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An Evidence-Based Approach To Infectious Disease

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An Evidence-Based Approach To Infectious Disease

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Goals & Objectives: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

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Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

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The Emergency Medicine Practice Clinical Excellence Series Volume VI

An Evidence-Based Approach To Infectious Disease

It is with great pleasure that we bring to you Volume VI of the *Emergency Medicine Practice Clinical Excellence Series*: *An Evidence-Based Approach To Infectious Disease.* We hope these select articles will engage you in a critical and clinically relevant look at several very interesting topics.

The 4 articles included in this volume update the extensive research and discussion on the diagnosis and management of several infectious disease topics from past issues of *Emergency Medicine Practice*, with all-new recommendations and analysis. In addition to the over 500 original references, 86 new references will bring you up to date on the latest research and guidelines in the field, with distinct, underlined paragraphs indicating the new research and commentary. The list of new references is numbered separately to make further research easier.

The topics for this volume include the diagnostic and therapeutic strategies for ED management of the febrile child, pharyngitis, and HIV-related diseases. The fourth chapter on antibiotics usage in the ED will certainly inform and impact the practice of all emergency clinicians. We believe these selections will stimulate thought-provoking discussion and aid in clinical decision-making.

Since 1999, *Emergency Medicine Practice* has been exceptional in its evidence-based approach to emergency medicine. It seeks to provide the etiology and pathophysiology behind a topic, as well as the full spectrum of literature and evidence on the topic, and to present it in a readable and clinically relevant way. This differs from the many management guidelines, consensus statements, and analyses that do not illuminate the critical thinking and evidence behind the recommendations.

Over the years, I have appreciated reading *Emergency Medicine Practice* because of its unique mission in reviewing "hot" topics in emergency medicine, written from an emergency physician's perspective. I hope you enjoy this volume of *The Emergency Medicine Practice Clinical Excellence Series*. I also hope that you will consider and enjoy the future volumes in this series.

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HIV-Related Illnesses: The Challenge Of Emergency Department Management

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CME Objectives

Upon completing this article, you should be able to:

1. Assess a patient's risk of being infected with HIV, describe the importance of the CD4 count in determining the stage of infection, and evaluate the risk of infection with opportunistic pathogens.
2. Describe the most common CNS, gastrointestinal, and respiratory complications of HIV-associated disease as well as their proper evaluation and treatment.
3. Evaluate and manage the febrile AIDS patient.
4. Describe the most common side effects and toxicities of drugs used to treat HIV infection and AIDS.

Date of original release: January 2, 2002
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The triage note is innocuous enough—"fever for 1 week"—but when you walk into the room, you realize something else is going on. This young man is cachetic with thinning hair, and his spindly arms are crusted with an awful rash. As he speaks, you notice ominous white patches covering his tongue. His voice rasps, "Doc, can you help me? I think I have a virus."

Patients infected with the human immunodeficiency virus (HIV) present unique challenges for the Emergency Department (ED) clinician. Many are asymptomatic and are at no special risk for unusual diseases. However, those who progress to AIDS are susceptible to a wide range of both typically encountered and opportunistic infections. Furthermore, the therapies themselves are often associated with significant complications and morbidity in persons infected with HIV.

Many of those infected with HIV are unaware of their serologic status. For this reason, it is important to consider the possibility of HIV-related illness in anyone presenting with complaints suggestive of infection.

For patients known or suspected to have HIV infection, determining the degree of immunosuppression will help the ED clinician evaluate the risk for opportunistic disease. HIV-infected patients may report vague constitutional symptoms such as fever, weight loss, and fatigue. Others have complaints localized to a specific organ system or area — pulmonary, neurologic, abdominal, head and neck, dermatologic, or psychiatric.[1] Infections of the lung and central nervous system (CNS) are the most common illnesses identified in HIV-positive patients who present to the ED.

Because AIDS-related infections tend to present atypically or with subtle findings, a high index of suspicion and an aggressive approach to diagnosis are crucial for successful management. Although AIDS-related infections often cannot be cured, many can be successfully treated in the short term, and perhaps controlled over the long term, using suppressive therapy.

Clinicians may be intimidated by the daunting array of diseases associated with HIV infection, as well as by the dizzying pace of new developments. But fear not! This article is intended to provide indispensable insights about how to manage the common complications of HIV infection seen in the ED.

Epidemiology

The earliest known HIV infection was discovered in a stored blood plasma sample dating from 1959. The victim, from Leopoldville (now Kinshasa), in the Democratic Republic of Congo, puzzled local physicians with his symptoms. While they were unable to save him, they did save his blood—which decades later proved to harbor HIV.[2] Computer models suggest that the epidemic may have begun in central West Africa around 1930.[3] The early origins of human infection are shrouded in controversy; one theory suggests transmission of a simian AIDS virus via cuts on the hands of human hunters, while another suggests unsanitary immunization practices.[4,5]

The first report of AIDS in the United States was in June of 1981 and involved 5 cases of unexplained immune deficiency in homosexual men in Los Angeles. From there, the epidemic exploded until, by the end of 2000, 774,467 Americans had met the case definition for the disease. In 2000, the Centers for Disease Control and Prevention (CDC) estimated that 650,000-900,000 Americans were infected with HIV, and over 320,000 had AIDS.[6] At the end of 2003, according to the CDC, an estimated 1,039,000 to 1,185,000 persons in the US were living with HIV/AIDS.[i] The CDC es-

timated in 2006 that there would be 56,300 new cases, both diagnosed and undiagnosed.

The dynamic of the epidemic has changed dramatically since the advent of highly active antiretroviral therapy (HAART), which includes protease inhibitors and other new agents in multidrug regimens. Although the rate at which new cases of HIV infection come to light has remained steady at about 40,000 per year, the death rate has dropped significantly (declines of 50% in 1997 and 21% in 1998).[7,8] This decrease in mortality has held steady in the first decade of the 21st century. Yet for some segments of the population, particularly Hispanics and African-Americans, the rates of infection are increasing. In 2006, the CDC found that although African-Americans make up only 13% of the population, they account for almost half the diagnoses.[ii] Heterosexual contact is the fastest-growing category of HIV transmission in the US.

The local prevalence of HIV infection may vary widely, from nearly 0% in some rural locales to over 10% in some inner-city hospital EDs, with an average of 0.56% for the US population as a whole.[9,10] The prevalence of HIV seen in the ED is steadily growing. A retrospective study conducted in 2 urban hospitals indicated that at least 4% of patients who presented to the ED were HIV-seropositive and 14% of all admissions were found to be seropositive. Since an unspecified number of patients are not aware of their HIV status, the prevalence of HIV-seropositivity in the ED is probably even higher.[iii]

Pathophysiology And Natural History

Initial Response To HIV

The mechanism for immune destruction by HIV is complex and remains the focus of intense investigation. The virus gains entrance into the target cell after binding with the CD4 receptor and 1 of several chemokine receptors. Complex protein interactions fuse the viral capsule and the cell membrane.[12] Although the CD4+ T lymphocyte (also known as the T helper cell) is the primary target, any cell expressing this receptor is susceptible to infection.

During the first 4 to 6 weeks of infection, the number of viral particles soars, and the virus disseminates throughout the circulation and lymphoid tissue. It is estimated that 55% to 92% of patients experience the acute retroviral syndrome — a mononucleosis-like illness characterized by fever and generalized lymphadenopathy. Patients may also develop pharyngitis, rash, myalgias, headache, nausea, and diarrhea.[13,14]

As the body generates an immune response to the virus, the viral load falls and a variable period of clinical latency ensues. During this stage, the CD4 count exceeds 500/mm^3. Opportunistic infections are rare, but patients may present with generalized lymphadenopathy or aseptic meningitis. The latency period may last 2 to 10 years or more, but despite the paucity of symptoms, levels of CD4+ cells decline. This depletion is due to both virus-mediated cell destruction and inhibition of normal T cell production.[15] Eventually, the loss of CD4+ cells and the resulting immunodeficiency permit infection from an opportunistic pathogen. At this stage of HIV infection — defined as AIDS — the viral load climbs steadily, and in the absence of therapy, clinical decline is inexorable. Once this stage is reached, the median survival is 9 to 12 months if the patient remains untreated.[16,17]

"Fear and ignorance about AIDS can so weaken people's senses as to make them susceptible to an equally virulent threat: bigotry."
—"AIDS and the New Apartheid,"
New York Times *Editorial, October 7, 1985*

Specific CD4 Levels

A patient with a reduced CD4 count of 200 to 500/mm^3 may develop lymphadenopathy, oral candidiasis, idiopathic thrombocytopenic purpura, or hairy leukoplakia. This stage also predisposes the patient to more virulent pathogens, such as *Mycobacterium tuberculosis* or *Streptococcus pneumoniae.*[18] Antiretroviral drugs are generally indicated for this degree of immunosuppression.

A CD4 count less than 200/mm^3 leads to more advanced disease. It is important to identify patients in this category, because they are at much higher risk of opportunistic infections, including *Pneumocystis* pneumonia (PCP), tuberculosis (TB), toxoplasmosis, cryptosporidiosis, isosporiasis, esophageal candidiasis, cryptococcosis, and histoplasmosis. [Note: although the name of the *Pneumocystis carinii* bacterium has changed to *Pneumocystis jiroveci,* the disease is typically referred to as "PCP."] Disseminated Mycobacterium avium complex (MAC) or cytomegalovirus (CMV) infection tend to occur in patients with CD4 counts below 50/mm^3.

Patients who report a previous opportunistic infection have, at some point, reached a critical CD4 nadir. At this stage they require both antiretroviral therapy and prophylaxis against opportunistic infections. An exception to this, however, is those in whom immune reconstitution has been successful — that is, their CD4 count has risen to above 200/mm^3. Such patients will continue antiretroviral therapy but may discontinue PCP prophylaxis.[19,iv]

Prehospital Care

The response of emergency medical service (EMS) units to a patient with HIV infection or AIDS should be no different than for an uninfected individual. Usually, the EMS personnel will be unaware of the

patient's serologic status (as might the patients themselves). EMS personnel should wear gloves and place a mask on patients who have a cough. Very little literature has been published that directly addresses prehospital care of the HIV-infected patient.

ED Evaluation

History

One of the most valuable questions an ED clinician can ask when faced with a febrile patient who has a cough or constitutional symptoms is: "Have you ever been tested for the AIDS virus?" Up to 30% of HIV patients may not spontaneously disclose such information when seeking medical care.[20] On the other hand, many HIV-infected people in the US are unaware of their serologic status. Unrecognized HIV infection is common in the ED, especially among women and the elderly.[21,22] A recent published study also found that subjects who were higher risk for HIV based on sexual preference (such as men who have sex with men [MSM]) were reluctant to disclose such behavior even when asked about it by their own physicians.[v] Blacks and Hispanics were more reluctant than whites to report their behavior to their physicians. Amazingly, a small percentage of patients who claim to have AIDS may, in fact, be HIV-negative. The deception may be engineered in order to receive preferential treatment with regard to housing, disability payments, prescription drugs, or medical care.[23]

Factors associated with an increased risk of HIV infection include men who have sex with men, injection drug use, prostitution, heterosexual exposure to a partner at risk, and exposure to a blood product in the US prior to 1985. Children born of mothers in such groups are also at risk. Because the number of people who fall into 1 or more of the high-risk groups is still a fairly small proportion of the general population, identification of risk factors remains important. However, as the epidemiology of HIV transmission continues to evolve and heterosexual transmission becomes more common, risk factor determination may become less useful.

ED clinicians should question patients about HIV risk factors if they present with signs and symptoms suggestive of infectious disease, especially respiratory illness, fever, headaches, diarrhea, and rashes. Possible risk factors in sexual partners are germane. Although some patients may hesitate to answer questions about such personal matters as sexuality and drug use, most will make an honest disclosure when questions are asked in a straightforward, nonjudgmental manner.[24]

If HIV infection is known or suspected, the next step is to try to determine the stage of the disease. The expected complications of HIV infection vary depending on the phase of the infection, and the ED clinician should inquire about prior hospitalizations or complications. (**See Table 1.**)

In the evaluation of patients known to be seropositive, the CD4 count can provide valuable insight into the stage of HIV disease and the risk of opportunistic infection. Any patient who reports a previous opportunistic infection has, at some point, had a CD4 count below 200/mm^3. Some patients may be able to report their latest CD4 count and when it was obtained. Those less medically sophisticated or lacking ready access to medical care may have no idea about their CD4 count. If the patient is receiving regular medical care, the list of medications may also suggest the stage of his or her disease.

Physical Examination

In addition to a careful and compassionate history, an appropriate physical examination is essential. The only study to address the sensitivity of the physical examination to detect HIV infection was conducted among infants.[25] However, cohort studies show that certain physical findings provide important clues to HIV-related infections.

Many patients in the advanced stages of AIDS can be identified by a "doorway diagnosis." Look to the general appearance of a patient for specific indications. Wasting (malnutrition) and lipodystrophy (caused by a combination of antiretroviral therapy, the infection itself, and immune reconstruction due to therapy) are the 2 major nutritional alterations in HIV infection, and temporal wasting and parietal hair loss are common manifestations.[26] Recent studies suggest that the wasting and lipodystrophy are reversible, but treatment is expensive and may be prohibitive for many HIV-infected persons.[vi]

Before embarking on the physical examination, the ED clinician should determine whether the patient is in respiratory distress and take appropriate steps to alleviate this problem.

During the oral examination, pay special attention to the presence of candidiasis or hairy leukoplakia, because in a patient with a fever these findings would suggests an HIV-related illness. Patients with oral lesions tend to have low CD4 counts and rapid progression of the disease (especially when they

Table 1. Staging Of HIV Disease

Stage	Clinical Appearance	CD4 Count
Acute	Mono-like syndrome	Normal
Early	Asymptomatic or lymphadenopathy, aseptic meningitis, skin disease	> 500/mm^3
Middle	Asymptomatic or lymphadenopathy, thrush, idiopathic thrombocytopenic purpura, hairy leukoplakia	200-500/mm^3
Late	Opportunistic infections, malignancy, dementia, wasting	< 200/mm^3

remain untreated).[27,28] Thrush does not necessarily equal AIDS; however, other causes for oral candidiasis include uncontrolled diabetes, recent antibiotic or inhaled steroid use, and chemotherapy.

While the lung examination may reveal rales or other signs of pulmonary disease, many patients with PCP pneumonia will have clear breath sounds. In addition to traditional auscultation, there is another useful test known as *auscultatory percussion.* To perform this maneuver, place the diaphragm of the stethoscope on the posterior chest of the patient, and lightly tap the manubrium with the tip of the index or middle finger. Compare the sounds in opposite sides of the posterior chest, taking care that the stethoscope is placed in the same interspace on the right and left sides. Differences in the quality, pitch, duration, or intensity of breath sounds suggest lung pathology. In 1 study of HIV-positive patients, auscultatory percussion was more predictive (sensitivity = 51.0%-69.6%) of chest x-ray abnormalities than was standard percussion or traditional auscultation.[29] However, the physical examination should be conducted with the knowledge that the traditional chest physical examination is highly inaccurate in the detection of pneumonia even in HIV-seronegative patients.[vii] In addition, these studies were conducted in ideal conditions away from the sometimes chaotic environment of the ED. Therefore, the most reasonable approach to the HIV-positive patient with a pulmonary complaint is auscultation, after which a chest film should be obtained regardless of the physical findings.

Other notable findings include generalized lymphadenopathy, Kaposi's sarcoma (raised, purplish skin lesions), severe persistent dermatosis, and "track marks" from injection drug use. Seborrheic dermatitis, onychomycosis, herpes simplex, widespread scabies, alopecia, and rashes from systemic mycoses are common in HIV disease. Any underlying chronic dermatologic condition (eg, psoriasis, seborrhea, eczema) may become exacerbated as immunosuppression progresses. Both HIV infection and the medications used to treat it may cause neuropathy, manifested as sensory loss or abnormal reflexes.

Primary HIV Infection

Some believe it is important to diagnose acute retroviral syndrome because intervention with antiretroviral treatment during this stage may improve the long-term course of HIV infection. However, this improvement seems to be short-lived.[30,31] As previously mentioned, 55% to 92% of patients initially exposed to HIV experience the acute retroviral syndrome, a mononucleosis-like illness with fever and generalized lymphadenopathy. In patients with more severe symptoms at the time of seroconversion, the disease progresses more rapidly.[32] Patients who present with compatible symptoms may be questioned about HIV risk factors, and those with likely exposure should be tested or referred for testing.

The HIV antibody test that is usually done to diagnose HIV infection is typically negative during the acute retroviral stage (the standard ELISA test requires a mean of 27 days after exposure to become positive).[33] Diagnosis at this stage would require testing for the p24 antigen or detecting HIV viral RNA directly. Not every patient with nonspecific viral symptoms warrants p24 testing. Determining which patients are at sufficiently high risk depends on the results of the history and physical examination. What is imperative, though, is educating the patient about the benefits of early testing involving HIV/AIDS.

"AIDS was ... an illness in stages, a very long flight of steps that led assuredly to death, but whose every step represented a unique apprenticeship. It was a disease that gave death time to live and its victims time to die, time to discover time, and in the end to discover life."
— Hervé Guibert, French writer (1955–1991)

Fever In HIV-Infected Patients

Etiology Of Fever In HIV-Infected Patients

HIV-infected patients commonly present with fever, which can pose a diagnostic challenge for the ED clinician. The differential diagnosis in such cases is broad and includes potentially life-threatening infections.[34] (**See Table 2.**) In addition, in this era of globalization and ease of international travel, disease entities usually seen in the more remote areas of the planet must be considered.[viii]

Fever is common in the patient who is HIV-seropositive. In 1 prospective study of 176 patients with advanced HIV, almost half had an episode of fever over a 9-month period, and a specific etiology for the fever was determined in 83% of these cases. Lung infection accounted for more than 25%, while CNS infection accounted for more than 10%. Other common etiologies included disseminated MAC, peripherally inserted central catheter line infection, sinusitis, and drug reaction. (**See Table 2.**) When the patients' fever required more than 2 weeks to diagnose, the most common etiologies were lymphoma, *Mycobacterium avium–intracellulare* bacteremia, and PCP.[35]

History And Physical Examination For HIV-Infected Patients With Fever

The history and physical examination will provide important clues to the etiology of the fever. First, determine how long or how often the patient has had fever. Prolonged fever is less likely to represent a treatable emergency. Ask about cough or shortness of breath. A new or worsening headache or neuro-

To read the rest of this chapter (including clinical pathways, treatment recommendations, risk management pitfalls to avoid, and additional ED management considerations) as well as the 3 additional chapters included in this resource, please order your copy today at www.ebmedicine.net/IDbook.

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