Evaluation And Treatment Of AIDS-Associated Illnesses: An Approach For The Primary Physician

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Abstract: The acquired immunodeficiency syndrome (AIDS) has become a problem of enormous clinical importance in the United States. This article describes the major clinical syndromes in adults with AIDS and offers approaches to their evaluation and treatment. (JABFP 1988; 1:112-30.)

The staggering morbidity and mortality of the acquired immunodeficiency syndrome (AIDS) and serious concern about transmission of the human immunodeficiency virus (HIV) are issues of major importance for most Americans and their health care providers. Today, only a few years after AIDS first appeared, our understanding of this disease is quite extensive. Considerable clarity has emerged regarding high-risk groups, routes of transmission, and antibody testing.[1-5] Guidelines have been developed for education and counselling of the public and for prevention of transmission in the health care setting.[5-6] The case definition of AIDS has been refined,[7] a classification system for HIV infections has been established,[8] and many investigational and standard therapies have been developed.[9-10]

This article focuses on the evaluation and treatment of a wide variety of illnesses in the AIDS patient. As this epidemic continues its rapid growth, an increasing number of physicians will be involved in the direct care of patients with AIDS. Although specific consultations are often required, most of the management of patients with AIDS can be accomplished by the primary physician, whose relationship with the patient and family is crucial during periods of health, illness, and during the dying process. The optimal approach emphasizes those investigations and therapeutic options that incur significant benefits while avoiding those exhaustive investigations that may identify conditions for which specific therapies are not available or effective.

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Screening for AIDS

There are no screening tests that identify an individual as having clinical AIDS. The presence of antibody to HIV usually indicates prior exposure to the virus but does not in itself diagnose AIDS. The definitive diagnosis is made by the occurrence of specific conditions defined by the Centers for Disease Control,[7] including opportunistic infections and malignancies. Low lymphocyte counts, abnormal helper:suppressor ratios, and intradermal skin test anergy are found in other conditions and are not by themselves diagnostic of AIDS. Individuals with antibody positivity in the presence of conditions such as oral candidiasis or hairy leukoplakia and extrainguinal adenopathy are considered to have "AIDS-related complex" or "ARC."

If there is concern about AIDS on the part of the patient or the physician, a complete history, physical examination, and basic laboratory tests, including complete blood count with platelet count, VDRL, urinalysis, tuberculin skin test, and chest roentgenogram, should be performed. Further testing is not routinely required in the asymptomatic patient.

Special Considerations in AIDS

Evaluation and treatment of AIDS-associated illnesses cannot be compared with traditional medical management. Most infections and malignancies are less responsive to therapy than similar infections in patients with intact immune systems. The infectious complications tend to be reactivations of latent infections, although primary infections (e.g., bacterial pneumonia) responsive to standard antimicrobial therapy also occur. Simultaneous opportunistic infections and malignancies as well as multisystem involvement are the rule rather than the exception. For example, a patient may present with *Pneumocystis carinii* pneumonia (PCP), oral candidiasis, and Kaposi's sarcoma of the skin and lung. Drug toxicities also occur more frequently than in non-AIDS patients. Prognosis and survival of AIDS patients appear to be best correlated with the overall degree of illness rather than with any one individual infection or malignancy.

Antiviral therapy against HIV with zidovudine (AZT) may be considered for (1) patients with AIDS who have a history of *Pneumocystis carinii* pneumonia, and (2) patients with AIDS or advanced AIDS-related conditions with T4 (helper/inducer) lymphocyte counts fewer than 200 cells/μL. Initial studies of this drug show significant temporary immunologic and clinical improvement with modest prolongation of life.[11,12] Because zidovudine causes severe anemia, bone marrow depression, and other toxicities,[13] it is advisable to use it primarily in patients in a "well" period and to consider using it cautiously with other marrow-suppressing agents commonly used in the treatment of AIDS-related illnesses (Table 1). It is not clear whether benefits of zidovudine outweigh its toxicity in milder forms of HIV infection.

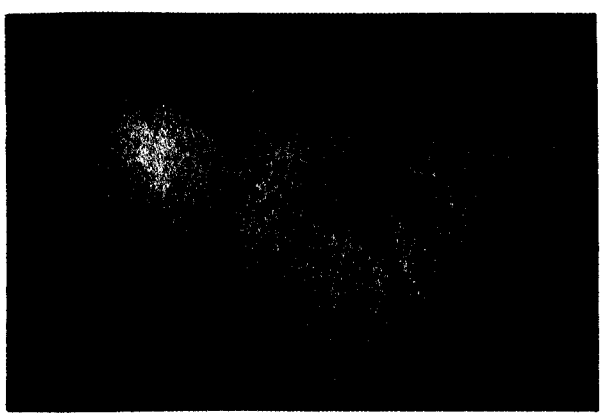

Figure 1. Kaposi's sarcoma in a necklace distribution.

Figure 2. Kaposi's sarcoma behind the ear.

General Symptoms and Signs

Nonspecific and multifactorial symptoms and signs such as weakness, malaise, anorexia, weight loss, fever, tachypnea, tachycardia, and hypotension are nearly universal in AIDS. HIV infection itself may be responsible. Bacteremias,[14-17] fungemias,[17-21] mycobacteremias,[22,23] and viremias[24,25] may account for some of these constitutional findings. Standard antimicrobial therapy may be effective, especially for bacteremias and fungemias. Salmonella and cryptococcal septicemias, however, tend to be persistent or recurrent and require chronic suppressive therapy. *Mycobacterium avium-intracellulare* (MAI) sepsis is continuous (often for many months) and responds poorly to antimicrobial therapy.

Many patients have persistent fevers without an identifiable cause. Periodic evaluation is required, with special attention directed toward identifying pulmonary pathogens. Bone marrow examination or computed tomographic (CT) scans of the abdomen or chest may reveal infectious or malignant processes. However, specific causes of the persistent fevers may not be found. It is likely that ongoing HIV or other viral infec-

Table 1. *Treatment Regimens for AIDS.*

System & Organism	Drug Regimen	Duration	Common Adverse Effects	Comments
General				
HIV	Zidovudine (AZT) (Retrovir™) 200 mg po q 4 hrs. Decrease dose to 100 mg po q 4 hrs if Hgb = 6.8–8.0 g/dl or absolute neutrophil count (ANC) = 500–750 cells/μL. Discontinue drug if Hgb<6.0 g/dl or ANC<500 cells/μL	Indefinitely?	Anemia, granulocytopenia, thrombocytopenia, headache, nausea, myalgias; insomnia; long-term effects unknown. Drug interactions: Tylenol™ administration may increase incidence of bone marrow suppression.	Consider in "well" patients with AIDS or ARC with T4<200 cubic mm, or after initial, treated episode of PCP. No data on long-term administration or in AIDS patients with multiple opportunistic infections or Kaposi's sarcoma. Transfusions may be necessary for anemia. Monitoring is required when given with other bone marrow suppressive drugs to avoid cumulative toxicity.
Cytomegalovirus (CMV)	Ganciclovir (DHPG) Initial: 2.5 mg/kg IV q 8 hrs or 5 mg/kg IV q 12 hrs (Investigational)	10–14 days for acute infection	Neutropenia, leukopenia, renal failure, hepatic failure, anemia, phlebitis, rash, thrombocytopenia, nausea. Dosage needs to be adjusted in renal dysfunction (CrCl<25 cc/min) and in severe neutropenia (ANC<1000 cells/μL).	Effective in treatment of retinitis, GI tract (colitis, proctitis, and esophagitis). Not clearly effective in pulmonary disease. Lifelong suppression therapy required to prevent recurrence.
	Maintenance: 2.5–5 mg/kg qd	Daily maintenance infusions 5–7 times/week	Discontinue therapy if ANC is <500 cells/μL.	
Skin/Mucocutaneous				
Herpes simplex/zoster	Acute: Acyclovir (Zovirax™) 200–800 mg po 5 times/day	7–10 days	Oral: Nausea, vomiting, diarrhea, dizziness.	Chronic maintenance therapy may be necessary to prevent recurrence. IV acyclovir required for extensive and persistent disease. Topical acyclovir ineffective for most episodes.
	Maintenance: Acyclovir 200–400 mg po tid	Indefinitely		
Extensive or persistent herpes infection	Acyclovir 5 mg/kg/dose (h. simplex) or 10 mg/kg/dose (h. zoster) IV q 8 hrs	5–7 days	IV: lethargy, tremors, confusion, hallucinations; phlebitis; increased serum creatinine; reversible crystalline nephropathy.	Severe herpes infections (e.g., esophagitis, colitis, encephalitis) require IV acyclovir.
Oral Cavity/ Esophageal				
Candida Albicans	Clotrimazole (Mycelex™) troches 10 mg dissolved slowly in mouth 5 times/day	Until resolved; maintenance usually required	Unpleasant taste, nausea, vomiting; minimal toxicity. Abnormal liver function tests.	Improvement seen within 7 days. Chronic suppression required. Clotrimazole or nystatin initially for oral thrush. Ketoconazole recommended for clotrimazole/nystatin failure and/or esophageal candidiasis.

	OR			
	Nystatin (Mycostatin™) 100,000 units/mL. Swish & swallow 5 mL po q 6 hrs or vaginal tabs 500 mg dissolved slowly in mouth q 6 hrs	Same	Large oral doses can produce diarrhea, nausea, vomiting.	
	OR			
	Ketoconazole (Nizoral™) 400 mg po qd	Same	Nausea; hepatocellular toxicity; anaphylaxis, urticaria. Higher doses can suppress testosterone levels.	Need acid media to be effective; avoid antacids.
	Amphotericin B 0.3–0.4 mg/kg IV qd	10 days	See under Cryptococcus for adverse effects.	Candidal esophagitis unresponsive to oral ketoconazole requires low dose amphotericin B.
Pulmonary				
Pneumocystis carinii	Trimethoprim-Sulfamethoxazole (TMP-SMX) (Septra™, Bactrim™) 20 mg TMP/100 mg SMX per kg daily given in 4 doses po or over 1–2 hr IV infusion. Lower doses (15 mg TMP/75 mg SMX per kg daily) may be effective and less toxic (investigational).	Treat for 21 days (minimum of 14 days) po/IV equally effective	Adverse effects commonly appear between 7–14 days in over 50% of patients.	Hospitalization recommended initially to monitor clinical course and drug toxicities.
			Rashes: maculopapular, exfoliative, Stevens-Johnson.	Mild rash does not necessitate stopping or changing treatment; institute antihistamine.
			Hematological: neutropenia, thrombocytopenia, anemia.	If absolute neutrophil is less than 800 cells/μL OR if platelets less than 30,000, switch to pentamidine.
			GI: nausea/vomiting; toxic hepatitis.	Pretreatment with lorazepam, prochlorperazine, or meclopropamide to reduce nausea. Nausea may be less with po TMP-SMX. Hepatitis: 4–5 times normal LFTs require treatment change.
			Renal: increased BUN/Cr.	TMP may decrease creatinine tubular secretion and increase serum creatinine.
			Hyponatremia (Na<125 mEq/dL).	May be due to large volume of D5W needed for IV administration; can dilute each 80 mg TMP in 75 mL D5W or change to oral TMP-SMX.
			Drug fever.	Drug fever may herald onset of neutropenia, rash, etc.

Continued on next page

Table 1. *Treatment Regimens for AIDS. (Continued from previous page.)*

System & Organism	Drug Regimen	Duration	Common Adverse Effects	Comments
Pulmonary	OR			
Pneumocystis carinii *(Continued from previous page)*	Pentamidine isethionate (Pentam™) 4 mg/kg/day as 1–2 hr IV infusion once daily. IM injections are painful; not recommended due to sterile abscess and greater risk of hypotension	Treat for 21 days (minimum of 14 days)	Orthostatic hypotension; hypoglycemia; hyperglycemia; neutropenia, thrombocytopenia; azotemia, renal failure; hypocalcemia, hypomagnesemia; hepatitis, pancreatitis; rare cardiac arrhythmias.	Slow IV infusion over 2 hours may decrease incidence of hypotension. Early or delayed hypoglycemia (may occur after discontinuation of therapy). Hypoglycemia can be profound, requiring IV glucose. Permanent diabetes may occur. Concomitant nephrotoxic agents and dehydration can increase risk of pentamidine nephrotoxicity.
	Inhaled pentamidine 600 mg/6 mL sterile H_2O or 4 mg/kg/day (Investigational) Note: requires specially designed nebulizer system, i.e., Respigard II™, UltraVent™	20 minute qd inhalation for 21 days	Adverse systemic effects are minimal due to low pentamidine serum concentrations. Bronchospasm and coughing is common, especially in smokers. Pretreatment with inhaled bronchodilators (i.e., albuterol) may help.	Inhaled pentamidine appears effective and less toxic in patients with *mild* PCP (pO_2>60). No data available in patients with more severe PCP.
	OR			
	Dapsone 100 mg po plus TMP (trimethoprim) 20 mg/kg/day po in 4 divided doses	Treat for 21 days (minimum of 14 days)	See toxicities for TMP-SMX. Methemoglobinemia; rash; fever; dose-related hemolysis; nausea, abdominal pain; bone marrow suppression; hyperkalemia; proteinuria, papillary necrosis.	Check G6PD before starting dapsone. Check methemoglobin levels weekly. Preliminary data suggest dapsone-trimethoprim may be less toxic than TMP-SMX and just as effective in mild illness (pO_2>60).
	Prophylaxis/Suppression			
	Pyrimethamine sulfadoxine (Fansidar™) 1 q week	Indefinitely?	Stevens-Johnson syndrome, toxic epidermal necrolysis; leukopenia, bone marrow suppression; GI, CNS toxicity.	No studies clearly demonstrate efficacy. The risks versus benefits of prophylactic agents used in combination with zidovudine or other bone marrow depressants is unknown.
	Pentamidine 4 mg/kg monthly IM or IV, or inhalation of 30–150 mg q 2 weeks or 300 mg q 4 weeks (investigational)	Indefinitely?	See pentamidine under PCP.	Same
	TMP-SMX 1 po bid	Indefinitely?	See TMP-SMX under PCP.	Same
	Dapsone 100 mg once daily	Indefinitely?	See dapsone under PCP.	Same

Gastrointestinal (Bowel)				
Giardia lamblia	Quinacrine HCL (Atabrine™) 100 mg po tid OR	7–10 days	Yellowing of urine, skin, sclera; dizziness, headache; fever; vomiting; antabuse-like reaction; thrombocytopenia, hemolytic anemia; toxic psychosis.	
	Metronidazole (Flagyl™) 250–500 mg po tid	7–10 days	Nausea, headache, metallic taste, disulfiram-like reaction; dark urine.	
Cryptosporidium	No effective regimen			
	Spiramycin (Rovamycin™) 1 gm po qid OR Clindamycin 300 mg po qid PLUS Quinine 250 mg po qid	Unknown	Rare adverse effects: nausea, vomiting, epigastric pain.	Spiramycin investigational; available from FDA.
Isospora belli	Trimethoprim-Sulfamethoxazole 160 mg TMP/800 mg SMX po qid	21 days	See TMP-SMX under pulmonary.	Efficacy not established.
Central Nervous System				
Toxoplasma gondii	Sulfadiazine 1 g po q 6 hrs PLUS Pyrimethamine 25–50 mg po qd PLUS Leukovorin calcium 5–10 mg po qd If sulfa allergy: Pyrimethamine 25–50 mg po qd PLUS Clindamycin (Cleocin™) 900–1200 mg po or IV qid	6–8 weeks	Allergy, rash, drug fever. Bone marrow suppression. Blood dyscrasias.	Clinical response or regression of lesions on imaging studies is seen over 2–3 weeks. Maintenance required indefinitely to prevent relapse. Drug toxicity may outweigh potential benefits of empiric therapy. Leukovorin may delay onset of bone marrow toxicity.
***Cryptococcus neoformans* (meningitis or disseminated)**	Amphotericin B 0.5 mg/kg/day to 0.8 mg/kg/day	6 weeks or total of 1.5–2 g	Renal failure, hypokalemia, hypomagnesemia, fever, chills, anemia, thrombophlebitis.	Pretreatment with diphenhydramine, acetaminophen, or meperidine may decrease fevers, chills, and rigors. Use of heparin and hydrocortisone can decrease phlebitis. Lifelong suppressive therapy with amphotericin or ketoconazole is usually required. 5-flucytosine not indicated due to high risk of bone marrow suppression and minimal additional benefits.

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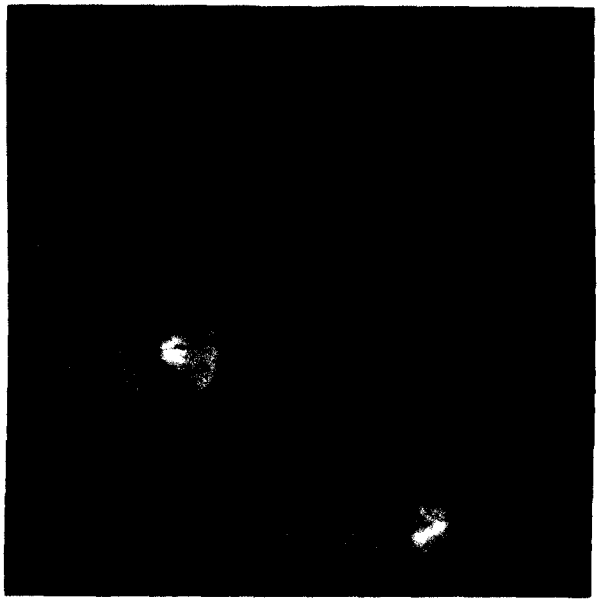

Figure 3. Cotton wool spots.

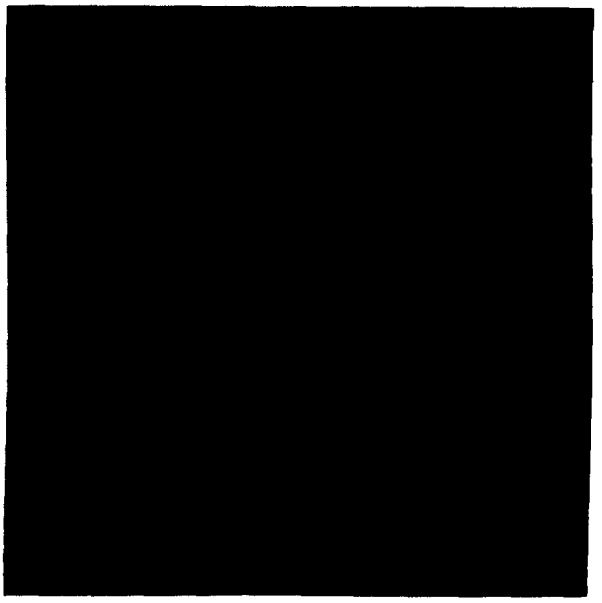

Figure 4. Cytomegalovirus retinitis, including extensive hemorrhages and edema causing a macular star.

tions are responsible in most cases. Although nonsteroidal anti-inflammatory drugs may reduce fevers in AIDS patients, serious nephrotoxicity appears common. These drugs should be reserved for those patients in whom the fever causes serious discomfort.

Skin

Kaposi's sarcoma (KS) characteristically appears as asymptomatic red, blue, or brown nodules 5–15 mm in diameter anywhere on the body (Figures 1, 2).[26] Biopsy documenting the presence of KS may be required to establish the diagnosis of AIDS or to plan specific therapy. Treatment of KS lesions with radiation or chemotherapy may be needed for symptomatic relief or cosmetic purposes.[10,27] Perioral and perianal herpes simplex infections present as painful ulcerations rather than the usual grouped vesicles. Oral acyclovir can control the lesions; however, intravenous acyclovir is often required. Other skin conditions include seborrheic dermatitis, folliculitis, herpes zoster, fungal infection, vascular lesions, and molluscum contagiosum.[28,29] These dermatoses are often severe, persistent, atypical, and recurrent despite therapy. Maculopapular rashes are frequently drug related, the most common offender being trimethoprim/sulfamethoxazole. Serologies must be obtained to exclude the possibility of syphilis, although there has been one case report of an AIDS patient with seronegative secondary syphilis.[30]

Eyes, Sinuses, Oral Cavity

Funduscopic examination can show nonspecific cotton-wool spots that do not threaten vision (Figure 3).[31-33] Hemorrhages, Roth's spots, microvascular changes, and numerous other conditions are also described. Cytomegalovirus (CMV) retinitis may progress over a period of weeks or months to blindness. Visual symptoms (blurry, foggy, or dim vision) occur late in the course of this disease. Typically, the funduscopic examination shows white, gray, or yellow discoloration, sometimes with associated hemorrhage (Figure 4). Since this condition begins in the peripheral retina, dilating the pupils is necessary for detection. Indirect ophthalmoscopy by an ophthalmologist is often more reliable. The intravenous drug ganciclovir (DHPG) can be effective in slowing the progression of CMV retinitis.[25]

Sinusitis with or without fever, headache, or nasal discharge can occur and requires standard therapies.[34]

Oral candidiasis (thrush)[35] is a common finding in patients with AIDS (Figure 5) and responds well to clotrimazole troches, nystatin tablets, or oral ketoconazole. Hairy leukoplakia (Figure 6) is usually an asymptomatic lesion in which the Epstein-Barr virus has been identified.[36] These elongated white lesions with a hairy appearance occur on the lateral border of the tongue, and their presence may wax and wane. Kaposi's sarcoma (Figure 7) occurs in the oral cavity or on

Figure 5. Candidiasis of the tongue.

any other mucous membrane; painful or bulky lesions respond to chemotherapy or radiation therapy.[10,37] Gingivitis, periodontal disease, and perioral herpesvirus infections are common.

Lymph Nodes and Hematopoietic System

Lymph Nodes

The presence of generalized lymphadenopathy in high-risk patients does not diagnose AIDS, and is not necessarily a forerunner of AIDS. Treatable causes of lymphadenopathy such as syphilis, lymphoma, tuberculosis, or fungal infection must be excluded.

In AIDS, generalized lymphadenopathy is usually due to benign follicular hyperplasia,[38] and rarely to Kaposi's sarcoma, mycobacterial infection (usually *M. avium-intracellulare*, occasionally *M. tuberculosis*), fungal infections, or lymphoma.[39] Unfortunately, these conditions (except some fungal and *M. tuberculosis* infections) do not respond well to standard treatment modalities. Biopsy or fine needle aspiration is not routinely indicated unless there is suspicion of treatable conditions.

Figure 6. Hairy leukoplakia, lateral border of tongue.

Peripheral Blood

Anemia, leukopenia, or thrombocytopenia due to marrow suppression, HIV, systemic infection, peripheral antibodies, and drug therapy occur in most AIDS patients.[40] Mild anemia is almost universally present; severe anemia requires transfusions. Total white blood cell counts are frequently in the range of 1,500 to 4,000 cells/μL. Total lymphocyte counts are typically low, reflecting the widespread destruction of the T4 ("helper") subset of lymphocytes. Clinically, bacterial infections in the neutropenic AIDS patient do not

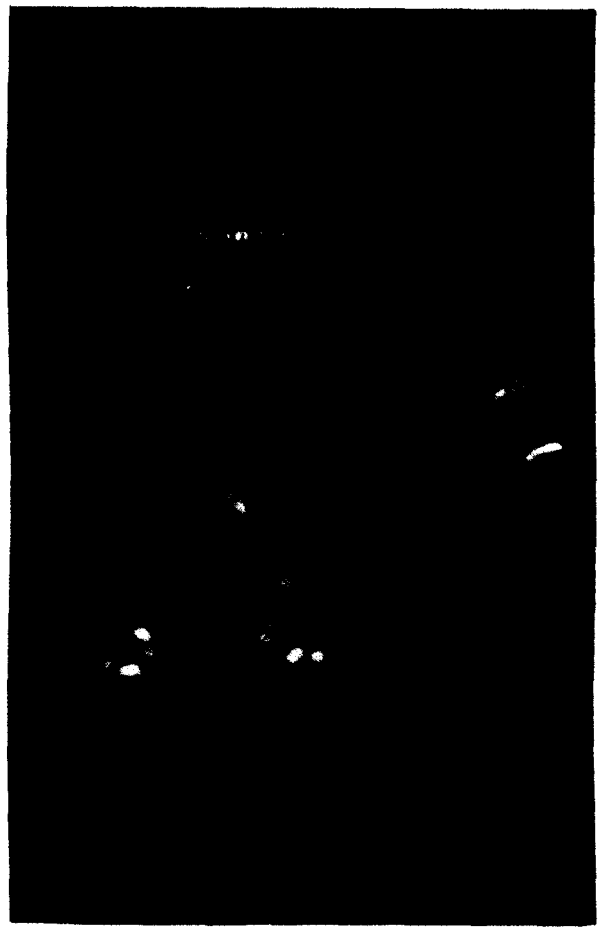

Figure 7. Kaposi's sarcoma of the hard palate; the upper lip also has an early herpetic lesion.

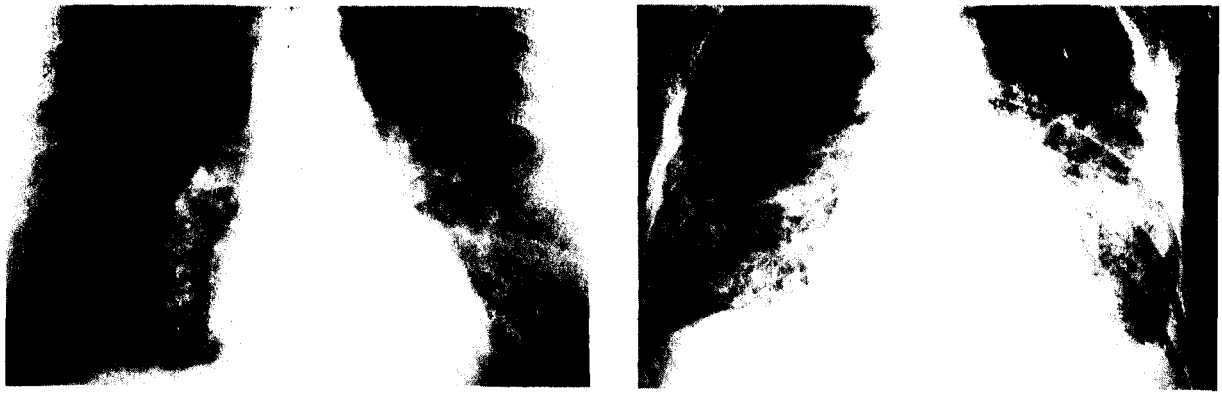

Figure 8. Chest radiographs in patients with AIDS.
Left: Diffuse interstitial markings in a patient with *P. carinii* pneumonia.
Right: Patchy infiltrates and a left pleural effusion in a patient with *M. tuberculosis*.

appear to be common. Nevertheless, patients with absolute neutrophil counts of 500 cells/μL or lower who are febrile or clinically deteriorating should be evaluated promptly and empiric antibiotics instituted to decrease the risk of bacterial infection.

The immune thrombocytopenia of AIDS[41,42] seldom results in bleeding. Treatment to increase platelet counts temporarily with steroids, splenectomy, or gammaglobulin infusions[43] is not usually indicated, as there is concern about the potential harm these interventions may pose to the asymptomatic immunosuppressed patient. Drug-induced thrombocytopenia is common and requires a change in therapy. Prolongation of the activated partial thromboplastin time (PTT or ACT) without clinical bleeding problems can occur from a lupus-type anticoagulant.[44]

Heart and Pericardium

Congestive cardiomyopathy, nonbacterial thrombotic endocarditis, incidental Kaposi's sarcoma of the myocardium and pericardium, and tuberculous and fungal pericarditis have been described.[45] Pericardiocentesis or pericardiectomy and appropriate antimicrobial therapy should be considered in patients with echocardiographic evidence of pericardial effusion.

Lungs

Opportunistic Infections and Kaposi's Sarcoma

Respiratory disease is the leading cause of morbidity, mortality, and hospital admission in AIDS patients. Therefore, major attention should be focused on the pulmonary evaluation of patients with respiratory symptoms, fever, pulmonary infiltrates, or significant weight loss.[46] Respiratory symptoms can range from mild shortness of breath on exercise to severe breathlessness and respiratory distress. Most patients have tachypnea and normal lung examinations, although a dry nonproductive cough and dry rales may be present. Chest roentgenograms in AIDS patients with pulmonary disease usually show a diffuse interstitial pattern or perihilar and lower lobe infiltrates (Figure 8) or on occasion may be normal.[46-48] The roentgenographic findings are not specific to the causative organism(s). Pleural effusions, although uncommon, are most frequently associated with Kaposi's sarcoma.[47-49] Principal arterial blood gas abnormalities are hypoxemia and primary respiratory alkalosis. Specific causes of pulmonary disease in AIDS are listed in Table 2. Other common causes of respiratory symptoms such as bronchospasm and fluid overload should not be overlooked.

Pneumocystis carinii pneumonia (PCP) is the most treatable serious illness in the AIDS patient. Bronchoscopy with bronchoalveolar lavage, transbronchial biopsy, or both, reliably diagnose this parasitic infection about 90 percent of the time.[50] Nonbronchoscopic bronchoalveolar lavage can also be diagnostic.[51] Sputum induction, which poses no significant risk to the patient, is successful in diagnosing PCP in more than 75 percent of patients at institutions experienced in this technique.[52,53] *P. carinii* cysts can usually be found for at least 2 to 3 weeks after institution of therapy.[54,55]

Treatment of *Pneumocystis Carinii* pneumonia with 21 days of trimethoprim-sulfamethoxazole

Table 2. *Pulmonary Involvement in AIDS.**

	Percent
Pneumocystis carinii pneumonia	85
Cytomegalovirus	17
M. avium-intracellulare	17
Kaposi's sarcoma	8
M. tuberculosis	4
Legionella	4
Fungi (cryptococcus, etc.)	4
Pyogenic bacteria	2

*From Murray, et al.[63]

(TMP-SMX) or pentamidine isethionate is equally effective in most cases.[46,56] Optimally, therapy should be initiated intravenously to assure adequate drug delivery and patients hospitalized initially to observe the clinical course and to monitor for drug toxicity. If, after 5–10 days of intravenous therapy, the patient is clinically stable, oral TMP-SMX or, alternatively, dapsone-trimethoprim can be used to complete the remaining days of therapy. Clinical improvement should occur within 7–10 days. Some clinical and/or radiographic worsening, however, may occur during the first 5 days of therapy and does not necessitate a change in treatment. Continued clinical deterioration or serious drug toxicity warrants changing to the alternate agent. Discontinuation of either drug is more often necessitated by drug toxicity than by failure to respond. However, following failure to respond to one agent, clinical response to the other agent is usually poor. Oral TMP-SMX appears to have comparable cure and relapse rates to those of intravenous therapy in outpatients who can tolerate oral therapy. Administration of the less toxic aerosolized pentamidine appears promising[57] and remains under investigation. Dapsone-trimethoprim is also effective and may become a first-line drug as well.[58] Recent studies of trimetrexate are also encouraging.[55] Therapy of recurrent episodes of PCP is similar to initial therapy.

Patients recovered from *P. carinii* pneumonia should be maintained on zidovudine if possible. Definitive studies are needed to determine if a combination of zidovudine plus any of the suppressive agents listed in Table 1 are beneficial in the prevention of recurrent episodes of PCP.[59,60] Until then, "well" patients on zidovudine should be given the option of a therapeutic trial. Prophylaxis for prevention of an initial episode of *P. carinii* pneumonia remains investigational.

Cytomegalovirus (CMV) is frequently isolated alone or with other organisms, but its contribution to pulmonary disease is unclear. Treatment of cytomegalovirus pneumonia does not appear effective.[24,25]

Mycobacterial pulmonary disease is most often due to *M. avium-intracellulare* complex rather than to *M. tuberculosis*. Nevertheless, it is recommended that therapy for presumptive *M. tuberculosis* be initiated upon finding acid-fast organisms.[61] Most cases of pulmonary and extrapulmonary disease from *M. tuberculosis* occur among intravenous drug users and individuals from poor socioeconomic areas where tuberculosis is common.[62] Apical, cavitary, and miliary patterns may be seen on chest roentgenograms.[63] Patients infected with *M. tuberculosis* generally respond well to standard antibiotic therapy. *M. avium-intracellulare* (MAI) pulmonary disease does not have a distinctive clinical or radiographic appearance. Unfortunately, treatment of MAI infection at any site has virtually no impact on the disease and may result in serious toxicity.[22]

Kaposi's sarcoma (KS) may be present in the lung parenchyma and on pleural and bronchial mucosal surfaces.[49] Chemotherapy and radiation therapy are marginally effective and not routinely indicated. Encapsulated bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae*[64] respond to usual antibiotic therapies. *Legionella, Cryptococcus neoformans* and other fungi,[21] herpes simplex virus, and *Toxoplasma gondii* are less common. Lymphoid interstitial pneumonia has been described in patients without other identified causes.[65]

Approach to Diagnosis and Treatment of Pulmonary Disease

Evaluation of patients with pulmonary symptoms can be based on an assessment of the patient's degree of respiratory symptoms (Figure 9). A full course of empiric therapy for PCP without careful evaluation is not recommended due to the potential for serious drug toxicity and the chance of missing other treatable conditions and pathogens.

Minimal Symptoms

This group includes patients with AIDS and members of high-risk groups who complain of intermittent cough or mild exertional dyspnea. If chest

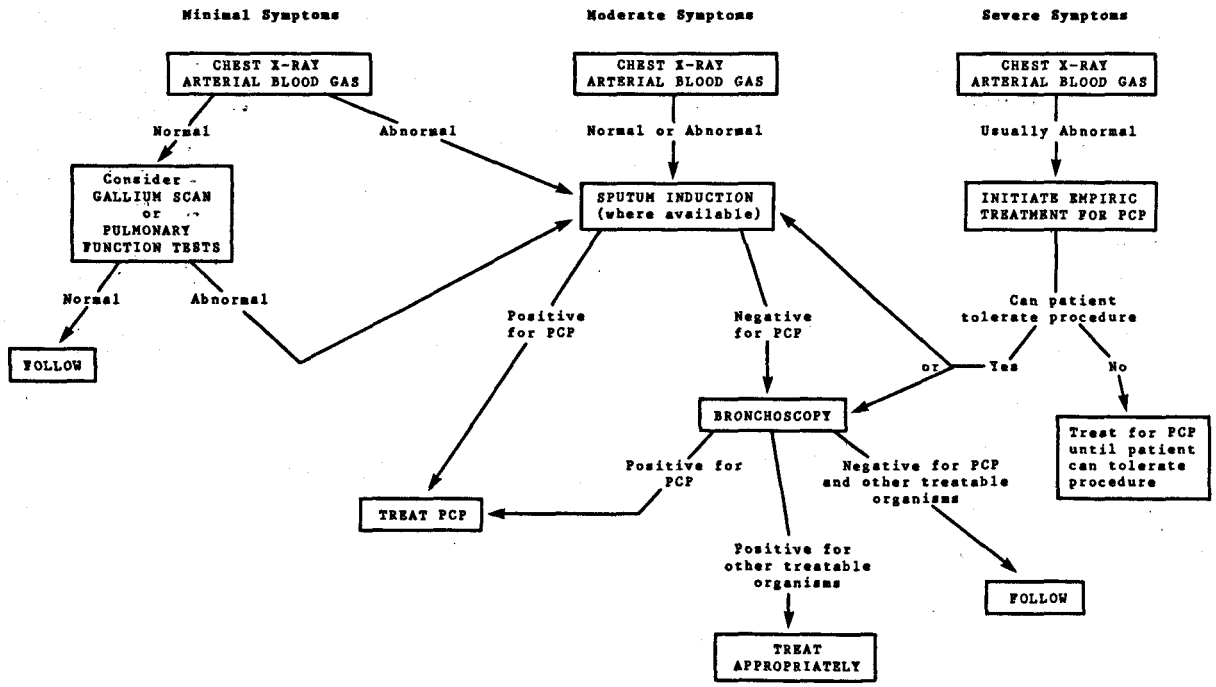

Figure 9. Evaluation of pulmonary symptoms.

roentgenogram and arterial blood gas determination are normal, a gallium scan or pulmonary function tests (PFTs) can serve as screening tests for active pulmonary disease.[48] Abnormalities of any of these tests require further investigation.

Moderate Symptoms

Moderate symptoms such as shortness of breath or chronic cough require more definitive evaluation. The selection of procedures is dependent on the laboratory capabilities of the individual institution. Only after a negative bronchoscopic procedure should a patient be considered free of treatable pulmonary disease including PCP.

Severe Symptoms

In the patient with extreme shortness of breath, respiratory distress, and potential respiratory failure, the benefits of empiric drug therapy outweigh the benefits of delaying therapy pending a definitive diagnosis. Empiric treatment of PCP with TMP-SMX[66] (which will also treat most bacterial pneumonias) or with pentamidine (and possibly additional antibiotics for bacterial pneumonia) should be instituted immediately. Bronchoscopy or sputum induction should then be done as soon as the patient can tolerate procedures. Institution of corticosteroid therapy (e.g., methylprednisolone 60 mg intravenously every 6 hours) is warranted for severe respiratory decompensation, but its efficacy requires further investigation.

Gastrointestinal System

Liver Abnormalities

Common causes of hepatic enzyme elevations include acute or chronic viral hepatitis, cytomegalovirus (CMV) hepatitis, and drug-induced hepatitis.[67] It is rarely necessary to document by biopsy the nature of the liver disease since treatment is usually not available. Alkaline phosphatase elevations to three or more times normal levels require evaluation by sonography and/or a CT scan. Bacterial, fungal, or rarely amoebic abscesses can produce large focal defects. Porta hepatis adenopathy (malignant, mycobacterial, or reactive), biliary tract strictures, or stenosis at the ampulla of Vater causing biliary duct dilation should prompt further biliary tract investigation.[68,69] Symptomatic acalculous cholecystitis has also been described.[70] A nonfocal (homogeneous) pattern on scan suggests chronic hepatitis, Kaposi's sarcoma, lymphoma, or infection with *M. avium-intracellulare* and less commonly *M. tuberculosis* or fungi.[63,71,72] Liver biopsy may be indicated in selected cases where there is strong suspicion of infection with

M. tuberculosis or fungi, which may respond to antimicrobial therapy. In many cases, however, disseminated infection with these organisms can be established by cultures or biopsies at sites other than the liver.

Esophageal Disease

AIDS patients with dysphagia and/or odynophagia who have oral candidiasis should receive an empiric trial of oral ketoconazole for presumptive esophageal candidiasis. If symptoms persist despite seven days of ketoconazole therapy or if oral thrush is not present, endoscopy with biopsies and cultures is required to direct specific therapy (Table 1). Biopsy-proven candidal esophagitis often responds to low-dose amphotericin therapy if ketoconazole fails. Herpetic esophagitis responds to acyclovir, and cytomegalovirus esophagitis may respond to ganciclovir.[73]

Enteropathies

Diarrhea with weight loss (termed the "diarrheal wasting syndrome") is a debilitating syndrome among AIDS patients.[74] Evaluation of stool specimens may reveal pathogens, but proctoscopic biopsies and cultures may be necessary for diagnosis. Colitis and proctitis can be caused by *Shigella* and *Salmonella* species, *Campylobacter, Neisseria gonorrhoeae,* chlamydia, herpes simplex virus, *Entamoeba histolytica,* and possibly by ordinarily nonpathogenic amoebae. Standard antimicrobial therapy is usually effective. Cytomegalovirus enteritis frequently responds to ganciclovir therapy.[73] If severe diarrhea due to *Giardia lamblia* is present, the diagnosis can be established by the presence of trophozoites on stool examination. Empiric treatment with quinacrine or metronizadole may result in dramatic improvement when *Giardia* is present despite negative stool examination. Other pathogens include the parasites *Isospora belli* and cryptosporidium. A trial of oral trimethoprim-sulfamethoxazole may be effective against isosporiasis,[75,76] but there is currently no consistently effective therapy for cryptosporidiosis.[77] Lymphomas, *M. avium-intracellulare,* and possibly other viruses can also cause diarrhea. Kaposi's sarcoma of the bowel is rarely a cause of diarrhea.

In many patients no specific pathogen can be found, and the enteropathy is attributed to HIV. Therefore, invasive evaluation is of low yield and should be restrained. Attention is best directed at symptomatic treatment with opiates or antimotility agents such as loperamide hydrochloride (Imodium™), with dosing carefully titrated to avoid toxicity (e.g., ileus).

Perianal Disease

Perianal disease may be from chronic ulcerative herpes simplex virus, condyloma accuminata, and rarely squamous cell carcinomas.[78]

Kidneys and Adrenals

The most common renal problem in AIDS is drug-induced nephrotoxicity (e.g., TMP-SMX, pentamidine, amphotericin B, nonsteroidals).[79] Glomerular disease with associated proteinuria and renal failure has been described, especially among intravenous drug users.[79,80] Multifactorial fluid and electrolyte abnormalities (hyponatremia, hypokalemia, hyperkalemia) are common. Pyelonephritis may require up to 4 weeks of antibiotics for cure, and renal abscesses from bacteria and fungi may require drainage.

A clinical picture suggestive of adrenal insufficiency (fatigue, weakness, anorexia, nausea, vomiting, hypotension, tachycardia) is present in the majority of patients with AIDS. Sepsis, gastrointestinal fluid losses, inadequate oral intake, and many other diseases may cause syndromes resembling adrenal insufficiency and should not be overlooked. True adrenal insufficiency, due to primary adrenal disease or hypothalamic/pituitary disease, may also occur.[81,82] Patients in whom adrenal insufficiency is suspected should have a cosyntropin (Cortrosyn™) stimulation test. When abnormal, confirmation with a 72-hour ACTH stimulation test is necessary to assess the need for chronic replacement therapy. Seriously ill patients in whom adrenal insufficiency is likely should receive hydrocortisone 50–100 mg intravenously every 6 hours along with fluid and electrolyte replacement pending results of the cosyntropin test. Steroid therapy should be tapered when clinically possible.

Musculoskeletal System

The musculoskeletal system is not frequently involved in AIDS. Myalgias without weakness, polymyositis with spontaneous resolution, arthralgias, and Reiter's syndrome have been reported.[83,84]

Neurologic System

Nervous system symptoms are present in 30 to 40 percent of AIDS patients, and the incidence of nervous system abnormalities is considerably higher at autopsy.[85-87] Direct involvement of nervous tissue by HIV is responsible for most of these problems.[88] Neurological abnormalities affect peripheral nerves (neuropathies), the spinal cord (myelopathies), and the brain (encephalopathies). Encephalopathies are by far the most common.

Peripheral Neuropathies

Peripheral neuropathy in AIDS patients presents as either a distal symmetrical neuropathy or a chronic inflammatory polyneuropathy.[88-90] Distal symmetrical neuropathies are characterized by painful dysesthesias of the feet, distal weakness, numbness, and hyporeflexia. Amitriptyline or nonsteroidal anti-inflammatory drugs may control the pain. Chronic inflammatory polyneuropathies have a mononeuritis multiplex presentation with progressive proximal and distal weakness of peripheral or cranial nerves. Deep tendon reflexes may be absent; sensory loss is minimal. Systemic symptoms of fever, night sweats, and malaise often accompany the neurologic findings. Lymphocytic pleocytosis of the cerebrospinal fluid (CSF) is usually present. Slowed nerve conduction studies and sural nerve biopsies can confirm the diagnosis. When progressive, the symptoms may respond to plasmapheresis.[91]

Myelopathies

Spinal cord involvement presents as a mono- or paraparesis, with weakness, spasticity, hyperactive reflexes, and upgoing toes. Decreased reflexes and flaccidity occur when peripheral neuropathy is superimposed. Painful dysesthesias and urinary or fecal incontinence may occur. Most are due to vacuolar degeneration,[92] viral infections,[93,94] and lymphomas with mass lesions and/or meningeal spread.[85,86]

Compressive spinal cord lesions can be identified by myelography or magnetic resonance imaging (MRI), which should precede lumbar puncture. Lymphomas may respond to radiation therapy, but treatment of lymphomatous meningitis is generally ineffective. The diagnosis of vacuolar degeneration of the spinal cord (presumably due to HIV infection) is made by exclusion of the other pathologic processes. Herpesvirus infections may respond to intravenous acyclovir. Painful sensory symptoms associated with myelopathies can be treated with nonsteroidal anti-inflammatory drugs and tricyclics.

Brain Disorders

Subtle decrements in cognitive function, such as diminished abstract reasoning, reduced speed of information processing, and mild difficulties in learning and remembering may occur in HIV-infected individuals well before the development of AIDS.[95] In AIDS, brain disorders present as disturbances of cognitive function, seizures, headache, and various focal neurologic symptoms and signs.[87,96] Most common in AIDS is a progressive dementia characterized by confusion, forgetfulness, poor coordination, apathy, and depression. An unusual conversational pattern may occur with pauses of 15–30 seconds in response to questions. Although seizures are most common with mass lesions, and headache is common with cryptococcal meningitis, the clinical presentation is not diagnostic of the pathologic process(es). Meningeal signs may be absent in AIDS patients.

Subacute encephalitis (SAE), probably due to HIV involvement of the brain,[88,97-99] is the most common cause of brain disorders. It presents with psychomotor slowing, impaired memory, ataxia, weakness, and tremor.[96] A steadily progressive deterioration occurs over months, sometimes culminating in severe dementia, incontinence, and paraparesis. Cerebrospinal fluid studies are abnormal in 85 percent (elevated protein and/or lymphocytic pleocytosis), and magnetic resonance imaging or CT scans show cerebral atrophy in more than 80 percent of affected patients.[96] Zidovudine may retard progression of the dementia.[12] Atypical aseptic meningitis is probably the meningeal counterpart of SAE.[85]

Toxoplasma gondii infection occurs in 10 percent of patients with neurologic abnormalities[100,101] and is the most treatable cause of cerebral disease seen in AIDS. Cognitive dysfunction, seizures, or focal neurologic signs may occur. Toxoplasma serologies are unreliable in diagnosing active disease in AIDS patients. However, a negative Sabin-Feldman dye test almost never occurs in patients with cerebral toxoplasmosis.[102] The cerebrospinal fluid findings are nonspecific and similar to those seen in subacute encephalitis. Toxoplasmosis most often produces mass lesions on CT scan or

magnetic resonance imaging; less commonly, it produces a diffuse infiltrative disease without abnormalities on imaging studies.[103] Treatment is with pyrimethamine and sulfadiazine; however, therapy is often limited by drug toxicities. A presumptive diagnosis of cerebral toxoplasmosis is made if neurologic improvement (which may be dramatic) or regression of lesion on imaging studies occurs after two to three weeks of therapy.

Cryptococcosis commonly presents with confusion and/or headache.[18,19] The cryptococcal serum antigen is positive in more than 75 percent of patients. A positive latex agglutination test, CSF India ink preparation, or culture confirms the diagnosis. Symptomatic improvement may occur following treatment with amphotericin B.

M. tuberculosis involvement of the CNS is rare among patients with AIDS.[85,86,104,105] Cerebrospinal fluid cultures may be positive, but smears rarely reveal acid fast organisms. Patients may respond to antituberculous therapy. Herpes simplex encephalitis is uncommon. The diagnosis is made by viral cultures of the cerebrospinal fluid or by brain biopsy; intravenous acyclovir can be effective.

Neurosyphilis must be considered whenever the serum serology is positive or the cerebrospinal fluid has pleocytosis with a positive serology. Progression of neurosyphilis in AIDS despite appropriate antibiotic therapy has been suggested,[106,107] but the validity of this observation has been questioned.[108]

Causes of mass lesions other than toxoplasmosis include progressive multifocal leukoencephalopathy (PML), an untreatable demyelinating disease of the white matter,[109] lymphoma,[110] and, rarely, tuberculomas or other fungal, bacterial, or viral abscesses.

Approach to Diagnosis and Treatment of Brain Disorders

The evaluation of brain disorders relies on cerebrospinal fluid examination and imaging studies. Cerebrospinal fluid studies are difficult to interpret, however, since the cell count and other parameters may be normal despite extensive disease (e.g., infectious meningitis). Cell counts, CSF pressures, protein, glucose, cryptococcal antigen, India ink stain, and bacterial, mycobacterial, and fungal cultures should be routinely obtained. Imaging studies should precede lumbar puncture unless obvious meningitis is present. If focal lesions are seen, a presumptive diagnosis of cerebral toxoplasmosis should be made and treatment instituted if possible (Table 1). If there is no response, stereotactic biopsy of a lesion should be considered. If focal lesions are not identified and the lumbar puncture is not diagnostic, empiric treatment for toxoplasmosis should be considered for patients with progressive encephalopathy. Failure to respond strongly suggests another diagnosis.

Psychosocial Aspects

The serious psychosocial problems of AIDS patients are unique.[111,112] These are usually young patients who are dealing with terminal illness while at the same time experiencing isolation and stigmatization from friends, family, health professionals, and society in general. For the individuals caring for the AIDS patient, the stresses of providing support for a loved one with a terminal illness may be combined with the fear of contagion. AIDS instantly becomes a family illness. Using the definition of family as "a group of intimates with a history and a future,"[113] family issues are critical for all AIDS patients, including those who are homosexual or intravenous drug users. Destruction of social and family relationships and/or a marked increase in social support and family bonding may occur.

The physician caring for the AIDS patient must be able to commit himself or herself to care that requires substantial time commitments and extraordinary understanding and sensitivity. The physician who cannot offer this should refer the patient to one who can.

Intensive Care, Intubation, Resuscitation, and Life Support

Extraordinary measures for patients with AIDS must be individualized. The extremely poor prognosis for patients with AIDS after intubation must be understood by both the physician and the patient before making such a decision. Some studies have shown that as few as 13 percent of patients who require intubation survive long enough to leave the hospital.[114,115] Most patients report no discussions of life-sustaining treatments with their physicians.[116] Frank discussions need to occur at a time when patients can understand the issues and make their desires known. In some cases, patients may wish to

execute a durable power of attorney to facilitate decision making if they are no longer able to participate.

Summary

With full recognition that the phenomenal advances in the understanding of AIDS will lead to new techniques of evaluation and new therapies, the approaches outlined in this article can serve as a current guide for the primary physician. The challenges to the physician to relieve suffering, to prolong life, and to decide with the patient which route to follow when options are in conflict are particularly difficult with this disease. Invasive diagnostic tests, hospitalization, intravenous therapies, and relatively toxic drugs all play key roles in palliation of illness in AIDS. At the same time, when the physician focuses on the most treatable syndromes and resists the temptation to pursue diagnostic and treatment avenues that do not have worthwhile therapeutic end points, he or she may be better able to focus on the major concerns of the patients and their families.

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