection has the potential to reduce infectivity in the community.

Reliable rapid testing is now available to screen for HIV in community settings, emergency departments, and public health clinics, and during labor for those not tested in the prenatal period. It is also useful when follow-up is uncertain.

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With early treatment of human immunodeficiency virus (HIV) infection, we can now expect patients to live a much longer life and, in some situations, have a near-normal lifespan.[1] Unfortunately, in screening for HIV infection, the United States lags behind many regions of the world, and infection is often not diagnosed until patients present with advanced disease, ie, the acquired immunodeficiency syndrome (AIDS). In this country there is a critical need to make HIV screening a routine part of medical care in all health settings in order to give patients their best chance for a healthy life, to prevent mother-to-child transmission, and to reduce the spread of HIV in the community.

HIV infection meets the criteria that justify routine screening, as laid out by the World Health Organization[2]:

- It is a serious health disorder that can be detected before symptoms develop
- Treatment is more beneficial if begun before symptoms develop
- Reliable, inexpensive, and acceptable screening tests exist
- The costs of screening are reasonable in relation to the anticipated benefits.

This article will review the epidemiology of the HIV epidemic, present the benefits of early treatment, and make the case for widely expanding screening for HIV infection in the US health care system.

HIV INFECTION CONTINUES TO BE A LARGE BURDEN

In 2008, an estimated 33.4 million people worldwide were HIV-positive. The vast majority of infected people—more than 22 million—live in sub-Saharan Africa.[3]

The United States has approximately 1.2 million cases.[4] Although this is a small pro-

portion of cases worldwide, it still represents a significant health care burden. In this country, the number of AIDS cases peaked in 1993, and the rate of deaths from AIDS began to decrease over the ensuing years as adequate therapy for HIV was developed. Standard therapy then and now consists of at least three drugs from two different classes.

Unfortunately, we have made little progress on the incidence of this disease. The estimated number of new HIV infections in the United States in 2008 was 56,000 and had remained about the same over the previous 15 years.[5,6] Because of improved rates of survival, the prevalence has risen steadily since the mid-1990s to the current estimate of 1.2 million persons living with HIV/AIDS in the US.

About 25% of people infected with HIV are unaware of it. This group accounts for more than half of all new infections annually, which highlights the importance of enhanced screening. Once people know they are infected, they tend to change their behavior and are less likely to spread the disease.[7]

The current state of HIV testing in the United States needs to improve

HIV disproportionately affects minority populations and gay men

Cases of HIV infection are reported among all age groups, although most patients tend to have been infected as young adults. Currently, the largest age group living with HIV is middle-aged. As this cohort grows older, an increasing burden of comorbidities due to aging can be expected. In 5 years, about half of the people with HIV in this country are expected to be 50 years of age or older. Although survival rates have steadily increased due to better treatment, survival tends to be shorter for older people newly diagnosed with HIV.

Worldwide, about an equal number of men and women are infected with HIV, but in the United States infected men outnumber women. In this country, about half the cases of HIV transmission among adults are by male-to-male sexual contact, about 30% are by high-risk heterosexual contact (ie, with a partner known to be HIV-infected or at high risk for being infected), and about 10% are by injection drug use.

In the United States, AIDS is predominantly and disproportionately a disease of minorities and those who live in poverty. African Americans account for the largest number of cases, followed by whites and then by Hispanics. Combined, African Americans and Hispanics account for two-thirds to three-fourths of all new cases, although they make up less than one-fourth of the US population. The incidence rate is nearly 137 per 100,000 for African Americans, 56 per 100,000 for Hispanics, and 19 per 100,000 for whites. The incidence is highest in New York and in the southeast, the geographic areas where the greatest number of minorities and people living in poverty reside. These groups also often lack access to health care.

HIV TREATMENT IS MORE EFFECTIVE IF STARTED EARLY

Treatment guidelines from the US Department of Health and Human Services (DHHS) have changed over the years. When effective medications were first introduced in the 1990s, the trend was to treat everyone as soon as they were diagnosed. As the burden of therapy began to unfold (side effects, cost, adherence, and drug resistance), the consensus was to wait until the CD4 T-cell count dropped to a lower level. As the medications have improved and have become better tolerated, the pendulum has swung back to treating earlier in the course of the disease. Currently, the DHHS recommends that therapy be started at CD4 counts of 350 cells/mL or lower (level of evidence: A1).[8] It also recommends therapy for CD4 counts between 350 and 500 cells/mL, but the level of evidence is lower.[8]

The CD4 T cell is the prime target of the HIV virus and also an important marker of the health of the immune system. The lower the CD4 count at the start of therapy, the more challenging it is to normalize.[9] If HIV infection is diagnosed early and therapy is started early, the likelihood is higher of normalizing the CD4 count and preserving immune function.

Progress is being made toward diagnosing HIV earlier. The CD4 count at presentation is increasing, but patients in the United States still present for care later than in other countries. In 1997, the median CD4 count at pre-

sentation was 234 cells/mL; in 2007, it was 327 (normal is about 550–1,000). Although this is a significant improvement, more than 50% of patients still have fewer than 350 cells/mL at presentation, which is the current threshold for beginning therapy, according to the most recent guidelines.[10]

Before triple therapy was available, almost all HIV-infected patients died of AIDS-related diseases. Now, about half of treated HIV-infected patients in Europe and North America die of other causes.[11] However, many diseases not previously attributed to AIDS are now also known to be exacerbated by HIV infection.

Cancer risk increases with lower CD4 counts

The cumulative incidence of AIDS-defining cancers (Kaposi sarcoma, non-Hodgkin lymphoma, cervical carcinoma) has decreased steadily from 8.7% in the 1980s to 6.4% during the years 1990 to 1995, and to 2.1% between 1996 and 2006. This is attributable to improved immune function as a result of treatment success with antiviral therapy.[12]

But the incidence of non-AIDS-defining cancers (Hodgkin disease, anal cancer, oral and respiratory cancers) has increased.[11] As therapy has regenerated the immune system, patients are surviving longer and are developing the more common cancers but with higher rates than in the general population.

Higher cancer risk is attributed to reduced immune surveillance. Many of these cancers are associated with viruses, such as human papillomavirus (anal and oral or pharyngeal cancers) and Epstein-Barr virus (Hodgkin disease), which can usually be controlled by a fully functioning immune system. The lower the CD4 count, the higher the risk of cancer, which highlights the need to diagnose HIV and start treatment early.[13]

Cardiovascular disease increases with lower CD4 counts

Associations have recently been identified between coronary disease and HIV as well as with HIV medications. Protease inhibitors tend to raise the levels of triglycerides, low-density lipoprotein cholesterol, and total cholesterol and increase the risk of heart attack.[14]

Regardless of therapy, HIV appears to be an independent risk factor for coronary disease. Arterial stiffness, as measured by carotid femoral pulse-wave velocity, was found to be increased among a sample of 80 HIV-infected men. This was associated with the usual risk factors of increasing age, blood pressure, and diabetes, as well as with lower nadir CD4 count.[15]

Fractures and neurocognitive disorders increase with HIV

Osteoporotic fractures are also more common in patients with HIV than in the general population. Risk factors include the traditional risks of older age, hepatitis C infection, diabetes, and substance abuse, but also nadir CD4 count less than 200.[16]

The risk of neurocognitive disorders is also associated with lower nadir CD4 counts. The lower the CD4 count, the higher the risk of developing neurocognitive deficits.[17] The potential benefits of earlier diagnosis and treatment are obvious based upon the multiple recent findings outlined above.

CLINICAL PRESENTATION OF PRIMARY HIV INFECTION

Screening for HIV infection in the United States lags behind that of many areas of the world, even some developing nations

During primary HIV infection, when patients are first infected, 50% to 90% are symptomatic. Symptoms usually appear in the first 6 weeks. The viral load tends to be highest at this time. Higher viral loads appear directly correlated with the degree of infectivity, highlighting the urgency of finding and treating new infections promptly to help avoid transmission to others.[18]

The clinical picture during primary infection is similar to that of acute mononucleosis. Signs and symptoms include fever, fatigue, rash, headache, lymphadenopathy, sore throat, and muscle aches. Although this presentation is common to many viral infections, questioning the patient about high-risk behavior (unprotected sex, multiple partners, intravenous drug use) will lead the astute physician to the correct testing and diagnosis.

Other early manifestations include mucocutaneous signs, such as seborrheic dermatitis, psoriasis, folliculitis, and thrush. Laboratory test results demonstrating leukopenia, throm-

bocytopenia, elevated total protein levels, proteinuria, and transaminitis are also suggestive of HIV infection.

THE CASE FOR INCREASED TESTING AND TREATMENT

The estimated prevalence of HIV in the United States is approximately 0.3%. However, its prevalence in Washington, DC, is 3%, which rivals rates in some areas of the developing world. From 2004 to 2008, health officials made a concerted effort in Washington, DC, to screen more people, particularly those at high risk. The number of publicly funded HIV tests performed increased by a factor of 3.7, and the number of newly reported cases increased by 17%. There was also a significant increase in the median CD4 count at the time of HIV diagnosis and a significant delay in time to progression to AIDS after HIV diagnosis.[19]

A study in British Columbia expanded access to highly active antiretroviral therapy during 2004 through 2009. High-risk individuals were targeted for increased screening. All those diagnosed with HIV were provided free medication. This resulted in a 50% reduction in new diagnoses of HIV infection throughout the community, especially among injectable drug users, a usually marginalized population. The proportion of patients with HIV-1 RNA levels above 1,500 copies/mL fell from about 50% to about 20%, indicating that the viral load—a measure of infectivity throughout the community—was reduced. Interestingly, this trend occurred during a time of increased rates of gonorrhea, syphilis, and other sexually transmitted diseases known to be associated with enhanced HIV transmission.[20]

About 25% of people infected with HIV are unaware of it

In Africa, antiretroviral therapy was offered to discordant couples (one partner was infected with HIV and the other was not). Among those who chose therapy, the rate of HIV transmission was 92% lower than in those not receiving antiretroviral drugs,[21] once again demonstrating that control of HIV by treatment can lead to decreased transmission.

US HIV testing is inadequate

The current state of HIV testing in the United States needs to be improved. Testing is not performed routinely, leading to delayed diagnosis when patients present with symptomatic, advanced disease. Patients who are tested late (within 12 months before being diagnosed with AIDS) tend to be younger and less educated and are more likely to be heterosexual and either African American or Hispanic than patients who are tested earlier.[22] When retrospectively evaluated, these patients often have been in the health care system but not tested. Routine universal screening and targeted testing could lead to a much earlier diagnosis and potential better long-term outcomes.

A 1996 survey of 95 academic emergency departments found that for patients with suspected sexually transmitted infections, 93% of physicians said they screen for gonorrhea, 88% for *Chlamydia* infection, 58% for syphilis, but only 3% for HIV.[23] Sexually transmitted infections and HIV are often transmitted together.

A similar 2002 survey of 154 emergency department providers who saw an average of 13 patients with sexually transmitted infections per week found that only 10% always recommend HIV testing to these patients. Reasons given for not testing were concern about follow-up (51%), not having a "certified" counselor (45%), HIV testing being too time-consuming (19%), and HIV testing being unavailable (27%).[24]

Although most HIV tests are given by private doctors and health maintenance organizations, the likelihood of finding patients with HIV is greatest in hospitals, emergency departments, outpatient clinics, and public community clinics.

The Advancing HIV Prevention initiative of the US Centers for Disease Control and Prevention (CDC) has four priorities:

- To make voluntary HIV testing a routine part of medical care
- To implement new models for diagnosing HIV infection outside medical settings
- To prevent HIV infection by working with patients with HIV and their partners
- To further decrease the rate of perinatal HIV transmission.

Rapid tests for HIV are available

There is a public health need to have rapid HIV testing available in all health care settings. With standard HIV tests, which

can take 48 to 72 hours to run, about one-third of patients do not return for results. Subsequently locating them can be a huge challenge and is sometimes impossible. The ability to have rapid test results can improve this situation. It is especially important in prenatal care settings, where the mother can be immediately treated to reduce the risk of transmission to the child. Rapid testing increases the feasibility of testing in multiple venues, particularly acute-care settings with almost immediate results and linkage to care.

Several rapid tests are available and can be performed on whole blood, serum, plasma, and oral fluid. The tests provide reliable results in minutes, with 99% sensitivity and specificity. Positive results must be confirmed by subsequent two-stage laboratory testing, enzyme-linked immunosorbent assay, and Western blot. Patients who have negative or have indeterminate results on Western blot testing should be tested again after 4 weeks.

The cost-effectiveness of routine screening for HIV, even in populations with a low prevalence, is similar to that of commonly accepted interventions.[25] In populations with a 1% prevalence of HIV, the cost is $15,078 per quality-adjusted life-year.[26] Even if the prevalence is less than 0.05%, the cost is less than $50,000 per quality-adjusted life-year, which is normally the cutoff for acceptability for screening tests.[25,26]

'OPT-OUT' TESTING

In the past, patients were asked if they would like to have HIV testing ("opt-in" testing). It is now recommended that physicians request testing to be performed ("opt-out" testing). This still allows the patient to decline but also conveys a "matter of fact" nonjudgmental message, indicative of a routine procedure no different than other screening tests. When testing was done on an opt-in basis, only 35% of pregnant women agreed to be tested. Some women felt that accepting an HIV test indicated that they engage in high-risk behavior. When testing was instead offered as routine but with an opportunity to decline, 88% accepted testing, and they were significantly less anxious about testing.[27]

CDC RECOMMENDATIONS

The CDC now recommends that routine, voluntary HIV screening be done for all persons ages 13 to 64 in health care settings, regardless of risk.[28] Screening should be repeated at least annually in persons with known risk. Screening should be done on an opt-out basis, with the opportunity to ask questions and the option to decline. Consent for HIV testing should be included with general consent for care. A separate signed informed consent is not recommended, and verbal consent can merely be documented in the medical record. Prevention counseling in conjunction with HIV screening in health care settings is not required.

Testing should be done in all health care settings, including primary care settings, inpatient services, emergency departments, urgent care clinics, and sexually transmitted disease clinics. Test results should be communicated in the same manner as other diagnostic and screening care. Clinical HIV care should be available onsite or reliable referral to qualified providers should be established.

For pregnant women, the CDC recommends universal opt-out HIV screening, with HIV testing as part of the routine panel of prenatal screening tests. The consent for prenatal care includes HIV testing, with notification and the option to decline. Women should be tested again in the third trimester if they are known to be at risk for HIV, and in areas and health care facilities in which the prevalence of HIV is high.

The clinical picture of acute HIV infection is similar to acute mononucleosis

In women whose HIV status is undocumented in labor and delivery, opt-out rapid testing should be performed, and antiretroviral prophylaxis should be given on the basis of the rapid test result. Rapid testing of the newborn is recommended if the mother's status is unknown at delivery, and antiretroviral prophylaxis should be started within 12 hours of birth on the basis of the rapid test result.

Widespread routine screening and earlier treatment could significantly reduce the incidence and improve the outcomes of HIV in this country. Health care providers are encouraged to adopt these practices. ■

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