

# 7 | Systems Review

(Complications are listed alphabetically by organ system)

## Cardiac Complications

### Dilated Cardiomyopathy (*N Engl J Med* 1998;339:1153)

**CAUSE:** Unknown, but hypotheses include: 1) Mitochondrial toxicity from AZT (*Ann Intern Med* 1992;116:311), 2) HIV infection of myocardial cells (*N Engl J Med* 1998;339:1093), 3) L-carnitine deficiency (*AIDS* 1992;6:203), and 4) Selenium deficiency (*J Parenteral Ent Nutr* 1991;15:347).

**FREQUENCY:** 6% to 8% in longitudinal studies (*Eur Heart J* 1992;13:1452; *Clin Immunol Immunopath* 1993;68:234). This refers to symptomatic cardiomyopathy. Rates of left ventricular diastolic dysfunction with routine echo are much higher and correlate with stage of immunosuppression (*Heart* 1998;80:184).

**SYMPTOMS:** CHF, arrhythmias cyanosis, and/or syncope

**DIAGNOSIS:** Echocardiogram showing ejection fraction <50% normal ± arrhythmias on EKG, not otherwise explained.

**TREATMENT** (*Am J Cardiol* 1999;83:1A)

- **HAART**
- **ACE inhibitor:** Enalapril 2.5 mg bid; titrate up to 20 mg bid. Alternatives: Captopril 6.25 mg tid up to 50 mg tid or lisinopril 10 mg/day titrated up to 40 mg/day
- **Persistent symptoms:** Add diuretic – hydrochlorothiazide 25-50 mg/day, furosemide 10-40 mg/day (up to 240 mg bid) or spirolactone 25 mg/day (up to 50 mg bid)
- **Refractory:** Consider digoxin 0.125-0.25 mg/day
- **Others options:** Treat hypertension, treat hyperlipidemia, discontinue EtOH, d/c cocaine, d/c AZT, (?) supplemental carnitine, and/or selenium if deficient.

## Pulmonary Hypertension

**CAUSE:** Unknown (*Ann NY Acad Sci* 2001;946:82)

**FREQUENCY:** Infrequent, does not correlate well with CD4 count. Histology is similar to primary pulmonary hypertension. The major

current hypothesis is cytokine-related endothelial proliferation (*Am J Respir Crit Care Med* 2001;52:31).

**SYMPTOMS:** Major symptom is exertional dyspnea. Other symptoms are exertional chest pain, syncope, cough, hemoptysis, and fatigue.

**DIAGNOSIS:** X-ray shows enlarged pulmonary trunk or central pulmonary vessels (early), massive right ventricular and right atrial enlargement (late). Echo shows dilated right atrium and ventricle ± tricuspid insufficiency. Doppler echo shows pulmonary arterial systolic BP >30 mm Hg. The best test is cardiac catheterization to show increased pulmonary artery pressure, increased right atrial pressure, and normal pulmonary capillary pressure. Lung scan and pulmonary function tests are normal.

**TREATMENT** (usually progressive despite treatment)

- **Epoprostenol** (*Angiology* 2000;162:1846)
- **Diuretics**
- **Oral anticoagulant**
- **Sildenafil** 25 mg/day. Increase by 25 mg every 3 to 4 days up to 25 mg qid (*AIDS* 2001;15:1747; *AIDS* 2002;16:1568; *N Engl J Med* 2000;343:1342). Note drug interactions with antiretroviral agents.

### Tricuspid Valve Endocarditis

**CAUSE:** *S. aureus* in 50% to 70%; streptococci in 20%

**FREQUENCY:** A longitudinal study of 2529 IDUs followed for 16,469 patient-years showed an endocarditis rate 4-fold higher with HIV infection (13.8/1000 patient-years vs 3.3/1000 patient-years) (*J Infect Dis* 2002;185:1761).

**SYMPTOMS:** Fever, dyspnea, weight loss

**DIAGNOSIS:** Duke criteria: Definite = 2 major, 1 major and 3 minor, or 5 minor. Possible = 1 major and 1 minor, or 3 minor.

- **Major:** 1) Positive blood culture for likely agent from ≥2 sticks or persistent bacteremia and 2) Endocardial involvement by echo or new murmur of valve regurgitation.
- **Minor:** 1) IDU or other predisposing cause; 2) Fever >38°C; 3) Vascular phenomena; 4) Immunologic phenomena; 5) bacteremia not meeting major criteria; and 6) Echo positive but not diagnostic (*Am J Med* 1994;96:200).

## TREATMENT

- **Nafcillin** 12 gm IV/day x 4 weeks plus tobramycin 1 mg/kg q8h x 3 to 5 days (*Ann Intern Med* 1988;109:619; *Eur J Clin Microbiol Infect Dis* 1994;13:559). Note: The 2-week nafcillin/tobramycin course is advocated for uncomplicated *S. aureus* tricuspid valve endocarditis in IDUs but should not be used for patients with HIV infection.
- **Vancomycin** 1 gm IV q12h x 4 weeks plus tobramycin 1 mg/kg q8h x 3 to 5 days.

## Dermatologic and Oral Complications

### Aphthous Ulcers

**CAUSE:** Unknown

**DIFFERENTIAL:** HSV, CMV drug induced ulcers

### CLASSIFICATION

- **Minor:** <1 cm diameter, usually self-limiting (usually heals in 10 to 14 days)
- **Major:** >1 cm, deep, prolonged, heals slowly, causes pain, and may prevent oral intake (*AIDS* 1992;6:963; *Oral Surg Oral Med Oral Path* 1996;81:141)

## TREATMENT

- **Topical treatment 2 to 4x/day**
  - Lidocaine solution before meals
  - Triamcinolone hexacetonide in *Orabase*
  - Fluocinonide gel (*Lidex*) 0.05% ointment mixed 1:1 with *Orabase* or covered with *Orabase*
  - Amlexanox 5% oral paste (*J Oral Maxillofac Surg* 1993;51:243)
- **Oral and intralesional therapy (refractory cases)**
  - Prednisone 40 mg/day PO x 1 to 2 weeks then taper
  - Colchicine 1.5 mg/day (*J Am Acad Derm* 1994;31:459)
  - Dapsone 100 mg/day
  - Pentoxifylline (*Trental*) 400 mg PO tid with meals
  - Thalidomide 200 mg/day PO x 4 to 6 weeks ± maintenance with 200 mg 2x/week. Note: Thalidomide is “experimental” for aphthous ulcers. See p. 310 for purchase instructions. Thalidomide has strict requirements for use, but the experience is very favorable (*N Engl J Med* 1997;337:1086; *Clin Infect Dis* 1995;20:250; *J Infect Dis* 1999;180:61; *Arch Derm* 1990;126:923).

### Bacillary Angiomatosis (*Arch Intern Med* 1994;154:524; *Dermatology* 2000;21:326)

**CAUSE:** *Bartonella henselae* and *quintana*. Both cause cutaneous lesions that do not differ in appearance, histopathologic findings, or treatment, although organ tropism differs.

**PRESENTATION:** Papular, nodular, pedunculated, and verrucous forms. Lesions usually start as red or purple papules that gradually expand to nodules or pedunculated masses. They appear vascular and may bleed extensively with trauma. There is usually one or several lesions, but there may be hundreds.

**DIFFERENTIAL:** Kaposi's sarcoma, cherry angioma, hemangioma, pyogenic granuloma, dermatofibroma.

**DIAGNOSIS:** Skin biopsy – lobular vascular proliferation with inflammation; Warthin Starry silver stain shows typical organisms as small black clusters. Serology is available (IFA and EIA), but utility in patients with AIDS is not established. IFA titers >1:256 usually indicates active infection.

**TREATMENT** (see p. 118)

- **Preferred regimen:** Erythromycin 500 mg PO qid x >3 months
- **Alternative:** Doxycycline 100 mg PO bid, azithromycin 0.5-1 g/day PO, or doxycycline + rifampin 300 mg IV or PO bid x >3 months

### Candidiasis, Cutaneous (*Clin Infect Dis* 2000;30:652)

**CAUSE:** Superficial infection of skin/mucous membranes, usually by *C. albicans*.

**PRESENTATION (SKIN):** Moist, beefy red with scaling and satellite papules. Variations: Intertrigo, balanitis, glossitis, angular cheilitis, paronychia, nail dystrophies.

**DIAGNOSIS:** Usually clinical; KOH prep or fresh mount shows pseudohyphae.

**TREATMENT**

- **Topical:** Ketoconazole, miconazole, clotrimazole, econazole, or nystatin – all bid.

- **Systemic:** Ketoconazole (200-400 mg PO qd) or fluconazole (100-200 mg PO qd).

## Candidiasis, Oropharyngeal (thrush) (see p. 120)

### PRESENTATION

- **White plaques** (pseudomembranous form) on inflamed base on buccal mucosa, gingiva palate, tongue, or oropharynx (most common).
- **Erythema without plaques** (atrophic form) with spotty or confluent red patches.
- **Angular cheilitis** ("perlèche") – painful fissure at the corner of the mouth.

**PROVOCATIVE FACTORS:** Antibiotics, radiation therapy, corticosteroids, dentures, immunosuppression.

**SYMPTOMS:** Taste loss, pain with eating and swallowing; often asymptomatic.

**DIAGNOSIS:** Usually clinical; KOH or gram stain of lesion shows budding yeast or pseudohyphae. Culture primarily for testing sensitivity.

**TREATMENT:** See p. 120

## Cholangiopathy, AIDS (*Dig Dis* 1998;16:205)

**CAUSE:** Cryptosporidiosis is the most common identified microbial cause. Other causes: Microsporidia, CMV, and Cyclospora. About 20% to 40% are idiopathic.

**FREQUENCY:** Relatively rare and seen primarily in late stage AIDS

**PRESENTATION:** Right upper quadrant pain, LFTs show cholestasis. Late stage HIV with CD4 count <100 cells/mm<sup>3</sup>

**DIAGNOSIS:** ERCP (preferred); ultrasound is 75% to 95% specific

**TREATMENT:** Based on cause. Treat pathogen when possible – CMV and Cyclospora. Usual treatment is mechanical and based on lesion.

- **Papillary stenosis:** ERCP with sphincterectomy for pain relief
- **Cholangiopathy without papillary stenosis:** Ursodeoxycholic acid 300 mg PO tid (*Am J Med* 1997;103:70). Experience limited.
- **Isolated bile duct structure:** Endoscopic stenting

## Cryptococcosis (*Clin Infect Dis* 2000;30:652)

**CAUSE:** Disseminated cryptococcosis usually from a pulmonary portal of entry

**PRESENTATION:** Nodular, papular, follicular, or ulcerative skin lesions; may resemble molluscum. Usual locations are face, neck, scalp.

**DIAGNOSIS:** Serum cryptococcal antigen assay is usually positive. Skin biopsy – Gomori methenamine silver stain shows typical encapsulated, budding yeast, and positive culture. Perform LP in any patient with a positive culture for *C. neoformans*.

**TREATMENT:** If negative LP, fluconazole 400 mg/day PO x 8 weeks, then 200 mg/day. If positive LP, see pp. 122-123.

## Dermatophytic Infections

**DEFINITION:** Fungal infection of skin, hair, and nails

**CAUSE:** *T. rubrum*, *T. mentagrophytes*, *M. canis*, *E. floccosum*, *T. tonsurans*, *T. verrucosum*, *T. soudanense* (*Candida* causes typical nail and skin lesions), *Malassezia furfur* causes tinea versicolor. (Note: *Candida* and *M. furfur* are not dermatophytes.)

### PRESENTATION

- **T. pedis:** Pruritic, red lesions between toes ± interdigital fissures, extension to adjacent skin and nails, scaling is always present.
- **Onychomycosis:** Starts with discoloration, usually on distal nail at one side and spreads toward the other side and toward the cuticle, leaving heaped up keratinous debris.
- **T. corporis:** Circular erythematous scaling that spreads with central clearing (ringworm).
- **T. cruris:** Red scaly patch on inner thigh with sharply demarcated borders.

**FORMS:** Tinea corporis (ringworm), tinea cruris (jock itch), tinea pedis (athlete's foot), tinea unguium or onychomycosis (nail involvement), and tinea capitis (ringworm of scalp)

**DIAGNOSIS:** Scrapings of skin lesion or discolored nail bed for KOH preparation. This may be supplemented with culture of scraping on Sabouraud's medium.

## TREATMENT

- **Onychomycosis:** Topical therapy is usually not effective.
  - Preferred treatment: Terbinafine 250 mg/day x 8 weeks (fingernails) or 12 weeks (toenails). Terbinafine is also hepatotoxic and is expensive but has better long term results than itraconazole (*Brit J Dermatol* 1999;141[Suppl 56]:15).
  - Itraconazole "pulse therapy," 400 mg/day for 1 week/month x 2 months (fingernails) or x 3 months (toenails). Main concerns are hepatotoxicity, drug interactions, cardiotoxicity, and cost of treating a benign infection.
- **Tinea corporis, tinea cruris, tinea pedis:** Topical agent for 2 weeks (T. cruris) to 4 weeks (T. pedis):
  - Clotrimazole (*Lotrimin*)\* 1% cream or lotion bid
  - Econazole (*Spectazole*) 1% cream qd or bid
  - Ketoconazole (*Nizoral*) 2% cream qd
  - Miconazole (*Monostat-Derm*)\* 2% cream bid
  - Butenafine (*Mentax*) 1% cream
  - Terbinafine (*Lamisil*)\* 1% cream or gel qd or bid
  - Tolnaftate (*Tinactin*)\* 1% cream, gel, polder, solution, or aerosol bid

\* Available over-the-counter.

- **Refractory, chronic, or extensive disease:** Griseofulvin 250-500 mg microsize bid; terbinafine 250 mg qd x 2 to 4 weeks; itraconazole 100-200 mg qd x 2 to 4 weeks.

## Drug Eruptions

**CAUSE:** Most common are antibiotics, especially sulfonamides, beta-lactams, NNRTI, amprenavir

**PRESENTATION:** Most common – morbilliform, macular, and maculopapular rash, usually pruritic ± low grade fever; usually within 2 weeks of new drug and days of re-exposure. Less common and more severe forms:

- Urticaria: Intensely pruritic, red and circumscribed
- Anaphylaxis: Laryngeal edema, nausea, vomiting ± shock
- "Hypersensitivity syndrome": Severe reaction with rash and fever ± hepatitis, arthralgias, lymphadenopathy, and hematologic changes with eosinophilia and atypical lymphocytes, usually at 2 to 6 weeks after drug is started (*N Engl J Med* 1994;331:1272). See abacavir (p. 164) and nevirapine (p. 267)

- Stevens-Johnson Syndrome: Fever, erosive stomatitis, disseminated dark red macules, ocular involvement; mortality – 5%
- Toxic epidermal necrolysis: Epidermal necrosis with scalded skin appearance ± mucous membrane involvement; mortality – 50% (*N Engl J Med* 1994;331:1272)
- Abacavir hypersensitivity: See p. 164
- NNRTI hypersensitivity: See p. 267

**TREATMENT:** Discontinue implicated agent (for TMP-SMX, see p. 318)

- Pruritic uncomplicated drug rashes – antihistamines, topical antipruritics, and topical corticosteroids
- Stevens-Johnson Syndrome and toxic epidermal necrolysis: Severe cases are managed as burns + support; corticosteroids are not indicated (*Cutis* 1996;57:223).

## Folliculitis

**CAUSE:** Bacterial is most common, due to *Staphylococcus aureus*, *Pityrosporum ovale* (intrafollicular yeast), *Demodex folliculorum* (intrafollicular mite), eosinophilic inflammation without a detectable infectious agent in eosinophilic folliculitis

**PRESENTATION:** Follicular papules and pustules on face, trunk, and extremities; usually very pruritic causing excoriations; multiple exacerbations and spontaneous remissions; usually seen with CD4 counts <250 cells/mm<sup>3</sup> and >50 cells/mm<sup>3</sup>.

**DIAGNOSIS:** Clinical presentation and biopsy – follicular inflammation ± follicular destruction and abscess formation. Special stains such as PASD and B+B may show infectious agent. Multiple eosinophils destroying the hair follicle wall and eosinophilic abscesses are seen in eosinophilic folliculitis. Culture of pustule may grow infectious agent if bacterial.

**TREATMENT:** Varies according to the etiologic agent involved.

- *S. aureus*: Topical erythromycin or clindamycin or systemic anti-staphylococcal antibiotic
- *P. ovale*: Topical or systemic antifungal agents
- *D. Folliculorum*: Permethrin cream or oral metronidazole
- Eosinophilic: Topical steroids, phototherapy with UVB and/or PUVA (*N Engl J Med* 1988;318:1183; *Arch Dermatol* 1995;131:360)
- General: Antihistamines (high dose, mixed classes together) for symptomatic relief

## Gingivitis

**CAUSE:** Anaerobic bacteria

**PHASES:** Linear gingival erythema → necrotizing gingivitis → necrotizing periodontitis → necrotizing stomatitis

■ **TABLE 7-1: Phases of Gingivitis**

Lesion	Location	Clinical Features
Linear gingival erythema	Gingiva	Painless, bright red at gingival margin
Necrotizing gingivitis	Gingiva	Painful, red gingiva, and ulceration
Necrotizing periodontitis	Gingiva and bone	Painful, red gingiva, and loose teeth
Necrotizing stomatitis	Gingiva, bone, and soft tissue	Painful, red gingiva, and removable teeth

### TREATMENT

- **Routine dental care:** Brush and floss ± topical antiseptics: *Listerine* swish x 30-60 seconds bid, *Peridex*, etc.
- **Dental consultation:** Curettage and debridement
- **Antibiotics** (necrotizing stomatitis): Metronidazole; alternatives – clindamycin and amoxicillin-clavulanate

Herpes Simplex (see p. 134)

Herpes Zoster (*N Engl J Med* 2002;347:340)

**CAUSE:** Varicella zoster virus (VZV). AIDS patients have high rate of VZV, zoster-associated complications, atypical disease, and refractory disease. HIV infected patients infrequently have post-herpetic neuralgia.

### FORMS

- **Dermatomal:** See p. 135
- **Neurologic:** Complications include encephalitis, myelitis, aseptic meningitis, and stroke syndromes.
- **Zoster ophthalmicus:** Involves 1st division of trigeminal nerve with lesions on forehead, periorbital area, and nose; high rate of ocular complications and needs ophthalmologist.
- **Acute retinal necrosis:** May result in acute vision loss that can progress to involve other eye; needs IV acyclovir to protect vision (see p. 136).

- **Ramsey Hunt syndrome:** Polycranial neuropathy with facial paralysis, ear pain, and vesicles in auditory canal and auricle.

**PRESENTATION:** Prodrome of headache, photophobia, and malaise, but usually no fever; then tingling or pruritus at skin site, then painful maculopapular rash that evolves to vesicles, pustules, and scabs over 3 to 5 days with healing over 2 to 4 weeks.

**DIAGNOSIS:** Alcohol wiped lesion is unroofed by needle with vesicular fluid for stain and culture. Tzanck smear shows multinucleate giant cell diagnostic of HSV or VZV but is insensitive. A viral culture is definitive, but the virus is difficult to grow. DFA stain compared with culture is faster (2 hours vs 3 to 5 days), more sensitive, and less expensive.

**TREATMENT** (see p. 135)

- **Antiviral**
  - Valacyclovir 1 g tid x 7 days
  - Acyclovir 800 mg 5x/day x 7 to 10 days
  - Famciclovir 500 mg tid x 7 days
- **Corticosteroids** (controversial)
- **Acyclovir resistant:** Foscarnet 60 mg IV q12h or cidofovir 5 mg/kg qwk x 2
- **Postherpetic neuralgia**
  - Oxycodone 5 mg q6h
  - Nortriptyline 10-25 mg hs
  - Gabapentin 300 mg/day
  - Capsaicin topical 3 to 4x/day
  - Lidocaine patch ≤3/day

### Kaposi's Sarcoma (KS) (see p. 363)

**CAUSE:** Human Herpesvirus Type 8 (HHV-8, KSHV)

**PRESENTATION:** Firm, purple to brown-black colored macules, patches, plaques, papules, nodules, or tumors; usually asymptomatic. Most common sites: Face, chest, genitals, oral mucosa, and feet; usually multiple; symmetric distribution. Visceral involvement and lymphatic obstruction are frequent.

**DIFFERENTIAL:** Pyogenic granuloma, hemangioma, hematoma, bacillary angiomatosis, B-cell lymphoma

**DIAGNOSIS:** Clinical presentation and biopsy confirmation

**TREATMENT:** Determined by symptoms, cosmetic concerns, and quality of life issues.

- **HAART:** Often induces resolution
- **Local:** 1) Surgical excision, 2) Intralesional vinblastine (0.1 mg/cm<sup>2</sup>) (*Lancet* 1989;2:1100), 3) Intralesional 3% Na tetradecyl sulfate (*N Engl J Med* 1993;328:210), 4) Radiation (may cause severe mucositis), 5) Cryotherapy, and 6) Laser ablation.
- **Extensive and widespread:** Treat systemically; usually with liposomal doxorubicin or paclitaxel. See p. 364

## Molluscum Contagiosum

**CAUSE:** A poxvirus

**PRESENTATION:** Flesh colored, pink, or whitish, dome-shaped papules with centra umbilication (dimpling). It can occur anywhere on the body, except palms and soles. Most common areas are the face (beard area), neck, and genitals. Lesions are usually less than 5 mm in diameter; occasionally lesions are greater than 1 cm (giant molluscum).

**DIFFERENTIAL:** Warts, folliculitis, cryptococcosis, and histoplasmosis

**DIAGNOSIS:** Clinical presentation; may be confirmed by KOH preparation, Tzanck smear, or biopsy that show intraepidermal molluscum bodies. EM shows a large brick-shaped virus resembling smallpox.

**TREATMENT:** An individual lesion may be treated with curettage, cryotherapy, electrocauterization (*Sex Trans Infect* 1999;75[suppl 1]:S80), chemical cauterization (trichloroacetic acid, cantharidin, podophyllin, 5-FU, tretinoin, silver nitrate, phenol), imiquimod, topical cidofovir. Lesions usually disappear in patients responding to HAART (*Eur J Dermatol* 1999;9:211).

## Oral Hairy Leukoplakia (OHL) (*Clin Infect Dis* 1997;25:1392)

**CAUSE:** Intense replication of EBV

**PRESENTATION:** Unilateral or bilateral adherent white/gray patches on lingual lateral margins ± dorsal or ventral surface of tongue. Patches are irregular folds and projections.

**DIFFERENTIAL:** Candidiasis – OHL does not respond to azoles and cannot be scraped off, unlike *Candida*; Others – squamous cell carcinoma or traumatic leukoplakia.

**DIAGNOSIS:** Appearance; biopsy rarely necessary

**IMPLICATIONS:** Found almost exclusively with HIV, indicates low CD4 count, predicts AIDS, and responds to immune reconstitution with HAART.

**TREATMENT** (*Clin Infect Dis* 1997;25:1392): Rarely symptomatic and rarely treated, but occasional patients have pain or have concern about appearance. The options include:

- **HAART** (preferred)
- **Topical podophyllin**
- **Surgical excision**
- **Cryotherapy**
- **Anti-EBV treatment:** Acyclovir 800 mg PO 5x/day x 2 to 3 weeks, then 1.2-2 gm/day. Other effective antivirals include famciclovir, valacyclovir, foscarnet, ganciclovir, and valganciclovir. The problem with anti-EBV agents is that the lesions recur when treatment is discontinued.

## Prurigo Nodularis

**CAUSE:** Unknown

**FREQUENCY:** Common usually with CD4 <200 cells/mm<sup>3</sup>

**PRESENTATION:** Hyperpigmented, hyperkeratotic, often excoriated papules and nodules up to 1 cm; 90% are above nipple line. Major symptom is severe pruritus. Usually associated with other signs of chronic pruritus or excoriations, including lichen simplex chronicus, patches of hyperpigmentation, linear erosions, ulcerations, and scars.

**DIFFERENTIAL:** Other causes of pruritus: Dry skin, seborrhea, staph folliculitis, drug eruption

**DIAGNOSIS:** Clinical features; biopsy may be necessary

**TREATMENT:** Must interrupt vicious cycle: Pruritus → scratch trauma → lichenification → increased pruritus. Treat with high potency topical steroids under occlusive dressing. May benefit from oral antihistamines or phototherapy.

## Salivary Gland Enlargement

**CAUSE:** May be lymphoid proliferation due to HIV (*Ann Intern Med* 1996;125:494)

**PRESENTATION:** Parotid swelling, cystic, unilateral or bilateral, non-tender, usually asymptomatic; may be painful, cosmetically disfiguring, or cause xerostomia (*Ear Nose Throat J* 1990;69:475).

**DIFFERENTIAL:** Must differentiate cystic vs solid lesion – CT scan (*Laryngoscope* 1998;98:772) and/or fine needle aspiration (FNA) for microbiology and cytology and decompression. May require biopsy.

### TREATMENT

- FNA for decompression of fluid-filled parotid cysts
- **Xerostomia:** Sugarless chewing gum, artificial saliva, pilocarpine

### Scabies (*MMWR* 2002;51[RR-6]:68)

**CAUSE:** *Sarcoptes scabiei* (mite)

**PRESENTATION:** Small red papules that are intensely pruritic, especially at night. Sometimes presentation is the “burrow,” a 3-15 mm line which represents the superficial tunnel the female mite digs at 2 mm/day to lay eggs. Usual locations are the interdigital webs of the fingers, volar aspect of the wrist, periumbilical area, axilla, thighs, buttocks, genitalia, feet, and breasts. Scabies crostosus is a severe form seen in compromised hosts, including AIDS patients. There is uncontrolled spread to involve large areas, sometimes the total skin surface with scales and crusts that show thousands of mites.

**DIAGNOSIS:** The mite is 0.4 x 0.3 mm, 8 legged, and shaped like a turtle. It is visible to the naked eye but burrowing precludes detection. Scrape infected area, place on a slide with a coverslip, and examine under 10x magnification to demonstrate mites or eggs.

**TREATMENT:** All family members and close contacts must be treated at the same time.

- **Permethrin cream** (5%) (*Elimite*) applied to total body, neck down, and washed off at 8 to 14 hours. Re-treat at 1 to 2 weeks if symptomatic or if live mites are present, but this is usually unnecessary. A 30 g tube of *Elimite* is usually adequate for an adult.
- **Lindane** (1%) 1 oz lotion or 30 g cream applied as a thin layer to total body, neck down, and washed off at 8 hours is an alternative. Lindane is less expensive than *Elimite*, but there is rare resistance and more side effects.
- **Ivermectin** (*Stromectol*) 200 µg/kg PO repeated at 2 weeks (*N Engl J Med* 1995;333:26).
- Rash and pruritus may persist up to 2 weeks post treatment – warn patients.
- Bedding and clothing must be decontaminated; machine wash in hot water and machine dry with high heat, or dry clean.
- **Itching:** Hydroxyzine (*Atarax*) or diphenhydramine (*Benadryl*)

- **Scabies crustosus (crusted or “Norwegian” scabies):** Isolate immediately and use strict barrier precautions. Treat with ivermectin 200 µg/kg PO followed by a second dose 1 to 2 weeks later, plus permethrin topically until scales and crust have resolved.

## Seborrheic Dermatitis

**CAUSE:** *Pityrosporum* yeast is the usual cause, but it may not play a central role in HIV-associated seborrhea (*J Am Acad Dermatol* 1992;27:37).

**PRESENTATION:** Erythematous plaques with greasy scales and indistinct margins on scalp, central face, post auricular area, trunk, and occasionally pubic area

**DIFFERENTIAL:** Psoriasis and tinea capis

**DIAGNOSIS:** Clinical features

### TREATMENT

- **Topical steroid:** Mid-potency such as triamcinolone 0.1% or weaker (desonide 0.05%), hydrocortisone 2.5% for the face ± ketoconazole 2% cream applied twice per day for the duration of the flare only.
- **Shampoos:** Tar-based (*Z-tar*, *Pentrax*, *DHS tar*, *T-gel*, *Ionil T plus*), selenium sulfide (*Selsun*, *Exelderm*), or zinc pyrithione (*Head & Shoulders*, *Zincon*, *DHS zinc*) applied daily, or ketoconazole shampoo applied twice per week.

## Gastrointestinal Complications

### Anorexia, Nausea, Vomiting

**MAJOR CAUSES:** Medications (especially antiretrovirals, antibiotics, opiates, and NSAIDs), depression, intracranial pathology, GI disease, hypogonadism, pregnancy, lactic acidosis, acute gastroenteritis

**EVALUATION:** Drug holiday, lactic acid level, fasting testosterone level, GI evaluation (endoscopy, CT scan), intracranial evaluation (head CT scan or MRI)

**TREATMENT:** Treat underlying condition.

#### ■ Anorexia

- *Megace* 400-800 mg qd. Weight gain is mostly fat. May decrease testosterone level; consider *Megace* + testosterone.
- Dronabinol (*Marinol*) 2.5 mg PO bid; active ingredient of marijuana. Weight gain is mostly fat.

## ■ Nausea and vomiting

- *Compazine* 5-10 mg PO q6h-q8h; *Tigan* 250 mg PO q6h-q8h; *Dramamine* 50 mg PO q6h-q8h; *Ativan* 0.025-0.05 mg/kg IV or IM; haloperidol 1-5 mg bid PO or IM; dronabinol 2.5-5 mg PO bid; ondansetron (*Zofran*) 0.2 mg/kg IV or IM.
- Note: Phenothiazines (*Compazine*, *Haldol*, *Tigan*, and *Reglan*) may cause dystonia. *Zofran* efficacy is established only for cancer chemotherapy and costs \$16.64/4 mg.
- PEG: May require percutaneous endoscopic gastrostomy (PEG) to deliver nutrition and meds, including HAART regimen.

## Diarrhea, Acute

(Acute diarrhea defined as  $\geq 3$  loose or watery stools for 3 to 10 days)

### DIAGNOSTIC EVALUATION

#### Medication-related

- Main antiretroviral agents: Nelfinavir, lopinavir/ritonavir, and saquinavir (*Fortovase*)
- Management (*Clin Infect Dis* 2000;30:908)
  - Loperamide 4 mg, then 2 mg every loose stool, up to 16/day
  - Calcium 500 mg bid; psyllium 1 tsp qd or 2 bars qd; oat bran 1500 mg bid
  - Pancreatic enzymes 1-2 tabs with meals

**Pathogen detection** (*Clin Infect Dis* 2001;32:331; *Arch Path Lab Med* 2001;125:1042)

- Blood culture: MAC, *Salmonella*
- Stool culture: *Salmonella*, *Shigella*, *C. jejuni*, *Vibrio*, *Yersinia*, *E. coli* 0157
- Stool assay for *C. difficile* toxin A and B
- O&P examination + AFB (*cryptosporidia*, *Cyclospora*, *Isospora*), trichrome or other stain for Microsporidia and antigen detection (*Giardia*)

#### Radiology

- Plain x-rays and contrast x-ray – usually not helpful
- CT scan – most helpful with CMV colitis and lymphoma

**Endoscopy:** Most useful for CMV, Kaposi's sarcoma, and lymphoma

### CAMPYLOBACTER JEJUNI

**FREQUENCY:** 4% to 8% of HIV infected patients with acute diarrhea

**CLINICAL FEATURES:** Watery diarrhea or bloody flux, fever, fecal leukocytes variable; any CD4 count

**DIAGNOSIS:** Stool culture; most laboratories cannot detect *C. cinaedi*, *C. fennelli*, etc.

**TREATMENT** (*Clin Infect Dis* 2001;32:331): Erythromycin 500 mg PO qid x 5 days; fluoroquinolone resistance rates are >20%.

### **CLOSTRIDIUM DIFFICILE**

**FREQUENCY:** 10% to 15% of HIV infected patients with acute diarrhea

**CLINICAL FEATURES:** Watery diarrhea, fecal WBCs variable; fever and leukocytosis common; prior antibacterial agents nearly always, especially clindamycin, ampicillin, and cephalosporins; any CD4 count

### **DIAGNOSIS**

- Endoscopy: pseudomembranous colitis (PMC), colitis, or normal (this procedure is not usually indicated)
- Stool toxin assay: Tissue culture or EIA preferred
- CT scan: Colitis with thickened mucosa

**TREATMENT** (*N Engl J Med* 2002;346:334)

- Metronidazole 250 mg PO qid or 500 mg PO tid x 10 to 14 days (preferred)
- Vancomycin 125 mg PO qid x 10 to 14 days
- Antiperistaltic agents (*Lomotil* or *Loperamide*) are contraindicated.

**RESPONSE:** Fever usually resolves within 24 hours and diarrhea resolves in an average of 5 days. About 20% to 25% have relapses at 3 to 14 days after treatment stopped.

### **ENTERIC VIRUSES**

**FREQUENCY:** 15% to 30% of HIV infected patients with acute diarrhea

**CLINICAL FEATURES:** Watery diarrhea, acute, but one-third become chronic; any CD4 cell count

**DIAGNOSIS:** Major agents: Adenovirus, astrovirus, picornavirus, calicivirus (*N Engl J Med* 1993;329:14); clinical laboratories cannot detect these viruses.

**TREATMENT:** Supportive treatment: *Lomotil* or *Loperamide*

## ESCHERICHIA COLI

■ TABLE 7-2: *E. coli* Strain and Treatment

Agent	Clinical Presentation	Treatment
Enterotoxigenic (ETEC)	Traveler's diarrhea	■ <i>Cipro</i> 500 mg bid x 3 days ■ TMP-SMX DS bid x 3 days
Enterohemorrhagic 0157:H7 (EHEC)*	Bloody diarrhea	Antibiotics contraindicated
Enteroinvasive (EIEC)	Dysentery	■ <i>Cipro</i> 500 mg bid x 5 days ■ TMP-SMX DS bid x 5 days
Enteropathic (EPEC)	Watery diarrhea	Usually no antibiotic or <i>Cipro</i> 500 mg bid x 3 days

\* Only *E. coli* that can be detected with stool analysis in most labs.

## SALMONELLA

**FREQUENCY:** 5% to 15% of HIV infected patients with acute diarrhea

**CLINICAL FEATURES:** Watery diarrhea, fever, fecal WBCs variable; any CD4 count

**DIAGNOSIS:** Stool culture, blood culture

### TREATMENT

- Ciprofloxacin 500 mg PO bid x  $\geq 14$  days
- TMP-SMX 1 to 2 DS PO bid x  $\geq 14$  days
- Third-generation cephalosporin or cefotaxime 4 to 8 g/day IV or ceftriaxone 2 g/day IV
- Treatment may need to be extended to  $\geq 4$  weeks
- AZT and TMP-SMX may prevent salmonellosis

## SHIGELLA

**FREQUENCY:** 1% to 3% of HIV infected patients with acute diarrhea

**CLINICAL FEATURES:** Watery diarrhea or bloody flux, fever, fecal WBCs common; any CD4 count

**DIAGNOSIS:** Stool culture

**TREATMENT** (*Clin Infect Dis* 2001;32:331)

- Ciprofloxacin 500 mg PO bid x 3 days
- TMP-SMX 1 DS PO bid x 3 days

**IDIOPATHIC**

**FREQUENCY:** 25% to 40% of HIV infected patients with acute diarrhea

**CLINICAL FEATURES:** Variable noninfectious causes; rule out medications, dietary, irritable bowel syndrome; any CD4 cell count

**DIAGNOSIS:** Negative studies including culture, O&P examination, and *C. difficile* toxin assay

**EMPIRIC TREATMENT, SEVERE ACUTE IDIOPATHIC DIARRHEA**

- Ciprofloxacin 500 mg PO bid
- Ofloxacin 200-300 mg PO bid x 5 days ± metronidazole (*Arch Intern Med* 1990;150:541; *Ann Intern Med* 1992;117:202; *Clin Infect Dis* 2001;32:331).

**Diarrhea, Chronic**

(Advanced HIV infection and chronic diarrhea defined as >2 loose or watery stools/day for ≥30 days.)

**CRYPTOSPORIDIA** (see p. 126)

**FREQUENCY:** 10% to 30% of chronic diarrhea in AIDS patients

**CLINICAL FEATURES:** Enteritis; watery diarrhea; no fecal WBCs; fever variable; malabsorption; wasting; large stool volume with abdominal pain; remitting symptoms for months; CD4 cell count <150/mm<sup>3</sup> is associated with recurrent or chronic disease.

**DIAGNOSIS:** AFB smear of stool to show oocyst of 4-6 μm

**TREATMENT** (*Clin Infect Dis* 2001;32:331)

- Best results are with HAART.
- Paromomycin 1000 mg bid or 500 mg PO bid x 7 days; efficacy is marginal.
- Nitazoxanide 1000 mg/day (not FDA-approved)
- Azithromycin 600 mg/day + paromomycin (above doses) x ≥4 weeks
- Nutritional support plus *Lomotil*; may require parenteral hyperalimentation in severe cases.

**RESPONSE:** The most effective treatment is immune reconstitution; even small rises in CD4 count often succeed in controlling diarrhea.

## **CYCLOSPORA**

**FREQUENCY:** <1% of chronic diarrhea in AIDS patients (not uniquely susceptible)

**CLINICAL FEATURES:** Enteritis; watery diarrhea; CD4 cell count <100/mm<sup>3</sup>

**DIAGNOSIS:** Stool AFB smear: Resembles cryptosporidia

**TREATMENT:** TMP-SMX 1 DS bid x 3 days

## **CYTOMEGALOVIRUS**

**FREQUENCY:** 15% to 40% of chronic diarrhea in AIDS patients

**CLINICAL FEATURES:** Colitis and/or enteritis; fecal WBC and/or blood; cramps; fever; watery diarrhea ± blood; may cause perforation; hemorrhage, toxic megacolon, ulceration; CD4 cell count <50/mm<sup>3</sup>

### **DIAGNOSIS**

- Biopsy to show intranuclear inclusion bodies, preferably with inflammation, vasculitis
- CT scan: segmental or pancolitis ± enteritis
- Cannot establish this diagnosis with CMV markers in blood or stool; need biopsy.

### **TREATMENT**

- HAART
- Valganciclovir 900 mg PO bid x 3 weeks, then 900 mg qd
- Ganciclovir 5 mg/kg IV bid x 2 weeks, then valganciclovir 900 mg/day
- Foscarnet 40-60 mg/kg IV q8h 2 x weeks, then 90 mg/kg/day

**RESPONSE:** Results of antiviral treatment variable (*Ann Intern Med* 1990;112:505; *J Infect Dis* 1993;167:278); foscarnet and ganciclovir are equally effective or ineffective (*J Infect Dis* 1995;172:622).

## **ENTAMOEBIA HISTOLYTICA**

**FREQUENCY:** 1% to 3% of chronic diarrhea in AIDS patients

**CLINICAL FEATURES:** Colitis; bloody stools; cramps; no fecal WBCs (bloody stools); most are asymptomatic carriers; any CD4 cell count

**DIAGNOSIS:** Stool O&P examination. Must distinguish from non-pathogenic *E. dispar*.

**TREATMENT:** Metronidazole 500-750 mg PO or IV tid x 5 to 10 days, then iodoquinol 650 mg PO tid x 21 days or paromomycin 500 mg PO qid x 7 days

***GIARDIA LAMBLIA***

**FREQUENCY:** 1% to 3% of chronic diarrhea in AIDS patients (not uniquely susceptible)

**CLINICAL FEATURES:** Enteritis; watery diarrhea ± malabsorption, bloating; flatulence; any CD4 cell count

**DIAGNOSIS:** Antigen detection

**TREATMENT:** Metronidazole 250 mg PO tid x 10 days

***ISOPORA BELLI*** (see p. 138)

**FREQUENCY:** 1% to 3% of chronic diarrhea in AIDS patients

**CLINICAL FEATURES:** Enteritis; watery diarrhea; no fecal WBCs; no fever; wasting; malabsorption; CD4 cell count <100/mm<sup>3</sup>

**DIAGNOSIS:** AFB smear of stool; oocysts: 20 to 30 µm

**TREATMENT:** TMP-SMX 3-4 DS/day; Pyrimethamine 50-75 mg/day PO x 7 to 10 days

**RESPONSE:** Most respond promptly.

**MICROSPORIDIA: *ENTEROCYTOZON BIENEUSI* OR *ENTEROCYTOZON (SEPTATA) INTESTINALIS*** (see p. 140)

**FREQUENCY:** 15% to 30% of chronic diarrhea in AIDS patients

**CLINICAL FEATURES:** Enteritis, watery diarrhea, no fecal WBCs; fever uncommon; remitting disease over months; malabsorption; wasting; CD4 cell count <100/mm<sup>3</sup>

**DIAGNOSIS**

- Special trichrome stain described (*N Engl J Med* 1992;326:161; *J Clin Microbiol* 1993;31:3264)
- Alternative: Florescent stains with similar sensitivity (*J Clin Microbiol* 1995;33:805)

**TREATMENT**

- Albendazole 400-800 mg PO bid x ≥3 weeks; efficacy is established only for *Septata intestinalis*.

- Fumagillin 60 mg PO qd x 14 days for *E. bienersi* (*N Engl J Med* 2002;346:1963); monitor for neutropenia and thrombocytopenia.

**RESPONSE:** Albendazole produces clinical response and pathogen clearance but only for *E. intestinalis*; fumagillin produces clinical response and microbial clearance for *E. bienersi*, which causes 80% of cases of microsporidiosis, but some relapse and marrow suppression is common.

### **MYCOBACTERIUM AVIUM COMPLEX (MAC)** (see p. 141)

**FREQUENCY:** 10% to 20% of chronic diarrhea in AIDS patients

**CLINICAL FEATURES:** Enteritis; watery diarrhea; no fecal WBCs; fever and wasting common; diffuse abdominal pain in late stage; CD4 cell count <50/mm<sup>3</sup>.

**DIAGNOSIS:** Positive blood cultures for *M. avium* complex; biopsy may show changes typical of Whipple's disease, but with AFB; CT scan may be supportive: Hepatosplenomegaly, adenopathy, and thickened small bowel.

### **TREATMENT**

- Clarithromycin 500 mg PO bid + EMB 15 mg/kg/day
- Azithromycin 600 mg/day + EMB 15 mg/kg/day ± rifabutin 300 mg/day

**RESPONSE:** Slow response over several weeks

### **IDIOPATHIC (PATHOGEN-NEGATIVE)**

**FREQUENCY:** 20% to 30% of chronic diarrhea in AIDS patients who undergo a full diagnostic evaluation including endoscopy

**CLINICAL FEATURES:** Usually low-volume diarrhea that resolves spontaneously or is controlled with antimotility agents (*Gut* 1995;36:283). Typically not associated with significant weight loss and often resolves spontaneously.

**DIAGNOSIS:** Biopsy shows villus atrophy, crypt hyperplasia/no identifiable cause despite endoscopy with biopsy and EM for microsporidia (*Clin Infect Dis* 1992;15:726). These histologic changes are unlikely to explain diarrhea because they are seen in symptom-free persons with HIV (*Lancet* 1996;348:379). With pathogen-negative, persistent, large volume diarrhea, must rule out KS and lymphoma.

**TREATMENT:** Supportive care (frequent small feedings, bland food, avoid caffeine and lactose): *Lomotil* or *Loperamide*, nutritional support. Consider gluten-free diet.

## Esophagitis

■ TABLE 7-3: Esophageal Disease in Patients With HIV Infection

	<i>Candida</i>	Cytomegalovirus (CMV)	Herpes Simplex Virus	Aphthous Ulcers
<b>Frequency as cause of symptoms</b>	50% to 70%	10% to 20%	2% to 5%	10% to 20%
<b>Clinical features</b>				
Dysphagia	+++	+	+	+
Odynophagia	++	+++	+++	+++
Thrush	50% to 70%	<25%	<25%	<25%
Oral ulcers	Rare	Uncommon	Often	Uncommon
Pain	Diffuse	Focal	Focal	Focal
Fever	Infrequent	Often	Infrequent	Infrequent
<b>Diagnosis</b>				
Endoscopy	<ul style="list-style-type: none"> <li>■ Usually treated empirically</li> <li>■ Pseudo-membranous plaques; may involve entire esophagus</li> </ul>	<ul style="list-style-type: none"> <li>■ Biopsy required for treatment</li> <li>■ Erythema and erosions/ulcers, single or multiple discrete lesions, often distal.</li> </ul>	<ul style="list-style-type: none"> <li>■ Biopsy required for treatment</li> <li>■ Erythema and erosions/ulcers, usually small, coalescing, shallow</li> </ul>	<ul style="list-style-type: none"> <li>■ Similar in appearance and location to CMV ulcers</li> </ul>
Microbiology	<ul style="list-style-type: none"> <li>■ Brush: Yeast and pseudo-mycellum on KOH prep or PAS</li> <li>■ Culture with sensitivities may be useful with suspected resistance</li> </ul>	<ul style="list-style-type: none"> <li>■ Biopsy: Intracellular inclusions and/or positive culture.</li> <li>■ Highest yield with histopath of biopsy and culture. Culture is often not recommended due to false positives.</li> </ul>	<ul style="list-style-type: none"> <li>■ Brush/biopsy: Intracytoplasmic inclusions + multinucleate giant cells, FA stain, and/or positive culture.</li> </ul>	<ul style="list-style-type: none"> <li>■ Negative studies for <i>Candida</i>, HSV, CMV, and other diagnoses.</li> </ul>
<b>Treatment</b>				
Acute	<ul style="list-style-type: none"> <li>■ Fluconazole 200 mg/day PO, up to 800 mg/day.</li> <li>■ Refractory cases: Itraconazole 200 mg/day or voriconazole 200-300 mg PO or IV bid</li> <li>■ Amphotericin 0.5-0.7 mg/kg/day IV</li> <li>■ Caspofungin 70 mg/day IV x 1 then 50 mg/day</li> <li>■ Efficacy of fluconazole is 85% (<i>Ann Intern Med</i> 1993;118:825)</li> </ul>	<ul style="list-style-type: none"> <li>■ Ganciclovir 5 mg/kg IV bid x 2 to 3 weeks or valganciclovir 900 mg bid x 3 weeks, then 900 mg/day (when able to swallow).</li> <li>■ Foscarnet 40-60 mg/kg q8h x 2 to 3 weeks.</li> <li>■ Efficacy of antiviral treatment is 75%.</li> </ul>	<ul style="list-style-type: none"> <li>■ Acyclovir 200-800 mg PO 5x/day or 5 mg/kg IV q8h x 2 to 3 weeks or valacyclovir 1 gm PO tid (when able to swallow).</li> </ul>	<ul style="list-style-type: none"> <li>■ Prednisone 40 mg/day PO x 7 to 14 days, then taper 10 mg/week or more slowly.</li> <li>■ Thalidomide 200 mg/day PO (<i>BJM</i> 1989;298:432; <i>J Infect Dis</i> 1999;180:61).</li> <li>■ Corticosteroids by intralesional injection.</li> </ul>

■ TABLE 7-3: Esophageal Disease in Patients With HIV Infection  
(Continued)

	<i>Candida</i>	Cytomegalovirus (CMV)	Herpes Simplex Virus (HSV)	Aphthous Ulcers
Maintenance	<ul style="list-style-type: none"> <li>■ Fluconazole 100 mg/day PO (indicated with frequent or severe occurrences)</li> <li>■ Lower dose or less frequent dosing may reduce resistance</li> </ul>	<ul style="list-style-type: none"> <li>■ Maintenance treatment is arbitrary.</li> <li>■ May await relapse, then ganciclovir 5 mg/kg/day IV</li> <li>■ Possible role for oral ganciclovir.</li> </ul>	<ul style="list-style-type: none"> <li>■ Maintenance treatment is arbitrary; acyclovir 200-400 mg PO 3 to 5x daily.</li> </ul>	<ul style="list-style-type: none"> <li>■ None</li> </ul>

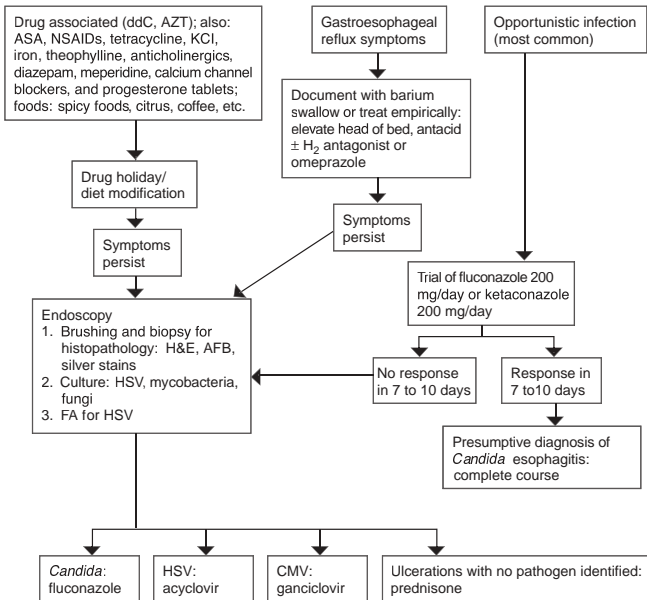
**Notes:**

1. One-third of AIDS patients develop esophageal symptoms (*Gut* 1989;30:1033). Esophageal ulcers are usually due to CMV (45%), or they are idiopathic/aphthous ulcers (40%); HSV accounts for only 5% (*Ann Intern Med* 1995;122:143).
2. Diagnostic studies may include barium swallow, but diagnostic yield is low (20% to 30%) compared with esophagoscopy; with endoscopy a diagnosis is established in about 70% to 95% (*Arch Intern Med* 1991;151:1567). Response to empiric treatment often precludes need for endoscopic diagnosis of fungal esophagitis.
3. Other diagnostic considerations: Drug-induced dysphagia (*Am J Med* 1988;88:512), including AZT (*Ann Intern Med* 1990;162:65) and ddC; infection, including *M. avium*, TB, cryptosporidia, *P. carinii*, primary HIV infection (acute retroviral syndrome), histoplasmosis, and tumor, including KS or lymphoma (*BMJ* 1988;296:92; *Gastrointest Endosc* 1986;32:96).
4. Esophageal brushing: Nonendoscopic method to establish the diagnosis of *Candida* esophagitis. Procedure is: pharyngeal anesthesia, 16 French nasogastric tube inserted to distal esophagus sheathed sterile brush extended through tube, brushing is done during withdrawal, brushings for cytopathy and fungal stain (*Arch Intern Med* 1991;151:1567; *Gastrointest Endosc* 1989;35:102). This procedure is inadequate to establish other diagnoses.
5. Fluconazole is the preferred treatment for *Candida* because of established efficacy, more predictable absorption, and fewer drug interactions compared with voriconazole, ketoconazole, and itraconazole.

## EVALUATION

- Medication or food related
- Gastroesophageal reflux disease (heartburn ± regurgitation and dysphagia)
- Opportunistic infection or tumor
  - Common: *Candida* sp.
  - Less common: HSV, CMV, idiopathic (aphthous)
  - Rare: TB, *M. avium*, histoplasmosis, PCP, cryptosporidia, Kaposi's sarcoma, lymphoma

■ FIGURE 7-1: Odynophagia in Patients With AIDS



# Hepatitis, Forms and Treatment

■ TABLE 7-4: Hepatitis Forms

Type	Seroprevalence* Transmission	Incubation Period	Diagnosis	Course
A	Fecal-oral; food ■ Gen. population: 40% to 50% immune ■ Acute hepatitis: 50%	15 to 50 days	■ Acute: IgM ■ Prior infection: Total HAV antibody	■ Fulminant and fatal in 0.6% ■ Self limited in >99% ■ No chronic form
B	Sex and blood ■ Gen. population: 3% to 14% ■ IDU: 60% to 80% ■ MSM: 35% to 80%	45 to 160 days	■ Acute: HBsAg + anti-HBc IgM ■ Chronic: HBsAg x 6 months + anti- HBc IgG ■ Vaccinated: HBsAb	■ Fulminant and fatal in 1.4% ■ Chronic hepatitis in 6%
C	Blood (primarily) ■ General population: 1.8% ■ IDU: 60% to 90% ■ Hemophilia: 60% to 90% ■ MSM: 2% to 8%	15 to 50 days	EIA Ab + HCV RNA	■ Chronic hepatitis in 85% ■ Cirrhosis in 10% to 15% in 20 years

\* Seroprevalence for adults in the U.S.

## HEPATITIS B TREATMENT

### ■ Indications

- HBsAg positive >6 months
- Evidence of active viral replication (HBeAg + HBV DNA positive)
- Active liver disease (elevated ALT + hepatitis on liver biopsy)

## ■ Regimens

■ TABLE 7-5: Treatment of HBV

Agent	Regimen	Comment
Interferon alfa	5 million units qd or 10 millions units 3x/week x 12 to 24 weeks	The response rate is lower than for non-HIV infected patients.
Pegylated interferon	90 or 180 mcg/week ( <i>Hepatology</i> 2001;34:349A)	
Lamivudine	<ul style="list-style-type: none"> <li>■ 150 mg bid, duration indefinite</li> <li>■ 100 mg qd if anti-HIV activity not needed</li> </ul>	At 12 months most have decreased ALT and loss of HBV DNA, but not HBe → anti-HBe seroconversion; YMDD mutations for lamivudine resistance in most patients.
Lamivudine + tenofovir	Lamivudine 300 mg/day + tenofovir 300 mg/day	No data
Adefovir ± lamivudine	Adefovir 10 mg/day ± lamivudine 300 mg/day	Adefovir is FDA-approved for HBV

## HEPATITIS C TREATMENT

- Indications
  - HCV RNA >50 IU/mL
  - Liver biopsy with portal or bridging fibrosis and at least moderate inflammation and necrosis
  - No contraindications (see p. 276)
  - Stable HIV infection
- Regimens: Table 6-33, p. 277

■ TABLE 7-6: Treatment of HCV

Genotype	Treatment
Genotype 1	Pegylated interferon + ribavirin x 48 weeks
Genotypes 2 and 3	Interferon or pegylated interferon, each with ribavirin x 24 weeks. Some experts would continue treatment for 48 weeks with HIV co-infection.

\* Treatment should be stopped if HCV/RNA has not decreased  $\geq 2 \log_{10}$  IU/mL at 12 weeks (*N Engl J Med* 2002;347:975).

## Pancreatitis (*Am J Med* 1999;107:78)

### MAJOR CAUSES

- **Drugs**, especially ddl or ddl + d4T ± hydroxyurea. May be complication of lactic acidosis (NRTI-associated mitochondrial toxicity) or secondary to PI-associated hypertriglyceridemia with elevated triglyceride levels – usually >1000 mg/dL. Other drugs: d4T, 3TC (pediatrics), RTV, INH, rifampin, TMP-SMX, pentamidine, corticosteroids, sulfonamides, erythromycin, paromomycin.
- **Opportunistic infections:** CMV. Less common: MAC, TB, cryptosporidium, toxoplasmosis, cryptococcus
- **Conditions that cause pancreatitis in general population**, especially alcoholism. Less common: Gallstones, hypertriglyceridemia (avg level is 4500 mg/dL), post ERCP (3% to 5% of procedures), trauma

### DIAGNOSIS

- **Amylase** >3x ULN [p-isoamylase is more specific but not usually measured (*Mayo Clin Proc* 1996;71:1138)]. Other causes hyperamylasemia – other intra-abdominal conditions, diseases of salivary gland, tumors (lung and ovary), renal failure; sensitivity: 85% to 100% (*Am J Gastroenterol* 1990;85:356).
- **Other tests**
  - Lipase: Compared with amylase shows same sensitivity but more specificity. Need for amylase plus lipase is arbitrary.
  - CT Scan: Best method to image (*Radiology* 1994;193:297). Used to: 1) Exclude other serious intra-abdominal conditions, 2) Stage pancreatitis, and 3) Detect complications.

**TREATMENT:** Supportive – IV fluids, pain control and NPO

## Hematologic Complications

### Anemia

■ TABLE 7-7: Definition of Anemia

		Men	Women
<b>Normal</b>	Hematocrit %	46.0 ± 4.0	40.0 ± 4.0
	Hemoglobin (g/dL)	15.7 ± 1.7	13.8 ± 1.5
	Reticulocytes	1.6 ± 0.5	1.4 ± 0.5
	Mean corpuscular Vol	88.0 ± 8.0	88.0 ± 8.0
<b>Anemia</b>	Hematocrit	<41%	<36%
	Hemoglobin (g/dL)	13.5	12.0

**SYMPTOMS:** Oxygen delivery becomes impaired with hemoglobin levels <8-9 g/dL and becomes impaired at rest with hemoglobin levels <5 g/dL (*JAMA* 1998;279:217). Symptoms of chronic anemia include exertional dyspnea, fatigue, and a hyperdynamic state (bounding pulses, palpitations, roaring in ears). Late complications include confusion, CHF, angina. Symptoms due to acute bleeding are those of hypovolemia with postural dizziness, lethargy, postural hypotension, and shock.

### CAUSES

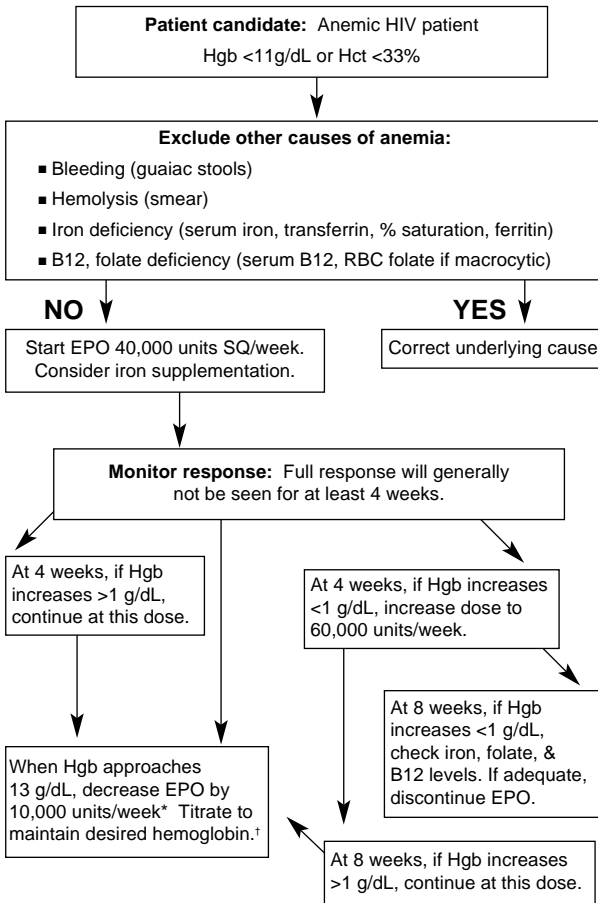
- **HIV:** HIV infection of marrow progenitor cells (*Clin Infect Dis* 2000;30:504). Incidence correlates with immune state: 12% with CD4 count <200 cells/mm<sup>3</sup>, 37% with AIDS-defining OI (*Blood* 1998;91:301), and predicts death independently from CD4 count and viral load (*Semin Hematol Suppl* 4;6:18; *AIDS* 1999;13:943; *AIDS Rev* 2002;4:13).
  - Findings: Normocytic, normochromic, low reticulocyte count, low EPO level
  - Treatment: HAART. With immune reconstitution, prior reports show increases in Hgb of 1.0-2.0 gm/dL at 6 months (*J Acquir Immune Defic Syndr* 2001;28:221), but results are inconsistent (*Clin Infect Dis* 2000;30:504). Consider EPO (see Figure 7-2, p 360).
- **Marrow-infiltrating infection or tumor** (lymphoma, especially non-cleaved cell type, or Kaposi's sarcoma, rare) or infection (MAC, tuberculosis, CMV, histoplasmosis)
  - Findings: Normocytic, normochromic, low platelet count, evidence of etiologic mechanism
  - Treat underlying cause
- **Parvovirus B19:** Infects erythroid precursors; symptoms reflect marginal reserve (sickle cell disease, etc.) and inability to eradicate infection due to immune deficiency.
  - Findings: Normocytic, normochromic anemia, without reticulocytes, positive IgG and IgM serology for parvovirus, positive serum dot blot hybridization or PCR for parvovirus B19; the diagnosis is most likely with severe anemia, i.e., hematocrit <24%, no reticulocytes and CD4 count <100 cells/mm<sup>3</sup> (*J Infect Dis* 1997;176:269).
  - Treatment: IVIG 400 mg/kg/day x 5 days (*Ann Intern Med* 1990; 113:926)
- **Nutritional Deficiency:** Common in late stage HIV, including B12 deficiency in 20% of AIDS patients (*Eur J Haematol* 1987;38:141) and folate deficiency due to folic acid malabsorption (*J Intern Med* 1991;230:227).

- Findings: Megaloblastic anemia (MCV >100 not ascribed to AZT or d4T) ± hypersegmented polymorphonuclear cells, low reticulocyte count with serum B12 (cobalamin) level <125-200 pg/mL (*Semin Hematol* 1999;36:75) or a serum folate level <2-4 ng/mL (<2 ng/mL is more definitive). Note: A good hospital meal may normalize the folate level.
- Treatment: Folate deficiency – folic acid 1-5 mg/day x 1 to 4 months. B12 deficiency – cobalamin 1 g IM qd x 7 days, then every week x 4, then every month or 1-2 g PO qd (*Blood* 1998;92:1191).
- **Iron deficiency:** Usually indicates blood loss, especially from GI tract.
  - Findings: Most studies of iron indicate findings of anemia of chronic disease with decreased Fe (<60 ug/dL), low transferrin (<300 ug/dL), and normal or increased ferritin. Ferritin level <40 ng/mL suggests iron deficiency; <15 ng/mL is 99% sensitive for this diagnosis but only 50% specific (*J Gen Intern Med* 1992;7:145).
  - Treatment: Detect and treat source of loss + ferrous sulfate 300 mg tid between meals.
- **Drug-induced marrow suppression ± red cell aplasia:** Most common with AZT; less common with ganciclovir, amphotericin, ribavirin, pyrimethamine, interferon, TMP-SMX, phenytoin (also seen with HIV *per se*, parvovirus B19, and non-Hodgkin's lymphoma).
  - Findings: Normocytic, normochromic anemia (macrocytic with AZT or d4T), low or normal reticulocyte count.
  - Treatment: Discontinue implicated agent ± EPO (see algorithm, p. 360).
- **Drug-induced hemolytic anemia:** Most common with dapsone, primaquine, and ribavirin (Hemolytic anemia is also seen with TTP). The risk with dapsone and primaquine is dose related and most common with G6PD deficiency.
  - Findings: Reticulocytosis, increased LDH, increased indirect bilirubin, methemoglobinemia, and reduced haptoglobin. The combination of a haptoglobin <25 mg/dL + elevated LDH is 90% specific and 92% sensitive for hemolytic anemia (*JAMA* 1980;243:1909). The peripheral smear may show spherocytes and fragmented RBCs. Note: Coombs test is commonly positive.
  - Treatment: Consists of oxygen, packed RBC transfusions and discontinuation of implicated drug. Severe cases in absence of G6PD deficiency are treated with IV methylene blue (1 mg/kg) (*J Acquir Immune Defic Syndr* 1996;12:477). Activated charcoal may be given to reduce dapsone levels (see p. 197).

■ FIGURE 7-2: Guidelines for Use of Erythropoietin (EPO) in the Anemic HIV Patient

**GOALS OF THERAPY:**

- Resolution of anemia: Hgb  $\geq 12$  g/dL or Hct  $\geq 36\%$
- Increased energy, activity, and overall quality of life for patients, prolonged survival
- Reduced need for transfusions



\* If Hgb  $> 15$  g/dL at any point, hold EPO and restart when Hgb  $< 12$  g/dL, using dose reduced by 10,000/week.

† During dose adjustment phase, hemoglobin should be monitored every 2 to 4 weeks. Allow at least 4 weeks to assess response to dose changes.

Algorithm by Joel E. Gallant M.D., M.P.H., Associate Professor of Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD

## Idiopathic Thrombocytopenia Purpura (ITP)

**DEFINITION:** Unexplained platelet count <100,000/mL

### CAUSES

- **Most cases** are ascribed to HIV infection of multi-lineage hematopoietic progenitor cells in the marrow (*Clin Infect Dis* 2000;30:504; *N Engl J Med* 1992;327:1779).
- **Drug induced:** Review of 561 reports showed the best supporting data for a causal role for drugs were for heparin, quinidine, gold, and TMP-SMX (*Ann Intern Med* 1998;129:886). Others with “level 1 evidence” that are used in HIV infected patients: Rifampin, amphotericin, vancomycin, ethambutol, sulfisoxazole, and lithium.

**TREATMENT** (*Clin Infect Dis* 1995;21:415; *N Engl J Med* 1999;341:1239)

- **HAART:** Two reports showed that with viral suppression and CD4 count rebound, median platelet count increase was 18,000/mL and 45,000/mL at 3 months (*Clin Infect Dis* 2000;30:504; *N Engl J Med* 1999;341:1239).
- **Drug induced:** Median time to recovery with discontinuation of the implicated agent is 7 days (*Ann Intern Med* 1998;129:886).
- **Standard treatments of ITP** (prednisone, IVIG, splenectomy, etc.): Response rates are 40% to 90%; the main problem is durability (*Clin Infect Dis* 1995;21:415).

■ **TABLE 7-8: Treatment of ITP by Clinical Presentation**

Clinical Status	Treatment
Asymptomatic	<ul style="list-style-type: none"> <li>■ HAART</li> <li>■ Discontinue implicated drug and monitor response.</li> </ul>
Persistent symptomatic or required for procedure	<ul style="list-style-type: none"> <li>■ Above</li> <li>■ Prednisone 30-60 mg/day with rapid taper to 5-10 mg/day. Risk of OI. Only 10% to 20% have sustained response.</li> <li>■ IVIG 400 mg/kg days 1, 2 and 14, then every 2 to 4 weeks. Raises platelet count within 4 days; median peak response time is 3 weeks. Very expensive.</li> <li>■ <i>WinRho</i> 25-50 µg/kg over 3 to 5 minutes, repeat day 3 to 4 prn, then at 3 to 4 week intervals as needed. Similar to IVIG but rapid infusion and less expensive.</li> <li>■ Splenectomy – experience is variable: Some good (<i>Arch Surg</i> 1989;124:625), some bad (<i>Lancet</i> 1987;2:342).</li> </ul>
Hemorrhage	Packed red cells/platelet transfusions plus prednisone 60-100 mg/day or IVIG 1 g/kg days 1, 2, and 14.

## Neutropenia

**DEFINITION:** Absolute neutrophil count  $<750/\text{mm}^3$  (Some use thresholds of  $500/\text{mm}^3$  or  $1000/\text{mm}^3$ )

**CAUSE:** Usually due to HIV *per se* or to drugs.

**SYMPTOMS:** Reported risk of bacterial infections is variable, but the largest review shows an increase in hospitalization with an ANC  $<500/\text{mm}^3$  (*Arch Intern Med* 1997;157:1825). Other reviews show that few HIV infected patients have excessive neutropenia-associated infections (*Clin Infect Dis* 2001;32:469).

### TREATMENT

- **HIV associated:** HAART – ANC increase with immune reconstitution is variable (*Clin Infect Dis* 2000;30:504; *J Acquir Immune Defic Syndr* 2001;28:221). Severe and persistent neutropenia may respond to G-CSF or GM-CSF.
- **Drug associated:** Most common causes are AZT, ganciclovir, or valganciclovir; other causes include d4T, ddI, foscarnet, ribavirin, flucytosine, amphotericin, sulfonamides, pyrimethamine, pentamidine, antineoplastic drugs, and interferon. Treatment is to discontinue the implicated drug and/or give G-CSF or GM-CSF.
- **G-CSF or GM-CSF:** Usually initial dose is  $5\ \mu\text{g}/\text{kg}/\text{day}$  with increases of  $1\ \mu\text{g}/\text{kg}/\text{day}$  at 5 to 7 day intervals to maintain ANC  $\geq 1000\text{--}2000/\text{mm}^3$ ; usual maintenance dose is  $300\ \mu\text{g}$  3 to 7x/week (*N Engl J Med* 1987;371:593). Monitor CBC during cytokine treatment 2x/week.

## Thrombotic Thrombocytopenia Purpura

**CAUSE:** Platelet thrombi in selected organs

**FREQUENCY:** Unclear, may be early or late in course (*Ann Intern Med* 1988;109:194)

### LAB DIAGNOSIS

- **Anemia**
- **Thrombocytopenia** (platelet count  $5,000\text{--}120,000/\text{mL}$ )
- **Peripheral smear shows fragmented RBCs** (schistocytes, helmet cells)  $\pm$  nucleated cells
- **Increased creatinine**
- **Evidence of hemolysis:** Increased reticulocytes, indirect bilirubin, and LDH
- **Normal coagulation parameters**

**CLINICAL FEATURES:** Fever, neurologic changes, renal failure – may be acute requiring dialysis

**TREATMENT:** The usual course is progressive with irreversible renal failure and death. Standard treatment is plasma exchange until platelet count is normal and LDH is normal (*N Engl J Med* 1991;325:393). An average of 7 to 16 exchanges are required to induce remission. With poor response, add prednisone 60 mg/day.

## Malignancies

### Kaposi's Sarcoma

**CAUSE:** HHV-8

**FREQUENCY:** Rate is 20,000-fold higher with HIV compared with general population and 300-fold higher than other immunosuppressed patients (*Lancet* 1990;335:123; *J Natl Cancer Inst* 2002;94:1204). The incidence is 10-20x higher in men and MSM; the rate has decreased in the HAART era (*JAMA* 2002;287:221).

**PRESENTATION:** Firm purple to brown-black macules, patches, nodules, papules that are usually asymptomatic – neither pruritic, nor painful, and usually on legs, face, oral cavity, and genitalia. Complications include lymphedema (especially legs, face, and genitalia) and visceral involvement (especially mouth, GI tract, and lungs).

**DIFFERENTIAL:** Bacillary angiomatosis (biopsy with silver stain to show organisms); hematoma, nevus, hemangioma, B-cell lymphoma, and pyogenic granuloma

■ TABLE 7-9: Diagnosis of Kaposi's Sarcoma

Site	Frequency*	Diagnosis
Skin	>95%	■ Appearance; biopsy if atypical
Oral	30%	■ Lesion – purple nodule usually on palate or gingiva; biopsy if atypical
GI	40%	■ Any level; screen – stool guaiac ■ Diagnosis: Endoscopy – hemorrhagic nodule ( <i>Gastroenterology</i> 1985;89:102); biopsy often negative due to submucosal location
Lung	20% to 50%	■ X-ray variable – nodule(s), infiltrates, effusions, and/or mediastinal node ■ Diagnosis: Bronchoscopy shows cherry-red bronchial nodule ( <i>Chest</i> 1995;105:1314)

\* Frequency in HIV infected patients with Kaposi's sarcoma at any anatomical site.

**PROGNOSIS:** CD4 count plus tumor burden staging (ACTG – *J Clin Oncol* 1989;7:201). TIS: Extent of Tumor (T), Immune status (I), Severity of systemic illness (S). TIS predicts survival (*J Clin Oncol* 1997;15:385). Good prognosis – lesions confined to skin, CD4 count >150 cells/mm<sup>3</sup>, no “B” symptoms.

#### TREATMENT

- **HAART:** Associated with lesion regression, decreased incidence, and prolonged survival (*J Clin Oncol* 2001;19:3848; *J Med Virol* 1999;57:140; *AIDS* 1997;11:261; *Mayo Clin Proc* 1998;73:439; *AIDS* 2000;14:987).
- **Antiviral therapy:** Foscarnet, cidofovir, and ganciclovir are active vs HHV-8 (*J Clin Invest* 1997;99:2082); long-term use of foscarnet or ganciclovir is associated with reduced incidence of Kaposi’s sarcoma (*N Engl J Med* 1999;340:1063) but does not appear to cause tumor regression (*J Acquir Immune Defic Syndr* 1999;20:34).
- **Systemic vs local therapy:** Systemic treatment is preferred if extensive tumor burden (>25 skin lesions, visceral involvement with symptoms, extensive edema, “B” symptoms, or failure to respond to local treatment) (*Lancet* 1995;346:26).

■ TABLE 7-10: Treatment of Kaposi's Sarcoma

Local Treatment	Comment
Vinblastine	<ul style="list-style-type: none"> <li>■ Inject 0.1 mL/0.5 cm<sup>2</sup> of solution with 0.2-0.3 mg/mL and repeat every 3 to 4 weeks as needed.</li> <li>■ Most frequently used; lesions usually regress but don't disappear (<i>J Oral Maxillofac Surg</i> 1996;54:583).</li> </ul>
Panretin gel	<ul style="list-style-type: none"> <li>■ Topical 9-cis retinoic acid gel.</li> </ul>
Liquid nitrogen	<ul style="list-style-type: none"> <li>■ Usually restricted to small lesions.</li> </ul>
Radiation	<ul style="list-style-type: none"> <li>■ Usually low dose, 400 rads/week x 6 weeks; well tolerated on skin; mucositis common with oral lesions, usual indication is lesions that are too extensive for local treatment.</li> </ul>
Cryosurgery	
Laser	
Systemic Treatment	Comment
Liposomal anthracyclines	<ul style="list-style-type: none"> <li>■ Two FDA-approved formulations: Pegylated liposomal doxorubicin (<i>Doxil</i>) and liposomal daunorubicin (<i>DaunoXome</i>) – considered preferred over conventional chemotherapy for better response and reduced toxicity (<i>J Clin Oncol</i> 1998;16:2445; <i>J Clin Oncol</i> 1998;16:683; <i>J Clin Oncol</i> 1996;14:2353).</li> <li>■ Doses: <i>Doxil</i> – 20 mg/m<sup>2</sup> every 2 to 3 weeks; <i>DaunoXome</i> – 40 mg/m<sup>2</sup> every 2 weeks.</li> </ul>
Paclitaxel ( <i>Taxol</i> )	<ul style="list-style-type: none"> <li>■ FDA-approved for Kaposi's sarcoma. Considered second line to anthracyclines due to greater toxicity (neutropenia and thrombocytopenia) (<i>J Clin Oncol</i> 1998;16:1112).</li> <li>■ Lower doses (100 mg/m<sup>2</sup> every 2 weeks) appears to preserve efficacy with reduced toxicity (<i>Cancer</i> 2002;95:147).</li> </ul>
Interferon alfa	<ul style="list-style-type: none"> <li>■ Efficacy established especially with modest disease, but toxicity is great (<i>J Clin Oncol</i> 1998;16:1736).</li> <li>■ Dose is 8,000 units SC/day.</li> </ul>
Conventional chemotherapy	<ul style="list-style-type: none"> <li>■ Commonly used combinations include adriamycin, bleomycin plus vincristine or vinblastine (ABV); bleomycin plus vinca alkaloids or vincristine/vinblastine (alone).</li> <li>■ Newer treatments (paclitaxel and anthracyclines) are usually preferred.</li> </ul>

**RESPONSE:** Kaposi's sarcoma cannot be cured; goals of therapy are to reduce symptoms and prevent progression. HAART is associated with reduced tumor burden. Antiviral drugs directed against HHV-8 have no established benefit.

- **Local therapy:** Local injections of vinblastine cause reduced lesion size but not elimination in most patients (*Cancer* 1993;71:1722).
- **Systemic therapy:** Liposomal anthracyclines usually show good results with few side effects. Paclitaxel is as effective but more toxic due to neutropenia and thrombocytopenia; side effects are dose related; lower doses appear as effective with less marrow suppression.

## Non-Hodgkin's Lymphoma (NHL)

**CAUSE:** Immunosuppression (CD4 count <100 cells/mm<sup>3</sup>) and EBV (50% to 80%)

**FREQUENCY AND TYPE:** NHL occurs 200- to 600-fold more frequently with HIV compared with the general population (*Int J Cancer* 1997;73:645). The rate is about 3% for patients with AIDS (*J Acquir Immune Defic Syndr* 2002;29:418). Most (70% to 90%) are high-grade diffuse large cell or Burkitt-like lymphomas (*Am J Med* 2001; *Brit J Haematol* 2001;112:863).

**PRESENTATION:** Compared with NHL in the general population, HIV infected patients have high rates of stage IV disease with "B" symptoms and sparse node involvement. Common sites of infection and forms of clinical presentation are fever of unknown origin, hepatic dysfunction, marrow involvement, lung disease (effusions, multinodular infiltrates, consolidation, mass lesions, or local or diffuse interstitial infiltrates, hilar adenopathy), GI involvement (any level – pain and weight loss), and CNS (aseptic meningitis, cranial nerve palsies, CNS mass lesions).

**DIAGNOSIS:** Screening tests include biopsy (usually required), but site depends on symptoms and results of CT scan to detect nodes and extranodal sites of involvement. Fine needle aspirate (FNA) of enlarged nodes is helpful if positive, but most are falsely negative, necessitating a biopsy. Bone marrow biopsy will often yield the diagnosis. With GI tract and hepatic involvement, the screening test is CT scan; endoscopy is not usually useful. Lung involvement usually shows an exudative pleural effusion; bronchoscopy is usually negative unless accompanied by lung biopsy, which has a diagnostic yield of about 60% (*Chest* 1996;110:729).

### TREATMENT

- **Standard:** CHOP (cyclophosphamide, doxorubicin, adriamycin, vincristine, and prednisone). Intrathecal methotrexate or cytosine arabinoside may be given for CNS prophylaxis and should be given with meningeal involvement.
- **Alternatives to CHOP**
  - M-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone + G-CSF) (*N Engl J Med* 1997;336:16)
  - EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)

**RESPONSE:** Initial response rates are 50% to 60%, but the long-term prognosis is poor with median survival <1 year. The usual cause of death is progressive lymphoma or progressive HIV with OIs (*Semin Oncol* 1998;25:492). The prognosis is significantly better with HAART; one report showed an 84% 1 year survival with HAART + chemotherapy (*AIDS* 2001;15:1483).

## Primary CNS Lymphoma (PCNSL) (see p. 373)

### Primary Effusion Lymphoma

**CAUSE:** HHV-8 (*N Engl J Med* 1995;332:1186)

**FREQUENCY:** Rare – tumor registries crossed with AIDS registries show a frequency of 0.004% or 0.14% of non-Hodgkin's lymphoma in patients with AIDS (*J Acquir Immune Defic Syndr* 2002;29:418)

**PRESENTATION:** Serous effusions (pleural, peritoneal, pericardial, joint spaces) with no masses (*Hum Pathol* 1997;28:801)

**DIAGNOSIS:** Effusions are serous, contain high-grade malignant lymphocytes and HHV-8.

#### TREATMENT

- **HAART plus radiation ± CHOP** every 28 days
- **Alternatives:** Pegylated liposomal doxorubicin or liposomal daunorubicin

**RESPONSE:** This tumor usually does not extend beyond serosal surfaces, but prognosis is poor, with median survival of 2 to 3 months (*J Acquir Immune Defic Syndr* 1996;13:215). Most patients show response to therapy with decrease in effusion size. Failure to respond to two cycles of CHOP indicates additional cycles will fail, indicating a role for *DaunoXome* or *Doxil*.

## Neurologic Complications

### Acute Neuropathy and Lactic Acidosis Syndrome

**CAUSE:** Postulated to be mitochondrial toxicity attributed to deoxy NRTIs, primarily d4T (*N Engl J Med* 2002;346:811).

**FREQUENCY:** 25 cases reported to the FDA including 22 treated with d4T (9th CROI, Seattle, Washington, 2002, Abstract LB14).

**CLINICAL FEATURES:** Ascending paresis, areflexia, and cranial neuropathies; usually associated with prolonged dideoxynucleosides, especially d4T. Laboratory tests usually show elevated CPK and lactate levels.

**DIAGNOSIS** (ACTG, 2002)

- New onset limb weakness ± sensory involvement that is acute (1 to 2 weeks) or subacute (>2 weeks) involving legs or legs and arms
- Absence of alternative confounding illnesses: Myasthenia gravis, myelopathy, hypokalemia, stroke

**TREATMENT:** Discontinue d4T and/or other causative NRTIs

### Cytomegalovirus Radiculitis

**FREQUENCY:** Uncommon (*Ann Neurol* 1994;35:53)

**DIAGNOSIS:** Advanced HIV with CD4 count <50 cells/mm<sup>3</sup>, flaccid paralysis of legs, sacral pain, and sphincter dysfunction. CSF shows polymorphonuclear pleocytosis, elevated protein, and low glucose. CMV is detected in CNS by PCR in 50% to 60% (*Neurology* 1993;43:493). Many patients also have CMV retinitis.

**TREATMENT:** Standard treatment has been IV ganciclovir (*Neurology* 1993;43:493), but some patients develop this complication while receiving ganciclovir, and some presumably develop ganciclovir resistance, requiring alternative therapy with foscarnet. The role of valganciclovir for initial treatment is unclear. (See p. 131)

**RESPONSE:** Most patients achieve stabilization with IV ganciclovir but often worsen during the first 2 weeks (*Ann Neurol* 1994;35:53).

■ TABLE 7-11: Differential Diagnosis of Lower Extremity Symptoms in Patients With HIV Infection

Syndrome	Symptoms	Clinical Features	Ancillary Studies/ Treatment
Distal sensory neuropathy (DSN)	<ul style="list-style-type: none"> <li>■ Pain and numbness in toes and feet; ankles, calves, and fingers involved in more advanced cases</li> <li>■ CD4 cell count &lt;200 cells/mm<sup>3</sup>, but can occur at higher CD4 level</li> </ul>	<ul style="list-style-type: none"> <li>■ Reduced pinprick/vibratory sensation</li> <li>■ Reduced or absent ankle jerks</li> <li>■ Contact allodynia (hypersensitivity) present most cases</li> </ul>	<ul style="list-style-type: none"> <li>■ Skin biopsy shows epidermal denervation</li> <li>■ Electromyography/nerve conduction velocities (EMG/NCV) show a predominantly axonal neuropathy</li> <li>■ Quantitative sensory testing or thermal thresholds may be helpful</li> </ul>
Antiretroviral toxic neuropathy (ATN)	<ul style="list-style-type: none"> <li>■ Same as DSN (above), but symptoms occur after initiation of ddI, ddC, d4T.</li> <li>■ Any CD4 cell count.</li> <li>■ More common in older patients and patients with diabetes</li> </ul>	<ul style="list-style-type: none"> <li>■ Same as DSN (above)</li> </ul>	<ul style="list-style-type: none"> <li>■ EMG/NCVs show a predominantly axonal neuropathy</li> <li>■ Discontinuation of presumed neurotoxic medication if severe</li> <li>■ Symptoms may worsen for a few weeks (coasting) before improving</li> </ul>
Tarsal tunnel syndrome	<ul style="list-style-type: none"> <li>■ Pain and numbness predominantly in anterior portion of soles of feet</li> </ul>	<ul style="list-style-type: none"> <li>■ Reduced sensation over soles of feet</li> <li>■ Positive Tinel's sign at tarsal tunnel</li> </ul>	<ul style="list-style-type: none"> <li>■ Infiltration of local anesthetic in tarsal tunnel may provide symptomatic relief</li> </ul>
Acute neuropathy and lactic acidosis syndrome	<ul style="list-style-type: none"> <li>■ Ascending paresis with areflexia ± cranial nerve or sensory involvement</li> <li>■ Usually associated with prolonged d4T use</li> </ul>	<ul style="list-style-type: none"> <li>■ Lactate and CPK levels usually ↑</li> <li>■ EMG/nerve conduction studies – axonal neuropathy and myopathy</li> </ul>	<ul style="list-style-type: none"> <li>■ Discontinue NRTIs, especially d4T</li> </ul>
HIV-associated myopathy/AZT myopathy	<ul style="list-style-type: none"> <li>■ Pain and aching in muscles, usually in thighs and shoulders.</li> <li>■ Weakness with difficulty when rising from a chair or reaching above shoulders</li> <li>■ Any CD4 cell count</li> </ul>	<ul style="list-style-type: none"> <li>■ Mild/moderate muscle tenderness</li> <li>■ Weakness, predominantly in proximal muscles (i.e., deltoids, hip flexors)</li> <li>■ Normal sensory exam/normal reflexes</li> </ul>	<ul style="list-style-type: none"> <li>■ CPK ↑</li> <li>■ EMG shows irritable myopathy</li> <li>■ Discontinue AZT and follow CPK every 2 weeks. Symptoms/signs/CPK should improve within 1 month</li> </ul>

*continued on next page*

■ TABLE 7-11: Differential Diagnosis of Lower Extremity Symptoms in Patients With HIV Infection (*Continued*)

Syndrome	Symptoms	Clinical Features	Ancillary Studies/ Treatment
Polyradiculitis	<ul style="list-style-type: none"> <li>■ Rapidly evolving weakness and numbness in legs (both proximally and distally), with bowel/bladder incontinence</li> <li>■ CD4 count &gt;500 cells/mm<sup>3</sup> or &lt;50 cells/mm<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>■ Diffuse weakness in legs</li> <li>■ Diffuse sensory abnormalities in legs and buttocks</li> <li>■ Reduced/absent reflexes at knees and ankles</li> </ul>	<ul style="list-style-type: none"> <li>■ EMG/NCV show multilevel nerve root involvement</li> <li>■ Spinal fluid helpful in determining CMV or HSV as cause</li> <li>■ Treat CMV polyradiculopathy with ganciclovir or foscarnet</li> </ul>
Vacuolar myelopathy	<ul style="list-style-type: none"> <li>■ Stiffness and weakness in legs with leg numbness.</li> <li>■ Bowel/bladder incontinence in advanced cases</li> <li>■ CD4 cell count &lt;200 cells/mm<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>■ Weakness and spasticity, mainly in hip, knee, and ankle flexors</li> <li>■ Brisk knee jerks, upgoing toes</li> <li>■ If sensory neuropathy coexists, then distal sensory loss and reduced/absent jerks</li> </ul>	<ul style="list-style-type: none"> <li>■ Spinal fluid may show elevated protein 0-10 cells/mm<sup>3</sup></li> <li>■ Exclude B-12 deficiency and HTLV-1 co-infection</li> <li>■ Thoracic spinal imaging normal</li> <li>■ No established therapy, but physical therapy or methionine (3 g bid) may be helpful (<i>Neurology</i> 1998;51:266)</li> </ul>
Inflammatory demyelinating polyneuropathies	<ul style="list-style-type: none"> <li>■ Predominantly weakness in arms and legs, with minor sensory symptoms.</li> <li>■ CD4 count &gt;500 cells/mm<sup>3</sup> or &lt;50 cells/mm<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>■ Diffuse weakness including facial musculature, asymmetric in early cases, with diffuse absent reflexes</li> <li>■ Minor sensory signs</li> </ul>	<ul style="list-style-type: none"> <li>■ EMG/NCVs show a demyelinating polyneuropathy</li> <li>■ Spinal fluid shows a very high protein with mild to moderate lymphocytic pleocytosis, but all cultures are negative</li> </ul>
<i>Mononeuritis</i> or <i>mono-neuritis</i> multiplex	<ul style="list-style-type: none"> <li>■ Mix of motor and sensory defects</li> <li>■ Asymmetric</li> <li>■ Evolves over weeks</li> <li>■ CD4 count is variable</li> </ul>	<ul style="list-style-type: none"> <li>■ EMG and nerve conduction – asymmetric and multifocal defects</li> <li>■ R/O CMV (CSF or sural nerve biopsy) and HCV</li> </ul>	<ul style="list-style-type: none"> <li>■ CD4 count &gt;200 cells/mm<sup>3</sup> – possible steroids</li> <li>■ CD4 counts &lt;50 cells/mm<sup>3</sup> and severe – treat for CMV</li> </ul>

## Cytomegalovirus Encephalitis

**CAUSE:** CMV + CD4 count <50 cells/mm<sup>3</sup>

**FREQUENCY:** <0.5% of AIDS patients

**PRESENTATION:** Rapid progressive delirium, cranial nerve deficits, nystagmus, ataxia, headache with fever ± CMV retinitis

**DIAGNOSIS:** MRI shows periventricular confluent lesions with enhancement. CMV PCR in CSF shows sensitivity of >80% and specificity of 90%; cultures of CSF for CMV are usually negative.

**TREATMENT:** Ganciclovir, foscarnet, or both IV (see p. 131).

**RESPONSE:** Trial of foscarnet plus ganciclovir showed a median survival of 94 days compared with 42 days in historic controls (*AIDS* 2000;14:517).

## Dementia (HIV-Associated Dementia or HAD)

**CAUSE:** Chronic encephalitis with progressive or static encephalopathy due to CNS HIV infection with prominent immune activation

**INCIDENCE:** 7% after AIDS in pre-HAART era; 2% to 3% more recently (*Neurology* 2001;56:257). Prevalence is increasing with longer survival.

**PRESENTATION:** Late stage HIV with CD4 count <200 cells/mm<sup>3</sup> and subcortical dementia. See Table 7-12 and 7-13. Early symptoms: Apathy, memory loss, cognitive slowing, depression, and withdrawal. Motor defects include gait instability and reduced hand coordination. Late stages show global loss of cognition, severe psychomotor retardation, and mutism. There may be seizures, which are usually easily controlled. The rate of progression is highly variable, but the average from first symptoms to death in the pre-HAART era was 6 months (*Medicine* 1987;66:407). Physical examination in early disease shows defective rapid eye movement, rapid limb movement, and generalized hyperreflexia. In late stages, there is tremor, clonus, and frontal release signs.

## TESTING

■ TABLE 7-12: HIV Dementia Scale (*AIDS Reader 2002;12:29*)

Maximum Score	Test*
See below	Memory registration: 4 words given (hat, dog, green, peach) and have the patient repeat them.
6	Psychomotor speed: Record the time, in seconds, that it takes the patient to write the alphabet. Score: <21 sec = 6, 21.1-24 sec = 5, 24.1-27 sec = 4, 27.1-30 sec = 3, 30.1-33 sec = 2; 33.1-36 sec = 1, >36 = 0
4	Memory recall: Ask for the four words from above. For words not remembered give semantic clue, e.g. "animal" (dog), "color" (green), etc. 1 point for each correct answer.
2	Construction: Copy a cube and record time. Score: <25 sec = 2, 25-35 sec = 1, >35 = 0

\*  $\geq 7/12$  is threshold for dementia but is non-specific requiring additional neurologic evaluation.

■ TABLE 7-13: AIDS Dementia Complex Staging

Stage 0	Normal
Stage 0.5	Subclinical: Minimal – equivocal symptoms; no work impairment.
Stage 1.0	Mild – minimal intellectual or motor impairment; able to do all but more demanding work or ADL.
Stage 2.0	Moderate – cannot work or perform demanding ADL; capable of self care.
Stage 3.0	Severe – major intellectual disability; unable to walk unassisted.
Stage 4.0	End stage – near vegetative stage; paraplegia or quadriplegia.

**DIAGNOSIS:** History, physical examination, and screening with HIV Dementia Scale as noted above. Formal testing includes: Trail Making B, Digital Symbol, Grooved Pegboard, and the HIV Dementia Scale. MRI shows cerebral atrophy (which can be present without symptoms), typically with rarefaction of white matter (*J Neurol Neurosurg Psych 1997;62:346*). CSF shows increased protein with 0-15 mononuclear cells; pleocytosis is absent in 65%. Main goal is to exclude alternative diagnosis because no test is specific for HAD.

**TREATMENT:** The HIV Dementia Scale (see Table 7-12) can be used to follow response to HAART. HAART has reduced the frequency of HAD, but there are sparse data to show efficacy of HAART for reversing established HAD (*J Neuroviral 2002;8:136*). It is also unclear if CNS penetration is important in the selection of agents. Antiretroviral agents with the best CNS penetration based on CSF levels are AZT,

d4T, ABC, NVP, and IDV; levels are somewhat less for EFV, ddI, 3TC, and APV (*J Acquir Immune Defic Syndr* 1998;235:238; *AIDS* 1998;12:537). Adjunctive therapies to block immune activation are being tested in trials of NMDA receptor antagonists and antioxidants such as selegiline.

## Inflammatory Demyelinating Polyneuropathy

**CAUSE:** Unclear; immunopathogenic mechanism with inflammation and breakdown of peripheral nerve myelin is suspected.

**FREQUENCY:** Uncommon

**DIAGNOSIS:** There are two forms: Acute demyelinating neuropathy (AIDP, Guillain-Barré Syndrome), that occurs early in the course of HIV, and a more chronic relapsing motor weakness, CIDP, that usually occurs in late-stage HIV. Both present with a progressive ascending paralysis with mild sensory involvement. CSF shows increased protein and mononuclear pleocytosis; EMG and nerve conduction studies are critical for diagnosis. Nerve biopsy may be needed and shows mononuclear, macrophage infiltrate, and internodal demyelination (*Ann Neurol* 1987;21:3240).

### TREATMENT

#### ■ AIDP

- Plasmapheresis: Five exchanges with maintenance as needed
- Alternative is IVIG 0.4 g/kg/day x 5 days (monitor renal function)

■ **CIDP:** Oral prednisone (1 mg/kg/day) or intermittent plasmapheresis or IVIG; each in continued until there is a therapeutic response.

**RESPONSE:** Treatment usually halts progression; CIDP may require prolonged courses (*Ann Neurol* 1987;21:3240).

## Primary CNS Lymphoma (PCNSL)

**CAUSE:** Virtually all are EBV-associated (*Lancet* 1991;337:805).

**FREQUENCY:** 2% to 6% in pre-HAART era – 1000x higher than in the general population (*Lancet* 1991;338:969). Incidence reduced post HAART but not as much as other HIV complications (*J Acquir Immune Defic Syndr* 2000;25:451).

**PRESENTATION:** Focal or non-focal signs. Symptoms include confusion, headache, memory loss, aphasia, hemiparesis, and/or seizures without fever for <3 months. CD4 count is usually <50 cells/mm<sup>3</sup>.

**DIAGNOSIS:** MRI shows single lesion or multiple lesions that are isodense or hypodense and usually homogeneous, but sometimes ring forms (*Am J Neuroradiol* 1997;18:563). With contrast, CT and MRI scans show enhancement that is usually irregular (due to rapid growth). These lesions usually involve the corpus callosum, periventricular area, or periependymal area; they are often >4 cm in diameter and usually show a mass effect (*Neurology* 1997;48:687). Major differential diagnosis is toxoplasmosis. Factors favoring CNS lymphoma are: 1) Typical neuro imaging results (above), 2) Negative *T. gondii* serology, 3) Failure to respond to empiric treatment of toxoplasmosis within 1 to 2 weeks, 4) Lack of fever, and 5) Thallium SPECT scan with early thallium uptake. CSF EBV DNA is >94% specific and 80% sensitive (*Clin Infect Dis* 2002;34:103; *J Natl Cancer Inst* 1998;90:364; *Lancet* 1992;342:398). Stereotactic brain biopsy is definitive and usually reserved for patients who fail to respond to toxoplasmosis treatment (*AIDS* 1995;9:1243; *Clin Infect Dis* 2002;34:103). A review of five reports with 486 AIDS patients undergoing stereotactic brain biopsy showed a 4% morbidity rate (*Clin Infect Dis* 2002;34:103).

#### THERAPY

- **Standard:** Radiation plus corticosteroids (*J Neuro Sci* 1999;163:32)
- **Chemotherapy:** May be combined with radiation plus corticosteroids. Usually for patients with elevated CD4 counts. Preliminary results with methotrexate without radiation were promising (*AIDS* 1997;11:1725)

**RESPONSE:** Response rates to radiation treatment plus corticosteroids is 20% to 50%, but these results are temporary, and the average duration of life following the onset of symptoms was only about 4 months in the pre-HAART era (*Crit Rev Oncol* 1998;9:199; *Semin Oncol* 1998;25:492). Prolonged survival is possible with HAART response.

### Progressive Multifocal Leukoencephalopathy (PML)

**CAUSE:** Activation of JC virus (which is ubiquitous) in patients who are immunodeficient.

**FREQUENCY:** 1% to 2% of AIDS patients (*J Infect Dis* 1999;180:261)

**PRESENTATION:** Cognitive impairment, visual field deficits, hemiparesis speech defects, incoordination with *no* fever. CD4 count is usually 35-100 cells/mm<sup>3</sup>, but a subset of 7% to 25% have CD4 counts >200 cells/mm<sup>3</sup> (*Clin Infect Dis* 2002;34:103).

#### DIAGNOSIS

- MRI shows hypodense lesions of white matter without edema or enhancement.

- PCR for JCV in CSF with sensitivity of 80% and specificity of 95%.

**TREATMENT:** None with established merit. One report shows PML response to HAART with enhancing lesions on MRI (*AIDS* 1999;13:1426). There is conflicting evidence for cidofovir (*AIDS* 2002;16:1791; *J Neurovirol* 2001;7:364; *J Neurovirol* 2001;7:374).

**PROGNOSIS:** Median duration of survival is 1 to 6 months. Response to HAART is possible, but some patients have developed PML while receiving HAART (*Clin Infect Dis* 2002;34:103). The most important predictor of survival is baseline CD4 cell count.

## Sensory Neuropathies

Distal sensory neuropathy (DSN) and antiretroviral toxic neuropathy (ATN)

**CAUSE:** HIV infection *per se*, usually with CD4 count <200 cells/mm<sup>3</sup> and/or dideoxy NRTIs (d-drugs) – ddI, d4T, and ddC; most common with ddI + d4T (*AIDS* 2000;14:273). DSN and ATN are indistinguishable by clinical features or biopsy.

**FREQUENCY:** 20% with advanced HIV over 1 year and 52% over 2 years (*Neurology* 2002;58:1764)

**DIFFERENTIAL:** Toxic neuropathies due to drugs (metronidazole, B6 overdose, dapson, INH, vincristine), diabetes, entrapment neuropathies, B12 deficiency, alcoholism, uremia, inflammatory demyelinating polyneuropathy, and acute neuromuscular syndrome

**DIAGNOSIS:** Dysesthesia and contact hypersensitivity of feet with decreased or absent ankle reflexes. Invasive neurodiagnostic tests may be useful but are usually unnecessary. Skin biopsy shows epidermal denervation. Electromyography/nerve conduction studies show predominantly axonal neuropathy. Quantitative sensory tests or thermal tests show elevated thresholds. See Table 7-12, p. 372.

### TREATMENT

- **ATN:** Avoid d4T, ddI, and ddC; acceptable alternative agents in this class are AZT, 3TC, ABC, and TDF.
- **DSN:** Possible response reported with HAART (*Lancet* 1998;352:1906).
- **Symptomatic treatment**
  - Lamotrigine (*Lamictal*) 25 mg bid increasing to 300 mg/day over 6 weeks; one of the few treatments with confirmed benefit in clinical trials (*Neurology* 2000;54:2115).

- Tricyclics nortriptyline 10 mg hs increasingly by 10 mg q5d to maximum 75 mg hs or 10-20 mg PO tid; other tricyclics (amitriptyline, desipramine, or imipramine) are considered comparable. One trial failed to show response to tricyclics (*JAMA* 1998;280:1590).
- Ibuprofen 600-800 mg tid
- Gabapentin 300-1200 mg PO tid
- Capsaicin-containing ointments (*Zostrix*, etc.); often not well tolerated.
- *Lidocaine* 20% to 30% ointment (not very effective)
- Phenytoin 200-400 mg/day
- Severe pain: Methadone – up to 20 mg qid; *Fentanyl* patch 25-100 mcg/hour q72h or morphine
- Acupuncture failed in one reported trial (*JAMA* 1998;280:1590).
- Avoid tight footwear, limit walking, bridge at foot of the bed, use feet soaks.



## Toxoplasmosis

**CAUSE:** Latent *T. gondii* infection

**FREQUENCY:** 30% of AIDS patients with latent *T. gondii* infection (positive serology) and no prophylaxis

**PRESENTATION:** Subacute symptoms with headache, fever, behavior change, lethargy, focal neurologic finding; over 80% have CD4 <100 cells/mm<sup>3</sup>.

### DIAGNOSIS

- MRI shows  $\geq 2$  ring-enhancing lesions with edema. SPECT can facilitate distinction from lymphoma, but this is usually not necessary.
- *T. gondii* serology is positive in >95%.
- Response to therapy is characteristically prompt and impressive.
- PCR for *T. gondii* in CSF is 50% sensitive and 96% to 100% specific.

**TREATMENT:** See p. 156

**RESPONSE:** Treatment with pyrimethamine and sulfadiazine results in clinical improvement in 80% by 7 days and in 95% by 14 days. MRI response is noted within 2 weeks.

■ TABLE 7-14: Central Nervous System Conditions in Patients With HIV Infection

Agent/Condition Frequency (All AIDS Patients)	Clinical Features	CT Scan/MRI	Cerebrospinal Fluid (CSF)	Other Diagnostic Tests
Toxoplasmosis (2% to 4%) (see p. 156)	<ul style="list-style-type: none"> <li>■ Fever, reduced alertness, headache, focal neurological deficits (80%), seizures (30%)</li> <li>■ Evolution: &lt;2 weeks</li> <li>■ CD4 count &lt;100 cells/mm<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>■ Location: Basal ganglia, gray-white junction</li> <li>■ Sites: Usually multiple</li> <li>■ Enhancement: prominent; Usually ring lesions (1 to 2 cm)</li> <li>■ Edema/mass effect: Usually not as great as lymphoma</li> </ul>	<ul style="list-style-type: none"> <li>■ Normal: 20% to 30%</li> <li>■ Protein: 10 to 150/mg/dL</li> <li>■ WBC: 0 to 40 (monos)</li> <li>■ Experimental: Toxo ag (ELISA) or PCR</li> </ul>	<ul style="list-style-type: none"> <li>■ Toxoplasmosis serology (IgG) false-negative in &lt;5%</li> <li>■ Response to empiric therapy: &gt;85%; most respond by day 7 (<i>N Engl J Med</i> 1993;329:995)</li> <li>■ MRI: Repeat at 2 weeks</li> <li>■ Definitive diagnosis: Brain biopsy</li> </ul>
Primary CNS Lymphoma (2%) (see p. 373)	<ul style="list-style-type: none"> <li>■ Afebrile, headache, focal neurological findings; mental status change (60%), personality or behavioral; seizures (15%)</li> <li>■ Evolution: 2 to 8 weeks</li> <li>■ CD4 count &lt;100 cells/mm<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>■ Location: Periventricular, anywhere, 2 to 6 cm</li> <li>■ Sites: One or many</li> <li>■ Enhancement: Prominent; usually solid, irregular</li> <li>■ Edema/mass effect: Prominent</li> </ul>	<ul style="list-style-type: none"> <li>■ Normal: 30% to 50%</li> <li>■ Protein: 10 to 150/mg/dL</li> <li>■ WBC: 0 to 100 (monos)</li> <li>■ EBV PCR in 50%</li> <li>■ EBV DNA in CSF (<i>Lancet</i> 1992;342:398)</li> </ul>	<ul style="list-style-type: none"> <li>■ Suspect with negative toxo. IgG, single lesion, or failure to respond to empiric toxoplasmosis treatment (MRI and clinical evaluation at 2 weeks)</li> <li>■ Thallium 201 SPECT scan (90% sensitive and specific)</li> </ul>
Cryptococcal meningitis (8% to 10%) (see p. 123)	<ul style="list-style-type: none"> <li>■ Fever, headache, alert (75%); less common are visual changes, stiff neck, cranial nerve deficits, seizures (10%); no focal neurological deficits</li> <li>■ Evolution: &lt;2 weeks</li> <li>■ CD4 count &lt;100 cells/mm<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>■ Usually normal or shows increased intracranial pressure</li> <li>■ Enhancement: Negative or meningeal enhancement</li> <li>■ Edema mass effect: Ventricular enlargement/obstructive hydrocephalus</li> </ul>	<ul style="list-style-type: none"> <li>■ Protein: 30 to 150/mg/dL</li> <li>■ WBC: 0 to 100 (monos)</li> <li>■ Culture positive: 95% to 100%</li> <li>■ India ink pos: 60% to 80%</li> <li>■ Crypt Ag: &gt;95% sensitive and specific</li> </ul>	<ul style="list-style-type: none"> <li>■ Cryptococcal antigen in serum – 95%</li> <li>■ Definitive diagnosis: CSF antigen and/or positive culture</li> </ul>

continued on next page

■ TABLE 7-14: Central Nervous System Conditions in Patients With HIV Infection (Continued)

Agent/Condition Frequency (All AIDS Patients)	Clinical Features	CT Scan/MRI	Cerebrospinal Fluid (CSF)	Other Diagnostic Tests
CMV (>0.5%) (see p. 131)	<ul style="list-style-type: none"> <li>■ Fever ±, delirium, lethargy, disorientation; headache; stiff neck, photophobia, cranial nerve deficits; no focal neurologic deficits</li> <li>■ Evolution: &lt;2 weeks</li> <li>■ CD4 count &lt;100 cells/mm<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>■ Location: Periventricular, brainstem</li> <li>■ Site: Confluent</li> <li>■ Enhancement: Variable, prominent to none.</li> </ul>	<ul style="list-style-type: none"> <li>■ CSF may be normal</li> <li>■ Protein: 100 to 1000/mg/dL</li> <li>■ WBC: 10 to 1000 (polys)/mL</li> <li>■ Glucose usually decreased</li> <li>■ CMV PCR positive</li> <li>■ CSF cultures usually negative for CMV</li> </ul>	<ul style="list-style-type: none"> <li>■ Definitive diagnosis: Brain biopsy with histopath and/or positive culture</li> <li>■ Hyponatremia (reflects CMV adrenalitis)</li> <li>■ Retinal exam for CMV retinitis</li> </ul>
HIV Dementia (7%) (see p. 371)	<ul style="list-style-type: none"> <li>■ Afebrile; triad of cognitive, motor, and behavioral dysfunction.</li> <li>■ Early: Decreased memory, concentration, attention, coordination; ataxia</li> <li>■ Late: Global dementia, paraplegia, mutism</li> <li>■ Evolution: Weeks to months</li> <li>■ CD4 count &lt;200 cells/mm<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>■ Location: Diffuse, deep white matter hyperintensities</li> <li>■ Site: Diffuse, ill-defined</li> <li>■ Enhancement: Negative</li> <li>■ Atrophy: Prominent</li> <li>■ No mass effect</li> </ul>	<ul style="list-style-type: none"> <li>■ Normal: 30% to 50%</li> <li>■ Protein: Increased in 60%</li> <li>■ WBC: Increased in 5% to 10% (monos)</li> <li>■ Beta-2 microglobulin elevated (&gt;3 mg/L)</li> </ul>	<ul style="list-style-type: none"> <li>■ Neuropsychological tests show subcortical dementia</li> <li>■ HIV dementia scale for screening (see p. 372)</li> </ul>
Neurosyphilis (0.5%) (see p. 158)	<ul style="list-style-type: none"> <li>■ Asymptomatic meningial: headache, fever, photophobia, meningismus ± seizures, focal findings, cranial nerve palsies</li> <li>■ Tabes dorsalis: Sharp pains, paresthesias, decreased DTRs, loss of pupil response</li> </ul>	<ul style="list-style-type: none"> <li>■ Aseptic meningitis: May show meningial enhancement</li> <li>■ General paresis: Cortical atrophy, sometimes with infarcts</li> <li>■ Meningovascular syphilis: Deep strokes</li> </ul>	<ul style="list-style-type: none"> <li>■ Protein: 45 to 200/mg/dL</li> <li>■ WBC: 5 to 100 (monos)</li> <li>■ VDRL positive: Sensitivity = 65%, specificity = 100% positive</li> <li>■ Experimental: PCR for <i>T. pallidum</i></li> </ul>	<ul style="list-style-type: none"> <li>■ Serum VDRL and FTA-ABS are clue in &gt;90%; false-negative serum VDRL in 5% to 10% with tabes dorsalis or general paresis</li> </ul>

■ TABLE 7-14: Central Nervous System Conditions in Patients With HIV Infection (Continued)

Agent/Condition Frequency (All AIDS Patients)	Clinical Features	CT Scan/MRI	Cerebrospinal Fluid (CSF)	Other Diagnostic Tests
Neurosyphilis (0.5%) – continued (see p. 158)	<ul style="list-style-type: none"> <li>■ General paresis: Memory loss, dementia, personality changes, loss of pupil response</li> <li>■ Meningo-vascular: Strokes, myelitis</li> <li>■ Ocular: Iritis, uveitis, optic neuritis</li> <li>■ Any CD4 cell count</li> </ul>			<ul style="list-style-type: none"> <li>■ Definitive diagnosis: Positive CSF VDRL (found in 60% to 70%)</li> <li>■ Note: Most common forms in HIV-infected persons are ocular, meningeal, and meningo-vascular.</li> </ul>
PML (1% to 2%) (see p. 139)	<ul style="list-style-type: none"> <li>■ No fever; no headache; impaired speech, vision, motor function, cranial nerves</li> <li>■ Late: ↓ cognition</li> <li>■ Evolution: Weeks to months</li> <li>■ CD4 count &lt;100 cells/mm<sup>3</sup>; some &gt;200 cells/mm<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>■ Location: White matter, subcortical, multifocal</li> <li>■ Sites: Variable</li> <li>■ Enhancement: Negative</li> <li>■ No mass effect</li> </ul>	<ul style="list-style-type: none"> <li>■ Normal CSF</li> <li>■ PCR for JC virus: 80%</li> </ul>	<ul style="list-style-type: none"> <li>■ Brain biopsy: Positive DFA stain for JC virus</li> </ul>
Tuberculosis (0.5% to 1%) (see p. 145)	<ul style="list-style-type: none"> <li>■ Fever, reduced alertness, headache, meningismus, focal deficits (20%)</li> <li>■ CD4 count &lt;350 cells/mm<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>■ Intracerebral lesions in 50% to 70% (<i>N Engl J Med</i> 1992;326:668; <i>Am J Med</i> 1992;93:524)</li> </ul>	<ul style="list-style-type: none"> <li>■ Normal: 5% to 10%</li> <li>■ Protein: Normal (40%) - 500/mL</li> <li>■ WBC: 5 to 2000 (average is 60% to 70% monos)</li> <li>■ Glucose: 4 to 0/mL</li> <li>■ AFB smear positive: 20%</li> </ul>	<ul style="list-style-type: none"> <li>■ Chest x-ray: active TB in 50%; PPD positive: 20% to 30%</li> <li>■ Definitive diagnosis: Positive culture CSF</li> </ul>

Normal values: Protein: 15 to 45 mg/dL; traumatic tap: 1 mg/1000 RBCs; glucose: 40 to 80 mg % or CSF/blood glucose ratio >0.6; leukocyte counts: <5 mononuclear cells/mL, 5 to 10 is suspect, 1 PMN is suspect; bloody tap: 1 WBC/700 RBC; opening pressure: 80 to 200 mm H<sub>2</sub>O.

CSF analysis in asymptomatic HIV infected persons shows 40% to 50% have elevated protein and/or pleocytosis (>5 mononuclear cell/mL); the frequency of pleocytosis decreases with progressive disease.

## Ophthalmologic Complications

### CMV Retinitis

**CAUSE:** CD4 count  $<50$  cells/mm<sup>3</sup> + latent CMV infection (50% to 80% HIV infected patients have latent CMV)

**FREQUENCY:** 30% of patients with CD4 count  $<50$  cells/mm<sup>3</sup>

**DIAGNOSIS:** Symptoms include blurring, blind spots, flashing lights (“photopsia”), and loss of central vision; acute vision loss suggests retinal detachment. Ophthalmoscopy by experienced clinician shows characteristic fluffy white lesions and hemorrhages usually close to retinal vessels (“cottage cheese and catsup”). Tests for CMV (pp65Ag, blood DNA PCR, urine DNA PCR, NASBA early Ag, blood culture, urine culture, throat culture) are usually not necessary or useful (*J Clin Microbiol* 2000;38:563).

**TREATMENT:** Standard – HAART + intraocular ganciclovir release device + oral valganciclovir (*N Engl J Med* 2002;346:1119). See p. 128 and Table 7-15.

■ TABLE 7-15: Treatments of CMV Retinitis

Treatment	Regimen	Comment
Intraocular ganciclovir release device ( <i>Vitrasert</i> )	Replace every 6 to 9 months	<p>Advantages</p> <ul style="list-style-type: none"> <li>■ Best record for time to relapse (average 216-226 days)</li> <li>■ Avoids IVs</li> <li>■ Can be done as an outpatient</li> </ul> <p>Disadvantage: Does not prevent CMV at other sites including other eye – must give oral valganciclovir or IV anti-CMV medication</p>
Valganciclovir (oral)	900 mg bid x 3 weeks, then 900 mg qd	<p>Advantages</p> <ul style="list-style-type: none"> <li>■ Avoids IV</li> <li>■ Levels are comparable with IV ganciclovir (<i>N Engl J Med</i> 2002;346:1119)</li> </ul> <p>Disadvantage: ADRs – marrow suppression and GI intolerance</p>
Ganciclovir (IV)	5 mg/kg IV q12h x 14/21 days then 5 mg/kg qd	<p>Advantage: Extensive experience and established efficacy</p> <p>Disadvantages</p> <ul style="list-style-type: none"> <li>■ Time to relapse averages 47-104 days</li> <li>■ ADRs – neutropenia, thrombocytopenia</li> <li>■ Requires IV</li> </ul>

■ TABLE 7-15: **Treatments of CMV Retinitis (Continued)**

Treatment	Regimen	Comment
Foscarnet (IV)	90 mg/kg IV q12h x 14-21 days, then 90 mg/day	<p>Advantages</p> <ul style="list-style-type: none"> <li>■ Extensive experience and established efficacy</li> <li>■ Active vs ganciclovir-resistant strains</li> </ul> <p>Disadvantages</p> <ul style="list-style-type: none"> <li>■ ADRs – nephrotoxic (dose related), electrolyte changes with decreased Ca, Mg, K, PO<sub>4</sub></li> <li>■ Requires infusion pump, long infusion time, saline hydration</li> <li>■ Contraindicated with creatinine clearance &lt;0.4 mL/min/kg</li> </ul>
Cidofovir (IV)	3-5 mg/kg IV every week x 2 then 3-5 mg/kg IV every week + probenecid with each dose 2 g 3 hours before and 1 g 2 and 8 hours after	<p>Advantage: Effective vs ganciclovir-resistant CMV</p> <p>Disadvantages</p> <ul style="list-style-type: none"> <li>■ Requires co-administration of probenecid</li> <li>■ ADRs – highly nephrotoxic, GI intolerance, anemia, neutropenia</li> <li>■ Requires supervised IV administration</li> <li>■ Contraindicated with creatinine &gt;1.5 mg/mL</li> </ul>
Fomivirsen	Intravitreal – 330 µg every 2 weeks x 2, then every month	<p>Advantages</p> <ul style="list-style-type: none"> <li>■ Avoids IVs</li> <li>■ FDA-approved for salvage therapy</li> </ul> <p>Disadvantages</p> <ul style="list-style-type: none"> <li>■ May cause ocular inflammation, increased ocular pressure, and/or vision loss (<i>Am J Ophthalmol</i> 2002;133:475)</li> <li>■ Fails to prevent systemic CMV disease or protect other eye without concurrent systemic treatment</li> </ul>
Intravitreal ganciclovir or foscarnet	<ul style="list-style-type: none"> <li>■ Foscarnet 1.2-2.4 mg in 0.1 mL (<i>N Engl J Med</i> 1994;330:868)</li> <li>■ Ganciclovir 2000 µg in 0.05-1.0 mL (<i>Brit J Ophthalmol</i> 1996;80:214)</li> </ul>	<p>Advantages</p> <ul style="list-style-type: none"> <li>■ Avoids IVs</li> <li>■ Easily done</li> </ul> <p>Disadvantages</p> <ul style="list-style-type: none"> <li>■ Not FDA approved for intravitreal injection</li> <li>■ Fails to prevent systemic disease or protect other eye</li> </ul>

## RESPONSE

- Vision loss prior to therapy typically is permanent.
- Effective therapy is usually accompanied by stabilization of vision in 80% to 90%. However, most patients relapse unless there is immune reconstitution.
- Time to relapse in absence of immune recovery depends on initial CMV treatment and averages from 40 to 220 days in various reports.

- Comparisons are difficult due to variable use of HAART, especially with *Vitrasert* + valganciclovir. The median time to relapse using standard treatment in the pre-HAART era using IV ganciclovir, foscarnet, or cidofovir was 50 to 120 days (*Ophthalmology* 1994;101:1250; *J Infect Dis* 1993;168:557; *N Engl J Med* 1995;333:615; *N Engl J Med* 1997;337:83). Early relapses (<3 months) following ganciclovir treatment are usually associated with ganciclovir-sensitive strains of CMV; late relapses usually involve ganciclovir-resistant strains.

### COMPLICATIONS OF CMV AND ITS TREATMENT

- **Retinal detachment:** Traditionally repaired with vitrectomy and silicone oil treatment (*Arch Ophthalmol* 1995;113:1401). With probable immune reconstitution, conventional retinal detachment surgery without silicone oil may be tried.
- **Cataract** (late complication of retinal detachment): Cataract surgery
- **Relapse:** Strategies vary and include
  - Reinduction of the currently used drug (IV ganciclovir or foscarnet 2x/day)
  - Switching to an alternative agent
  - Intravitreal injection of ganciclovir or foscarnet
  - Intravitreal injection of fomivirsen (FDA-approved for salvage therapy of CMV retinitis)
- **Immune recovery uveitis:** This is a complication of CMV retinitis treatment with immune reconstitution characterized by: 1) Quiescent CMV retinitis and 2) Visual loss with macular edema, epiretinal membrane formation of vitritis. Treatment may be effective using oral or periocular (*Am J Ophthalmol* 2000;130:49; *Retina* 2001;21:1).

### Retinal Necrosis, Acute (see p. 136)

**CAUSE:** Usually ascribed to varicella-zoster virus and more common in AIDS patients with CD4 counts <50 cells/mm<sup>3</sup> (*Clin Infect Dis* 1998;26:34).

**FREQUENCY:** Rare

**DIAGNOSIS:** Visual changes noted weeks to months after zoster resolution with involvement of any dermatome (*N Engl J Med* 2002;347:340) or without cutaneous zoster. Funduscopy examination shows granular, yellowish non-hemorrhagic lesions which extend and coalesce.

**TREATMENT:** Acyclovir IV 10 mg/kg q8h

**RESPONSE:** Usually poor in AIDS patients with progression to blindness despite antiviral agents.

## Zoster Ophthalmicus (see p. 135)

**FREQUENCY:** 0.6% AIDS patients (*AIDS* 2002;16:1045)

**DIAGNOSIS:** Herpes zoster on face in distribution of first branch of trigeminal nerve; usual diagnosis is made by appearance of lesion and can be confirmed by DFA stain of exudate (which is faster, less expensive, and more sensitive than culture).

### TREATMENT

- Acyclovir 10 mg/kg q8h IV x 10 to 14 days followed by oral therapy with valacyclovir (1 g tid) until lesions healed
- Oral therapy from the start until lesions heal using valacyclovir 1000 mg tid or famciclovir 500 mg tid (*Brit J Ophthalmol* 2000;107:1507; *Antimicrob Agents Chemother* 1995;39:1546)

**RESPONSE:** Without therapy, about 50% result in vision loss (*Curr Eye Research* 1987;6:195). With antiviral therapy, the rate of ocular complications is reduced to 20% to 30% (*N Engl J Med* 2002; 347:340).

## Psychiatric Complications

### Bipolar Disorder (Manic Depression)

**FREQUENCY:** 9% of AIDS patients referred for psychiatric evaluation

**DIAGNOSIS:** Manic episodes and depressive episodes and mixed episodes. Differential includes familial bipolar disorder and AIDS mania (no family history, no episodes prior to late stage HIV, co-morbid cognitive impairment).

### TREATMENT

- **AIDS Mania:** HAART
  - Haloperidol (*Haldol*) 2.5-10 mg bid
  - Fluphenazine (*Prolixin*) 2-10 mg bid
  - Risperidone (*Risperdal*) 1-4 mg bid
  - Olanzapine (*Zyprexa*) 10-40 mg hs

- One of the above ± lithium 300 mg bid titrated to level of 0.8-1.2 mEq/mL or valproic acid 20 mg/kg titrated to serum level of 75-100 ng/mL.
- **Adjunctive therapy:** Carbamazepine (*Tegreto*), gabapentin (*Neurontin*), lamotrigine (*Lamictal*)
- Care should be directed by a psychiatrist.

## Delirium

**DIAGNOSIS:** Impaired consciousness, inability to focus or sustain interest, cognitive changes, global derangement of brain function, acute onset, altered consciousness, or disorganized thinking

**TREATMENT:** Correct underlying condition, which may be infection or medication related.

- **Agitation:** Neuroleptics such as haloperidol (*Haldol*) or risperidone
- **Agitation that puts others at risk:** Neuroleptics + low dose of lorazepam for sedation

## Demoralization

**FREQUENCY:** 20% of AIDS patients referred for psychiatric evaluation

**DIAGNOSIS:** Exaggerated grief state, sad, hopelessness, often precipitated by life circumstances. Often mistaken for depression, but unlike depression, often can enjoy some facets of life, feels best in the mornings and does not respond to antidepressants.

**TREATMENT:** Psychotherapy

**RESPONSE:** Responds to psychotherapy and usually not to antidepressants

## Grief (Normal state of low mood focused on loss)

Treatment is psychological rather than pharmacological (support groups, buddy systems).

## Major Depression

**FREQUENCY:** 20% of AIDS patients referred for psychiatric evaluation (*JAMA* 2001;286:2849)

**PRESENTATION:** Depressed mood, loss of pleasure from activities (anhedonia), anorexia, morning insomnia or hypersomnia, difficulty concentrating, thoughts of suicide

**DIFFERENTIAL:** Dementia, delirium, demoralization, intoxications or withdrawal, neurologic diseases

**TREATMENT:** Antidepressants (Tables 7-16 and 7-17) starting with low doses and titrating slowly (“start low and go slow”) with appropriate attention to side effects and serum levels.

■ **TABLE 7-16: Depression: Drug Selection**

Agent	Advantages	Disadvantages
SSRIs	<ul style="list-style-type: none"> <li>■ Relatively safe and well tolerated</li> <li>■ Compared with tricyclics: Fewer drug interactions and side effects</li> <li>■ Safety with overdose</li> </ul>	<ul style="list-style-type: none"> <li>■ ADRs: Sexual dysfunction, substrate and inhibitor of P450 enzymes</li> <li>■ Use with PI or NNRTI may increase level of SSRI</li> </ul>
Tricyclics	<ul style="list-style-type: none"> <li>■ Equally effective compared with SSRIs</li> <li>■ Also useful for neuropathy insomnia and diarrhea</li> </ul>	<ul style="list-style-type: none"> <li>■ ADRs: Anticholinergic effects, dry mouth, blurred vision, orthostasis</li> <li>■ Use with PI or NNRTI may increase tricyclic level</li> <li>■ Refractory arrhythmia with overdose</li> </ul>

**RESPONSE:** Response rates to antidepressants is 85%; cure rate >50% (*Psychosomatic* 1997;38:423).

■ **TABLE 7-17: Antidepressants**

Drug (Trade Name)	<ul style="list-style-type: none"> <li>■ Start Dose</li> <li>■ Therapeutic Dose</li> </ul>	Serum Level*	Advantages	Interactions With HIV Medications
Nortriptyline ( <i>Pamelor</i> )	<ul style="list-style-type: none"> <li>■ 10 to 25 mg at bedtime</li> <li>■ 50-150 mg at bedtime</li> </ul>	70-125 ng/dL	Promotes sleep and weight gain; decreases diarrhea	Increases nortriptyline levels: Fluconazole, LPV/r, RTV
Desipramine ( <i>Norpramin</i> )	<ul style="list-style-type: none"> <li>■ 10 to 25 mg at bedtime</li> <li>■ 50 to 200 mg at bedtime</li> </ul>	>125 ng/dL	Promotes sleep and weight gain; decreases diarrhea	Increases desipramine levels: LPV/r, RTV
Imipramine ( <i>Tofranil</i> )	<ul style="list-style-type: none"> <li>■ 10 to 25 mg at bedtime</li> <li>■ 100 to 300 mg at bedtime</li> </ul>	>225 ng/dL	Promotes sleep and weight gain; decreases diarrhea	Increases imipramine levels: LPV/r, RTV
Amitriptyline ( <i>Elavil</i> )	<ul style="list-style-type: none"> <li>■ 10 to 25 mg at bedtime</li> <li>■ 100 to 300 mg at bedtime</li> </ul>	200 to 250 ng/dL	Promotes sleep and weight gain; decreases diarrhea	Increases amitriptyline levels: LPV/r, RTV
Clomipramine ( <i>Anafranil</i> )	<ul style="list-style-type: none"> <li>■ 25 mg at bedtime</li> <li>■ 100 to 200 mg at bedtime</li> </ul>	150 to 400 ng/dL	Promotes sleep and weight gain; decreases diarrhea	Increases clomipramine levels: LPV/r, RTV
Doxepin ( <i>Sinequan</i> )	<ul style="list-style-type: none"> <li>■ 10 to 25 mg at bedtime</li> <li>■ 50 to 250 mg at bedtime</li> </ul>	100 to 250 ng/dL	Promotes sleep and weight gain; decreases diarrhea	Increases doxepin levels: LPV/r, RTV

*continued on next page*

■ TABLE 7-17: Antidepressants (Continued)

Drug (Trade Name)	■ Start Dose ■ Therapeutic Dose	Serum Level*	Advantages	Interactions With HIV Medications
Fluoxetine (Prozac)	■ 10 mg each morning ■ 20 mg at bedtime	Unclear	Activating	Increases HIV med levels: APV, DLV, EFV, IDV, LPV/r, NFV, RTV, SQV; decreases fluoxetine levels: NVP
Sertraline (Zoloft)	■ 25 to 50 mg each morning ■ 50 to 150 mg each morning	Unclear		Increases sertraline levels: LPV/r, RTV
Citalopram (Celexa)	■ 20 mg each morning ■ 20 to 60 mg each morning	Unclear		Increases citalopram levels: LPV/r, RTV
Paroxetine (Paxil)	■ 10 mg at bedtime ■ 20 to 40 mg at bedtime	Unclear	Somewhat sedating	Increases paroxetine levels: LPV/r, RTV
Fluvoxamine (Luvox)	■ 50 mg at bedtime ■ 150 to 250 mg at bedtime	Unclear	Somewhat sedating	Increases HIV med levels: APV, DLV, EFV, IDV, LPV/r, NFV, RTV, SQV; decreases fluvoxamine levels: NVP
Venlafaxine (Effexor)	■ 37.5 mg each morning ■ 75 to 300 mg each morning	Unclear		Increases venlafaxine levels: LPV/r, RTV
Mirtazapine (Remeron)	■ 7.5 to 15 mg at bedtime ■ 15 to 45 mg at bedtime	Unclear		Promotes sleep and weight gain
Nefazodone (Serzone)	■ 50 mg bid ■ 300 to 400 mg/day in divided doses	Unclear	Somewhat sedating	Increases HIV med levels: EFV, IDV
Trazodone (Desyre)	■ 50 to 100 mg at bedtime ■ 50 to 150 mg at bedtime for sleep; 200-600 mg at bedtime for depression	Unclear	Promotes sleep	Increases trazodone levels: LPV/r, RTV
Bupropion (Wellbutrin)	■ 100 mg each morning ■ 150 to 400 mg/day in divided doses	Unclear	Activating; no sexual side effects	Increases bupropion levels (unclear if clinically significant): RTV, EFV, NFV

\* Correlation of serum level and therapeutic efficacy has been established with nortriptyline.

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## Obsessive Compulsive Disorder

**DIAGNOSIS:** Recurrent obsessions (preoccupying thoughts that the patient finds irrational and tries to resist) and/or compulsions (actions driven by obsessions to reduce anxiety)

**TREATMENT:** Refer to psychiatrist or a mental health specialist.

## Panic Attacks

**DIAGNOSIS:** Recurring anxiety attacks with fear plus somatic symptoms of excitation lasting <1 hour

**TREATMENT:** SSRI and refer to a psychiatrist

## Sleep Disturbance

Medications with FDA approval for insomnia have potential for reinforcement and habituation. Evaluate patient for cause (major depression, mania, substance use disorder, demoralization) and refer for appropriate treatment. Insomnia temporally related to a specific stress (pre-op, grief etc.) may be treated with sedatives or hypnotics up to 1 week or with trazodone 25-150 mg hs for up to 4 weeks.

## Substance Use Disorders

**DIAGNOSIS:** Use of substances despite clear evidence of negative consequences. Dependence: Persistent use or seeking use, withdrawal, tolerance, and physical dependence.

■ TABLE 7-18: Detoxification

Agent	Treatment
Sedative/hypnotic EtOH, benzodiazepines, and barbiturates	■ Long acting benzodiazepines (chlordiazepoxide – <i>Librium</i> , diazepam – <i>Valium</i> )
Alprazolam ( <i>Xanax</i> )	■ Substitute clonazepam and taper
Cocaine	■ Suicidal symptoms common; may need brief hospitalization
Opioids	■ Clonidine for autonomic instability. Buprenorphine or methadone tapers; dicyclomine for GI distress

## Pulmonary Complications

### Pneumonia (PCP)

**PRESENTATION:** Cough, dyspnea, and fever  $\pm$  sputum production

**CAUSE:** The single major prospective study of pulmonary complications of HIV was discontinued in the pre-HAART era – 1995 (*Am J Respir Crit Care Med* 1997;155:72). Data from 3 years (1992-1995) showed 521 infections: PCP – 232 (45%), pyogenic bacteria – 220 (42%), tuberculosis – 25 (5%), CMV – 19 (4%), *Aspergillus* – 12 (2%), and cryptococcosis – 7 (1%). Critical factors in evaluating the HIV infected patient with suspected pneumonia are

- **HIV stage** based on CD4 count (see Table 7-19, p. 391)
- **Tempo:** Pyogenic infections and influenza evolve rapidly with acute symptoms; most other causes evolve more slowly. PCP shows a slow tempo in HIV infected patients with an average duration of 3 weeks prior to presentation.
- **X-ray changes:** A negative chest x-ray generally excludes pneumonia, except 10% to 20% with PCP have a false negative x-ray (*J Acquir Immune Defic Syndr* 1994;7:39); infiltrates can be shown in these cases with thin-section CT scan (*Am J Radiol* 1997;169:967). Rare false-negative x-rays can be seen with tuberculosis, MOTT, and cryptococcosis (see Table 7-20, p. 392).
- **Injection drug use:** Associated with high rates of pneumococcal pneumonia, *S. aureus* endocarditis with septic pulmonary emboli, tuberculosis, and aspiration pneumonia.
- **Prophylaxis:** TMP-SMX (see Figure 7-5, p. 402) effectively reduces incidence of PCP, pyogenic pneumonia including *S. pneumoniae*, *Legionella*, *H. influenzae*, and *S. aureus*. Influenza vaccine appears to prevent influenza, which is associated with substantial morbidity and mortality in HIV infected patients (*Arch Intern Med* 2001;161:441). Pneumovax does not appear to be protective (*BMJ* 2002;325:292). INH or PZA/rifampin regimens substantially reduce the risk of TB.
- **Atypical:** Pneumonia due to *M. pneumoniae*, *C. pneumoniae*, and *Legionella* appears to be relatively uncommon in patients with HIV infection (*Eur J Clin Microbiol Infect Dis* 1997;16:720; *N Engl J Med* 1997;337:682; *N Engl J Med* 1995;333:845; *Am J Resp Crit Care Med* 1995;152:1309; *Clin Infect Dis* 1996;23:107; *Am J Resp Crit Care Med* 2000;162:2063).

**DIAGNOSTIC SPECIMENS** (see Figure 7-4, p. 400 and Table 7-21, p. 393)

- **Expectorated sputum:** Controversial, due in part to poor technique in collecting, transporting, and processing specimens.

- **Expectorated sputum for *M. tuberculosis*:** The yield with three specimens is 50% to 60% for AFB stain; the yield is somewhat higher with PCR at 75% to 85% (*Am J Respir Crit Care Med* 2001;164:2020).
- **Induced sputum:** Recommended as an alternative to expectorated sputum for detection of AFB in patients who cannot produce an expectorated sample and as an alternative to bronchoscopy for detection of PCP. Sensitivity for detection of TB by AFB smear is about the same as it is for expectorated sputum. For PCP, the sensitivity is 60% to 95% in published reports (*JAMA* 2001;286:2450), but it may be much lower in centers that don't publish their results.
- **Bronchoscopy:** The yield for PCP is 95% or about the same as it is for open-lung biopsy (*JAMA* 2001;286:2450). For *M. tuberculosis*, bronchoscopy shows a yield that is similar to that for expectorated sputum. For other bacteria, bronchoscopy is no better than expectorated sputum unless it is done by quantitative culture.

■ **TABLE 7-19: Etiology Correlated With CD4 Count**

CD4 count >200 cells/mm <sup>3</sup>	<i>S. pneumoniae</i> , <i>M. tuberculosis</i> , <i>S. aureus</i> (IDU), Influenza
CD4 count 50-200 cells/mm <sup>3</sup>	Above + <i>P. carinii</i> , cryptococcosis, histoplasmosis, coccidioidomycosis, <i>Nocardia</i> , <i>M. kansasii</i> , Kaposi's sarcoma
CD4 count <50 cells/mm <sup>3</sup>	Above + <i>P. aeruginosa</i> , <i>Aspergillus</i> , MAC, CMV

■ TABLE 7-20: Correlation of Chest X-ray Changes and Etiology of Pneumonia

Change	Common	Uncommon
Consolidation	Pyogenic bacteria, Kaposi's sarcoma, cryptococcosis	<i>Nocardia</i> , <i>M. tuberculosis</i> , <i>M. kansasii</i> , <i>Legionella</i> , <i>B. bronchiseptica</i>
Reticulonodular infiltrates	<i>P. carinii</i> , <i>M. tuberculosis</i> , histoplasmosis, coccidioidomycosis	Kaposi's sarcoma, toxoplasmosis, CMV, leishmania, lymphoid interstitial pneumonitis
Nodules	<i>M. tuberculosis</i> , cryptococcosis	Kaposi's sarcoma, <i>Nocardia</i>
Cavity	<i>M. tuberculosis</i> , <i>S. aureus</i> (IDU), <i>Nocardia</i> , <i>P. aeruginosa</i> , cryptococcosis, coccidioidomycosis, histoplasmosis, aspergillosis, anaerobes	<i>M. kansasii</i> , MAC, <i>Legionella</i> , <i>P. carinii</i> , lymphoma, <i>Klebsiella</i> , <i>Rhodococcus equi</i>
Hilar nodes	<i>M. tuberculosis</i> , histoplasmosis, coccidioidomycosis, lymphoma, Kaposi's sarcoma	<i>M. kansasii</i> , MAC
Pleural effusion	Pyogenic bacteria, Kaposi's sarcoma, <i>M. tuberculosis</i> (congestive heart failure, hypoalbuminemia)	Cryptococcosis, MAC, histoplasmosis, coccidioidomycosis, aspergillosis, anaerobes, <i>Nocardia</i> , lymphoma, toxoplasmosis, primary effusion lymphoma

■ TABLE 7-21: Pulmonary Infection: Differential Diagnosis

Agent	Course*	Frequency, Setting	Typical Findings	Diagnosis†	Treatment
<b>Bacteria</b>					
Gram-negative bacilli	Acute, purulent sputum	Uncommon, except with nosocomial infection or neutropenia. <i>Pseudomonas aeruginosa</i> is relatively common in late-stage disease, cavity disease, or chronic antibiotic exposure (median CD4 50 cells/mm <sup>3</sup> )	Lobar or bronchopneumonia	Sputum GS and culture (sensitivity is >80%, but specificity is poor)	<ul style="list-style-type: none"> <li>Need in vitro susceptibility tests</li> <li>Long-term ciprofloxacin usually results in relapse and resistance to <i>P. aeruginosa</i>.</li> </ul>
<i>Haemophilus influenzae</i>	Acute, purulent sputum	Incidence is 100-fold higher than in healthy controls; most infections are caused by unencapsulated strains	Bronchopneumonia	Sputum GS and culture (sensitivity of culture is 50%; prior antibiotics usually preclude growth)	<ul style="list-style-type: none"> <li>Oral: Amox-CA, azithromycin, TMP-SMX, fluoroquinolone, cephalosporin;</li> <li>Intravenous: Cefotaxime, ceftriaxone</li> </ul>
<i>Legionella</i>	Acute mucopurulent sputum	Uncommon. HIV-associated risk is debated.	Bronchopneumonia; sometimes multiple infiltrates in noncontiguous segments	Sputum culture; urinary antigen ( <i>Legionella pneumophila</i> serogroup 1)	Fluoroquinolone, macrolide, doxycycline
<i>Nocardia</i>	Chronic or asymptomatic; sputum production	Uncommon; frequency higher with chronic corticosteroid use (median CD4 count 50 cells/mm <sup>3</sup> )	Nodule or cavity	Sputum or fiberoptic bronchoscopy (FOB); GS, modified acid-fast bacillus (AFB) stain and culture; should alert lab if suspected (?)	Sulfonamide/TMP-SMX
<i>Staphylococcus aureus</i>	Acute; subacute, or chronic, purulent sputum	Uncommon, except with injected drug use and tricuspid valve endocarditis with septic emboli	Bronchopneumonia, cavity disease, septic emboli with cavities ± effusion	Blood sputum GS and culture (sputum culture is sensitive, but specificity is poor). Blood cultures are nearly always positive with endocarditis.	<ul style="list-style-type: none"> <li>MSSA: Nafcillin/oxacillin, cefuroxime, TMP-SMX, clindamycin</li> <li>MRSA: Vancomycin</li> </ul>

Systems Review: Pulmonary Complications

■ TABLE 7-21: Pulmonary Infection: Differential Diagnosis (Continued)

Agent		Course*	Frequency, Setting	Typical Findings	Diagnosis†	Treatment
<b>Bacteria (Continued)</b>						
Streptococcus pneumoniae	Acute, purulent sputum ± pleurisy	Common, all stages HIV infection; incidence is 100-fold higher than in healthy controls; recurrence rate at 6 months is 6% to 24%; higher with low CD4 counts and with smoking	Lobar or bronchopneumonia ± pleural effusion	Blood cultures often positive, sputum gram stain (GS), Quellung, culture (sensitivity of culture is 50%; prior antibiotics usually preclude growth)	<ul style="list-style-type: none"> <li>■ Oral: Amoxicillin, macrolide, cefdinir, cefprozil, cefpodoxime, fluoroquinolone;</li> <li>■ Intravenous: Cefotaxime, ceftriaxone, fluoroquinolone</li> </ul>	
<b>Fungi</b>						
Aspergillus	Acute or subacute	Up to 4% of AIDS patients; usually advanced HIV infection (median CD4 count 30 cells/mm <sup>3</sup> ); about 50% have severe neutropenia (ANC <500/mm <sup>3</sup> ) ± chronic steroids; disseminated disease is uncommon	Focal infiltrate; cavity – often pleural-based, diffuse infiltrates or reticulonodular infiltrates	Sputum stain and culture: false-positive and false-negative cultures common. Best tests: Tissue pathology or sputum smear and typical CT and clinical features	Amphotericin B or itraconazole or caspofungin	
Candida	Chronic or subacute	Common isolate, rare cause of pulmonary disease (median CD4 count 50 cells/mm <sup>3</sup> )	Bronchitis; rare cause of pneumonia (some say it does not exist)	Recovery in sputum or FOB specimen is meaningless (up to 30% of all expectorated sputum and FOB cultures in unselected patients yield <i>Candida</i> sp.); must have histologic evidence of invasion on biopsy	Fluconazole or amphotericin B	

Agent	Course*	Frequency, Setting	Typical Findings	Diagnosis †	Treatment
<b>Fungi (Continued)</b>					
Coccidioides immitis‡	Chronic or subacute	Up to 10% of AIDS patients in endemic area; usually advanced HIV infection (median CD4 count 50 cells/mm <sup>3</sup> ); disseminated disease in 20% to 40%	Diffuse nodular infiltrates, focal infiltrate, cavity, hilar adenopathy (Clin Infect Dis 1996;23:563)	Sputum, induced sputum, or FOB stain and culture; KOH of expectorated sputum is rarely positive; PAP stain or silver stain of BAL positive in 40%; culture of BAL usually positive; serology (CF) positive in 70%; skin test positive in <10%; blood cultures positive in 10%	Fluconazole, itraconazole, or amphotericin B
Cryptococcus	Chronic, subacute, or symptomatic	Up to 8% to 10% in AIDS patients; late-stage HIV infection (median CD4 count 50 cells/mm <sup>3</sup> ); 80% have cryptococcal meningitis	Nodule, cavity, diffuse or nodular infiltrates	Sputum, induced sputum, or FOB stain and culture; serum cryptococcal antigen usually positive; CSF analysis indicated if antigen or organism found at any site	Fluconazole without CNS involvement amphotericin B
Histoplasma capsulatum‡	Chronic or subacute	Up to 15% of AIDS patients in endemic area; usually advanced HIV infection with disseminated histoplasmosis (median CD4 count 50 cells/mm <sup>3</sup> ); common features: Fever, weight loss, hepatosplenomegaly, lymphadenopathy	Diffuse nodular infiltrates, nodule, focal infiltrate, cavity, hilar adenopathy (N Engl J Med 1986;314:83; Medicine 1990;69:361)	Best test for diagnosis and follow-up of treatment is serum and urine polysaccharide antigen assay, with yield of 85% (blood) and 97% (urine). Available only through J. Wheat (Indianapolis, IN) 800-HISTO-DG for \$70/assay; serology positive in 50% to 70%; yield with culture of sputum – 80%, marrow – 80%; blood cultures positive in 60% to 85%	Itraconazole or amphotericin B

## Systems Review: Pulmonary Complications

■ TABLE 7-21: Pulmonary Infection: Differential Diagnosis (Continued)

Agent	Course*	Frequency, Setting	Typical Findings	Diagnosis†	Treatment
<b>Fungi (Continued)</b>					
Pneumocystis carinii	Acute or subacute; nonproductive cough; dyspnea	Very common in late stages of HIV infection (CD4 <200 cells/mm <sup>3</sup> ) (median CD4, without prophylaxis, 100 cells/mm <sup>3</sup> ; with prophylaxis 20 cells/mm <sup>3</sup> ; >95% have CD4 <200 cells/mm <sup>3</sup> ); infrequent in patients compliant with TMP-SMX prophylaxis; main predictor of prophylaxis failure is late-stage disease with very low CD4 count (JAMA 1995;273:1197)	Interstitial infiltrates with characteristic ground glass appearance; negative x-ray in early stages, about 15% to 20%; atypical findings in 20%; atypical findings: Upper lobe infiltrates, focal infiltrates, nodules, cavitary disease, or mediastinal lymphadenopathy	Cytology of induced sputum (mean yield of 60% in proven cases) and bronchoalveolar lavage (BAL) (mean yield of 95%); yield is lower in patients receiving aerosolized pentamidine; yield depends on technical expertise, which is highly variable	<ul style="list-style-type: none"> <li>■ TMP-SMX or pentamidine dapsone/trimethoprim</li> <li>■ clindamycin/primaquine</li> <li>■ atovaquone trimetrexate</li> <li>■ pO<sub>2</sub> &lt;70 or A-a gradient &gt;35 mm: Prednisone</li> </ul>
<b>Mycobacteria</b>					
Mycobacterium avium complex (MAC)	Chronic or asymptomatic	Moderate for disseminated disease but uncommon for pulmonary disease: late stage HIV (median CD4 20 cells/mm <sup>3</sup> )	Variable	<ul style="list-style-type: none"> <li>■ Sputum, FOB, or induced sputum AFB stain and culture; must distinguish from MTB (DNA probe or radiometric culture technique); MAC may colonize airways without causing pulmonary disease; requires 1 to 2 weeks for growth in Bactec system</li> <li>■ Most positive AFB smears are TB and not MAC</li> </ul>	<ul style="list-style-type: none"> <li>■ Clarithromycin + ethambutol</li> <li>■ Azithromycin + ethambutol ± rifabutin</li> </ul>
Mycobacterium kansasii	Chronic or asymptomatic	Uncommon: Late-stage HIV (median CD4 50 cells/mm <sup>3</sup> )	Cavitary disease, nodule, cyst, infiltrate, or normal chest x-ray	Sputum, induced sputum, or FOB, AFB stain and culture	INH, ethambutol + rifampin ± clarithromycin or ciprofloxacin

Agent	Course*	Frequency, Setting	Typical Findings	Diagnosis †	Treatment
<b>Mycobacteria (Continued)</b>					
Mycobacterium tuberculosis (tuberculosis, miliary tuberculosis, MTB) †	Chronic, subacute, or asymptomatic; usually has productive cough ± hemoptysis	Frequency is 5% (170-fold increase) in all AIDS patients; higher in some cities; including New York, NY, Newark, NJ, and Miami, FL; with injected drug use; and in African-American patients (median CD4 count 200 to 300 cells/mm <sup>3</sup> )	Variable: Focal infiltrates, reticulonodular, cavitary disease, hilar adenopathy, lower and middle lobe involvement common, pleural effusion; early-stage HIV infection: upper lobe cavitary; late-stage HIV: pneumonitis mid or lower lobes or miliary pattern with minimal granuloma formation. Extrapulmonary TB is common – especially in meningitis, adenopathy	<ul style="list-style-type: none"> <li>■ Sputum AFB stain and culture, if no sputum production, induced sputum, or FOB; requires 1 to 4 weeks for growth in Bactec system with rapid ID by Gen Probe; requires 3 to 8 weeks for growth on conventional media; sensitivity of sputum AFB smear = 50%</li> <li>■ Most positive AFB smears indicate M. tuberculosis (not MAC)</li> <li>■ Drug sensitivity tests should be performed on all isolates. Requires reporting to health department.</li> </ul>	See pp. 145-148
<b>Viruses</b>					
Cytomegalovirus (CMV)	Subacute or chronic	Common isolate, rare cause of pulmonary disease; advanced HIV infection (median CD4 count 20 cells/mm <sup>3</sup> )	Interstitial infiltrates	Yield with FOB is 20% to 50%, culture requires more than 1 week; shell culture 1 to 2 days; diagnosis of CMV pneumonitis (disease) requires CMV seen on cytopath or biopsy, progressive disease, and no alternative pathogen	Ganciclovir, foscarnet or cidofovir

## Systems Review: Pulmonary Complications

■ TABLE 7-21: Pulmonary Infection: Differential Diagnosis (Continued)

Agent	Course*	Frequency, Setting	Typical Findings	Diagnosis†	Treatment
<b>Viruses (Continued)</b>					
Herpes simplex virus (HSV), varicella zoster (VZV), respiratory syncytial virus (RSV), parainfluenza	Acute	Rare causes of pneumonia	Diffuse or nodular pneumonia, bronchopneumonia	<ul style="list-style-type: none"> <li>■ Culture of sputum or FOB commonly yields HSV as a contaminant from upper airways</li> <li>■ RSV is rare in adults but has increased frequency in immunosuppressed host, is easily detected with DFA stain of respiratory secretions, and is possibly treatable with aerosolized ribavirin</li> </ul>	HSV, VZV: Acyclovir RSV: Ribavirin (?)
Influenza	Acute, purulent sputum	<ul style="list-style-type: none"> <li>■ Influenza is common; influenza pneumonia is rare</li> <li>■ Any stage of HIV infection.</li> <li>■ Frequency and course minimally different from patients without HIV infection</li> </ul>	Bronchopneumonia, interstitial infiltrates	<ul style="list-style-type: none"> <li>■ Culture of throat, nasopharyngeal aspirates, washing, and serology; most rely on epidemiology in community and typical symptoms.</li> <li>■ Bacterial super-infection is common with <i>S. pneumoniae</i>, <i>S. aureus</i> and <i>H. influenza</i></li> </ul>	Amantadine/ramantadine neuramidase inhibitors: Oseltamivir or zanamivir
<b>Miscellaneous</b>					
Aspiration pneumonia	Acute or subacute	Accounts for 5% to 10% of pneumonia cases	Infiltrates in dependent pulmonary segment + cough and fever ± cavitation/empyema	It is not possible to verify anaerobic bacterial pneumonia; putrid drainage is diagnostic	<ul style="list-style-type: none"> <li>■ Clindamycin</li> <li>■ Beta-lactam + Beta-lactamase inhibitor</li> </ul>
Enigmatic	Acute or subacute	Accounts for most acute pneumonias	Most are presumably due to <i>S. pneumoniae</i> or <i>P. carinii</i> ; distinguish based on CD4 count, tempo and radiographic changes	Antibiotic treatment precludes recovery of <i>S. pneumoniae</i> or <i>H. influenzae</i> ; it does not reduce yield of <i>P. carinii</i>	TMP-SMX/cephalosporin or fluoroquinolone

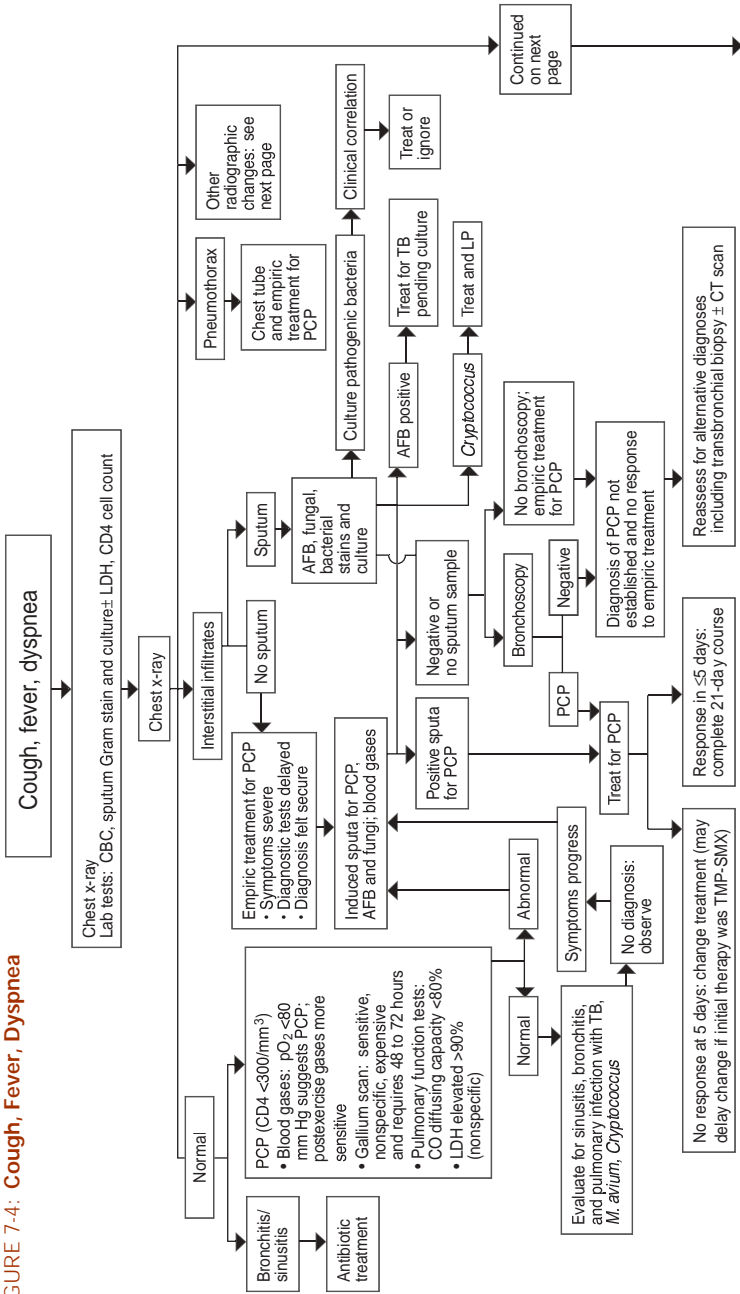
Agent	Course*	Frequency, Setting	Typical Findings	Diagnosis †	Treatment
<b>Miscellaneous (Continued)</b>					
Kaposi's sarcoma (KS)	Asymptomatic or chronic progressive cough and dyspnea	Moderately common in patients with cutaneous KS and advanced HIV disease	Interstitial, alveolar, or nodular infiltrates, hilar adenopathy (25%), scan usually negative, pleural effusions (40%); gallium	<ul style="list-style-type: none"> <li>■ FOB often shows discolored endobronchial node(s); yield of bronchial or trans-thoracic biopsy is only 20% to 30%. Pulmonary infiltrate on x-ray with negative gallium scan is highly suggestive</li> <li>■ Suspect with enigmatic pulmonary infiltrates, chronic course, cutaneous lesions, and/or bloody pleural effusion</li> </ul>	<ul style="list-style-type: none"> <li>■ Liposomal daunorubicin or doxorubicin</li> <li>■ Taxol</li> <li>■ Adriamycin, bleomycin/vincristin, or vinblastin</li> </ul>
Lymphocytic interstitial pneumonia (LIP)	Chronic or subacute	Uncommon in adults (median CD4 count 200 to 400 cells/mm <sup>3</sup> )	Diffuse reticulonodular infiltrates, resembles PCP on chest x-ray; CD4 count is higher and LDH is lower; course is subacute and resembles PCP	Requires tissue for histopathology; yield with FOB biopsy is 30% to 50%; open lung biopsy often required	Prednisone (?)
Lymphoma	Chronic or asymptomatic	Uncommon, but may be presenting site	Interstitial, alveolar, or nodular infiltrates; cavity, hilar adenopathy, pleural effusions	Requires tissue for histopathology; yield with FOB biopsy is poor; open lung biopsy often required	CHOP BACOD + G-CSF

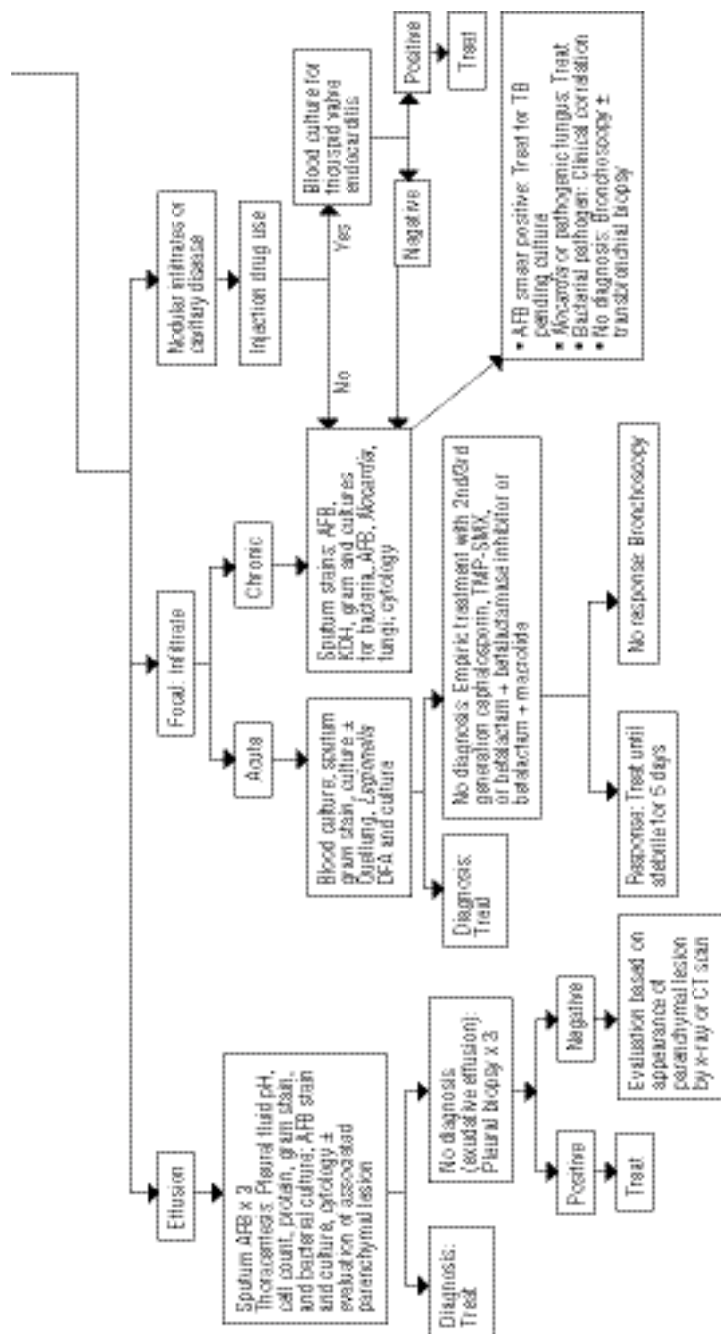
\* Course: Acute = symptoms evolve over days; subacute = symptoms evolve over 2-6 weeks; chronic = symptoms evolve over >4 weeks.

† Diagnosis: Expectorated sputum for bacterial culture should have cytologic screening to show predominance of PMN, GS, and Quellung (if GS suggests S. pneumoniae). Induced sputum often is reserved for patients with nonproductive cough and suspected PCP or M. tuberculosis. Culture for conventional bacteria gives results similar to expectorated sputum (J Clin Microbiol 1994;32:131). FOB assumes BAL + touch preps, bronchial washings, bronchial brush, or transbronchial biopsy; the usual specimen for PCP is BAL. Detection of fungi requires stains (KOH and/or Gomori methanamine silver stain) and culture (Sabouraud's media). Candida sp. grow on conventional bacterial media. Detection of viruses requires cytopathology for inclusions (herpes viruses, CMV, HSV, VZV); FA for HSV and influenza; cultures are for herpes viruses and with special request for influenza virus.

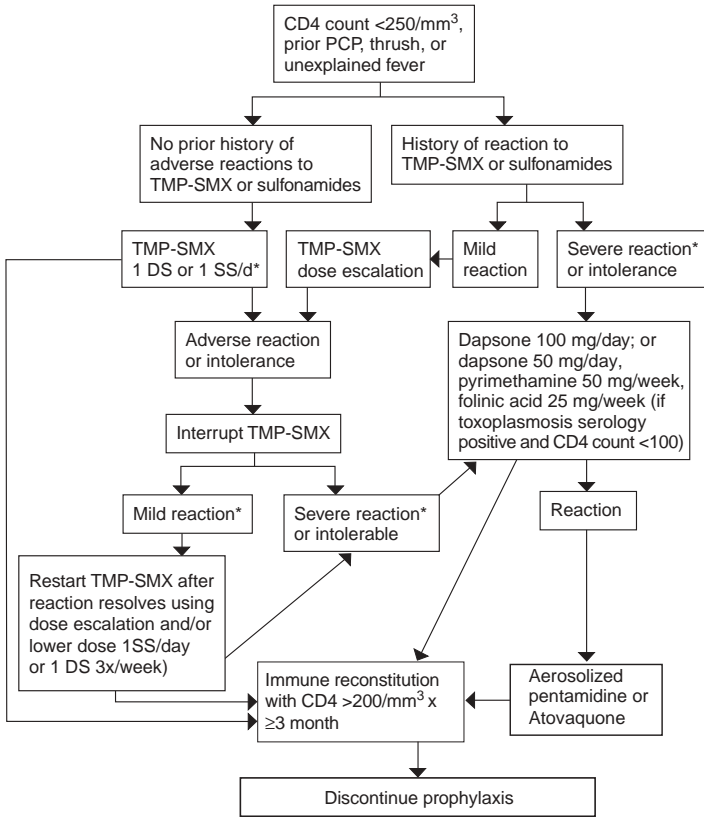
‡ Detection of these organisms in respiratory secretions is essentially diagnostic of disease; other organisms may be contaminants colonizing mucosal surfaces or commensals.

■ FIGURE 7-4: Cough, Fever, Dyspnea





■ FIGURE 7-5: PCP Prophylaxis



\* **Severe:** Urticaria, angioedema, Stevens-Johnson reaction, or fever. **Intolerance:** GI symptoms, rash/pruritis. **Mild:** Tolerable with aggressive supportive care and/or dose reduction.

## Renal Complications

Hepatitis C Co-Infection (see *J Am Soc Nephrol* 1999;10:1566)

**CAUSE:** Mixed cryoglobulinemia

**SYMPTOMS:** Palpable purpura, decreased complement, and renal disease

## DIAGNOSIS

- **Evidence of HCV** (Positive EIA + HCV RNA)
- **Renal disease** with hematuria and proteuria often in nephrotic range ± renal insufficiency
- **Low complement**
- **Renal biopsy** with evidence of HCV-related immune complexes
- **Circulating cryoglobulins** ± skin biopsy of purpuric lesion

**TREATMENT:** Pegylated interferon + ribavirin is preferred (see p. 276), but ribavirin is not recommended with creatinine clearance <50 mL/min due to increased risk of toxicity (e.g. hemolytic anemia).

## Heroin Nephropathy (HAN)

**CAUSE:** Unknown, possibly glomerular epithelial cell injury from toxin contaminant (*Am J Kidney Dis* 1995;25:689)

**FREQUENCY:** Unknown, but decreasing with increasing purity of street heroin. Frequency is increased in African Americans accounting for 94% of renal failure cases in one series of 98 patients (*JAMA* 1983;250:2935).

**DIFFERENTIAL:** Main differential is HIVAN. HAN shows: 1) Hypertension. 2) Small kidneys by echo. 3) Less rapid progression to end-stage renal disease (20 to 40 months vs 1 to 4 months). 4) Less proteinuria. 5) Differences on renal biopsy.

## HIV-Associated Neuropathy (HIVAN)

**CAUSE:** Unknown, possibly due to HIV infection of glomerular endothelial and mesangial cells (*N Engl J Med* 2001;344:1979)

**FREQUENCY:** 2% to 10% of HIV infected patients. Rates are higher in African American males; may occur with high CD4 counts.

**DIAGNOSIS:** Role of renal biopsy is controversial, but some have alternative treatable diagnoses (*Kidney Int* 1995;48:311). If done, findings include characteristic microcytic dilation of tubules plus focal and segmental glomerulosclerosis. Course is characterized by rapid progression of nephrosis and no hypertension.

**CLINICAL AND LABORATORY FEATURES:** Proteinuria >1 g/day + hypoalbuminemia and rapid progressive renal failure to end stage renal disease in 1 to 4 months (*Kidney Int* 1995;48:311). Echo shows enlarged or normal sized kidneys, which distinguishes this from many other causes of renal failure.

## TREATMENT

- **HAART:** Preliminary data based on biopsy results suggest benefit from HAART (*Lancet* 1998;352:783).
- **Dialysis** (*Am J Kidney Dis* 1997;29:549)
- **Corticosteroids** (60 mg/day x 2 to 11 weeks, then taper over 2 to 26 weeks) shows variable results (*Am J Med* 1994;97:145; *Kidney Int* 2000;58:1253).
- **ACE Inhibitors** (Captopril 6.25-25 mg PO tid) show variable results (*Am J Kidney Dis* 1996;28:202).

## Nephrotoxic Drugs

Amphotericin, aminoglycoside, cidofovir, foscarnet, pentamidine, IV acyclovir, TMP-SMX, indinavir (see below), sulfonamides (crystal induced)

**INDINAVIR:** Renal calculi ± nephropathy (*Ann Intern Med* 1997;127:119)

- **Cause:** Crystallization of indinavir
- **Prevention:** Should be taken without food, but with water ≥150 mL within 3 hours post dose and ≥1500 mL/day.
- **Dose dependent:** Especially with ritonavir in 800/100 mg bid regimen.
- **Diagnosis:** Urine shows indinavir sulfate crystals – rectangular plates of various sizes with needle-shaped crystals and pyuria (*Clin Nephrol* 2000;54:261; *N Engl J Med* 1997;336:139).
- **Symptoms:** Review of urinalysis from 140 IDV recipients showed 20% had crystalluria; 3% of these had renal colic and most of the rest had frequency plus dysuria and/or flank pain (*Ann Intern Med* 1997;127:119).
- **Treatment**
  - Remove stones by ureteroscopy or by passage.
  - Discontinue IDV in symptomatic patients (discontinue all antiretroviral drugs or substitutes).
  - May resume IDV (usually at a modified dose) and increase fluid consumption, especially post dose.

**Thrombotic Thrombocytopenic Purpura:** See p. 362

# Abbreviations

## Drug Abbreviations

3TC	Lamivudine	IDV	Indinavir
5-FC	Flucytosine	INH	Isoniazid
ABC	Abacavir	LPV/r	Lopinavir/Ritonavir
APV	Amprenavir	NFV	Nelfinavir
AZT	Zidovudine	NVP	Nevirapine
d4T	Stavudine	PZA	Pyrazinamide
ddC	Zalcitabine	RIF	Rifampin
ddI	Didanosine	RTV	Ritonavir
DLV	Delavirdine	SM	Streptomycin
EFV	Efavirenz	SMX	Sulfamethoxazole
EMB	Ethambutol	SQV	Saquinavir
EPO	Erythropoietin	TDF	Tenofovir disoproxil fumarate
G-CSF	Filgrastim	TMP	Trimethoprim
HU	Hydroxyurea	TMP-SMX	Trimethoprim-sulfamethoxazole

## Drug Administration Abbreviations

bid	Twice a day	m <sup>2</sup>	Meters squared
caps	Capsules	max	Maximum
cc	Cubic centimeter	mcg	Microgram
cm	Centimeter	mEq	Milliequivalent
cm <sup>2</sup>	Centimeters squared	mg	Milligram
d/c	Discontinue	mil	Million
dL	Deciliter	min	Minimum
DS	Double strength	mL	Milliliter
dx	Diagnosis	mm	Millimeter
g	Gram	mM	Millimole
H <sub>2</sub> O	Water	mo	Month
Hg	Mercury	MU	Million units
hr	Hour	N	Normal (solution) or total sample size
hs	Hours of sleep	ng	Nanogram
IM	Intramuscular	OTC	Over-the-counter
IU	International unit	PO	By mouth
IV	Intravenous	PSI	Pounds per square inch
kg	Kilogram	pt-yrs	Patient-years
L	Liter	q	Every
m	Meter		

## Drug Administration Abbreviations (Continued)

qd	Every day	VD	Volume of distribution
qhs	At bedtime	vol	Volume
qid	Four times a day	wk	Week
qod	Every other day	wgt	Weight
SQ	Subcutaneously	x	Times
sol'n	Solution	XL	Extended release
SS	Single strength	yr	Year
supp	Supply	µg	Microgram
tabs	Tablets	µL	Microliter
tid	Three times per day	µM	Micrometer
tiw	Three times per week	µmol	Micromole
U	Unit		

## General Abbreviations

ACTG	AIDS Clinical Trial Group (U.S.)	C-section	Cesarean section
ADL	Activities of daily living	CSF	Cerebrospinal fluid
ADR	Adverse drug reaction	CT	Computerized tomography
AETC	AIDS Education Training Center (U.S.)	CTL	Cytotoxic T lymphocyte
AFB	Acid-fast bacillus	DEXA	Dual energy x-ray absorptiometry
AHCPRA	Agency for Health Care Policy and Research (U.S.)	DFA	Direct fluorescent antibody
Al	Aluminum	DHHS	Department of Health and Human Services (U.S.)
ALT	Alanine aminotransferase	DOT	Directly observed therapy
ANC	Absolute neutrophil count	EBV	Epstein-Barr virus
anti-HAV	Hepatitis A antibody	EDTA	Ethylenediamine tetraacetic acid
anti-HBc	Hepatitis B core antibody	EIA	Enzyme immunoassay
anti-HBs	Hepatitis B surface antibody	EM	Electron microscopy
anti-HCV	Hepatitis C antibody	ERCP	Endoscopic retrograde cholangio-pancreatography
ART	Antiretroviral therapy	ETOH	Alcohol
ASCUS	Atypical squamous cells of undetermined significance	FOB	Fiberoptic bronchoscopy
AST	Aspartate aminotransferase	FDA	Food and Drug Administration (U.S.)
AWP	Average wholesale price	G6-PD	Glucose-6-phosphate dehydrogenase
BUN	Blood urea nitrogen	GFR	Glomerular filtration rate
Ca	Calcium	GI	Gastrointestinal
CBC	Complete blood count	HAART	Highly active antiretroviral therapy
CDC	Centers for Disease Control and Prevention (U.S.)	HAD	HIV-associated dementia
CF	Complement fixation	HAV	Hepatitis A virus
CMV	Cytomegalovirus	HBeAg <sup>†</sup>	Hepatitis B early antigen
CNS	Central nervous system	HBIG	Hepatitis B immune globulin
CPK	Creatine phosphokinase	HBV	Hepatitis B virus
CrCl	Creatine clearance		
CROI	Conference on Retroviruses and Opportunistic Infections		

## General Abbreviations (Continued)

HCFA	Health Care Financing Administration (U.S.)	MCV	Mean corpuscular volume
HCV	Hepatitis C virus	Mg	Magnesium
HCW	Health care worker	MSM	Men who have sex with men
HDL	High density lipoprotein	MSSA	Methicillin sensitive <i>Staph aureus</i>
Hgb	Hemoglobin	NASBA	Nucleic acid sequence-based amplification
HPV	Human papillomavirus	NCEP	National Cholesterol Education Program (U.S.)
HSIL	High-grade squamous intraepithelial lesion	NCI	National Cancer Institute (U.S.)
HSV	Herpes simplex virus	NIAID	National Institute of Allergy and Infectious Diseases (U.S.)
HSV-1	Herpes simplex virus 1	NIH	National Institute of Health (U.S.)
HSV-2	Herpes simplex virus 2	NNRTI	Non-nucleoside reverse transcriptase inhibitor
HTLV-1	Human T-cell leukemia virus 1	NRTI	Nucleoside reverse transcriptase inhibitor
HTLV-2	Human T-cell leukemia virus 2	NS	Not significant
IAS	International AIDS Society	NSAID	Nonsteroidal anti-inflammatory drug
IAS-USA	International AIDS Society-U.S.A.	OHL	Oral hairy leukoplakia
ICAAC	Interscience Conference on Antimicrobial Agents and Chemotherapy	OI	Opportunistic infection
ICL	Idiopathic CD4 lymphocytopenia	OP	Opening pressure
IDSA	Infectious Diseases Society of America	PAP smear	Papanicolaou smear
IG	Immune globulin	PBMC	Peripheral blood mononuclear cells
IgE	Immunoglobulin E	PCP	<i>Pneumocystis carinii</i> pneumonia
IgG	Immunoglobulin G	PCR	Polymerase chain reaction
IgM	Immunoglobulin M	PEP	Postexposure prophylaxis
IL-2	Interleukin 2	PGL	Persistent generalized lymphadenopathy
IM	Intramuscular	PHS	Public Health Service (U.S.)
IOM	Institute of Medicine	PID	Pelvic inflammatory disease
ITP	Idiopathic thrombocytopenic purpura	PI	Protease inhibitor
ITT	Intent-to-treat (analysis)	PML	Progressive multifocal leukoencephalopathy
IVIG	Intravenous immune globulin	PMN	Polymorphonuclear leukocyte
JCV	JC virus	PPD	Purified protein derivative of tuberculin
KOH	Potassium hydroxide	Pr	Protease
KS	Kaposi's sarcoma	PUVA	Psoralen ultraviolet A-range
LDH	Lactate dehydrogenase	RBC	Red blood cells
LDL	Low-density lipoprotein	rHU EPO	Recombinant human erythropoietin
LFT	Liver function test	RIBA	Recombinant Immunoblot assay
LFT	Liver function test		
LP	Lumber puncture		
LSIL	Low-grade squamous intraepithelial lesion		
LVEF	Left ventricular ejection fraction		
MAC	<i>Mycobacterium avium</i> complex		
MACS	Multicenter AIDS Cohort Study		
MAO	Monoamine oxidase		

## General Abbreviations (Continued)

RPR	Rapid plasma regain	TLC	Total lymphocyte count
RT	Reverse transcriptase	TNF-alpha	Tumor necrosis factor-alpha
RT-PCR	Reverse transcriptase polymerase chain reaction	TSH	Thyroid stimulating hormone
SIL	Squamous intraepithelial lesion	TST	Tuberculin skin test
SSRI	Selective serotonin reuptake inhibitors	ULN	Upper limit of normal
STD	Sexually transmitted disease	USPHS	Public Health Service (U.S.)
STEPS	Systems for Thalidomide Education and Prescribing Safety	UTI	Urinary tract infection
STI	Structured treatment interruption	UVB	Ultraviolet B
TAM	Thymidine analog mutation	VRDL	Venereal disease research laboratory
TB	Tuberculosis	vs	Versus
TEN	Toxic epidermal necrolysis	VZIG	Varicella zoster immune globulin
THC	Tetrahydrocannabinol	VZV	Varicella zoster virus
		WBC	White blood count
		WB	Western blot
		WHO	World Health Organization

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## Enfuvirtide (T-20)

**TRADE NAME (MANUFACTURER):** *Fuzeon* (Roche-Trimeris)

**FORMULATION:** Enfuvirtide is packaged in a 30-day kit containing: 60 (90 mg) single-use vials of enfuvirtide, 60 vials of sterile water for injection, 60 reconstitution syringes (3 cc), 60 administration syringes (1 cc), and alcohol wipes. Enfuvirtide kit can be stored at room temperature. However, once enfuvirtide powder has been reconstituted, it must be refrigerated and used within 24 hours.

**COST:** Approximately \$20,000/year

**MECHANISM OF ACTION:** Enfuvirtide binds to HR1 site in the gp41 subunit of the viral envelope glycoprotein and prevents conformational change required for viral fusion and entry into cells.

**DRUG RESISTANCE AND CROSS-RESISTANCE:** A 21-fold (range: <1-422-fold) decrease in susceptibility to enfuvirtide has been correlated with genotypic changes in gp41 amino acids 36-45 (36, 38, 40, 42, 43, and 45) (P<0.0001) [Greenberg, et al. 10th CROI 2003, Abstract 141]. *In vitro*, clinical isolates resistant to NRTI, NNRTI, or PIs retained susceptibility to enfuvirtide.

### PHARMACOKINETIC

- **Absorption:** Well absorbed from subcutaneous (SC) site with an absolute bioavailability of 84.3% (+/- 15.5%). Following 90 mg SC, the mean  $C_{max}$  was 5.0 +/- 1.7 mcg/mL,  $C_{min}$  was 3.3 +/- 1.6 mcg/mL, and AUC was 48.7 +/- 19.1 mcg/mL · hr.
- **Distribution:**  $V_d=5.5 +/- 1.1$  L
- **Protein binding:** 92%
- **Metabolism:** The exact pathway of enfuvirtide metabolism is unknown. *In vitro*, enfuvirtide undergoes a non-NADPH dependent hydrolysis.
- **T<sub>1/2</sub>:** 3.8 +/- 0.6 h

**USUAL ADULT DOSE:** 90 mg (1 mL) SC q12h into upper arm, anterior thigh or abdomen with each injection given at a site different from the preceding injection site (prior to administration, reconstitute with 1.1 mL of sterile water for infection giving a volume of 1.2 mL).

**PEDIATRIC DOSE:** Pediatric patients 6-16 years of age: 2 mg/kg (max 90 mg) SC q12h.

**DOSING WITH HEPATIC INSUFFICIENCY:** No data

**DOSING WITH RENAL INSUFFICIENCY:** Estimated CrCl >35 mL/min: 90 mg SC q12h; CrCl <35 mL/min: No data, usual dose likely.

**DRUG INTERACTIONS:** None. *In vitro*, enfuvirtide did not inhibit or induce the metabolism of CYP3A4, CYP2D6, CYP1A2, CYP2C19 or CYP2E1 substrates. Does not interact with SQV/r, RTV, or rifampin [Boyd, et al. 10th CROI 2003, Abstract 541].

### ADVERSE DRUG REACTIONS (ADRS)

- **Common ADRs:** Local site reaction (grade 3 or 4) including pain (9%), erythema (32%), pruritus (4%), induration (57%), and nodules or cysts (26%), with 3% requiring discontinuation. Injection site reactions can be managed by rotating sites and massaging the area. A small case series involving 7 HIV-infected patients with local site reactions who underwent an excisional biopsy of the lesion, showed an inflammatory infiltrate consistent with drug hypersensitivity [Ball, et al. 10th CROI 2003, Abstract 714].
- **Occasional ADRs:** Bacterial pneumonia (event rate per 100 patients-years in trials was 4.68 in the treatment arm vs 0.61 in controls)
- **Rare ADRs:** Worsening abacavir hypersensitivity, systemic hypersensitivity reaction, glomerulonephritis, thrombocytopenia, neutropenia, eosinophilia, fever, hyperglycemia, Guillain-Barré syndrome, sixth nerve palsy, elevation in amylase and lipase (note that for these rare ADRs, a causal relationship has not been established).

**PREGNANCY/BREASTFEEDING RISKS:** Category B. Not teratogenic in animal studies. No human data. Breastfeeding not recommended.

**CLINICAL TRIALS:** T-20-301 and T-20-302 (a.k.a. TORO 1–North America and Brazil, and TORO 2–Europe and Australia): Pooled data presented to the FDA are from two randomized, controlled, open-label studies involving 995 treatment-experienced HIV-infected patients. Efavirtide plus an individualized background regimen was superior to an individualized background regimen only. Patients had a baseline viral load of 5.2 log<sub>10</sub> c/mL, a mean of 12 prior antiretroviral agents, and 80% to 90% had ≥5 resistance mutations to NRTIs, NNRTIs, or PIs. The viral load change from baseline to week 24 was -1.52 log<sub>10</sub> c/mL for patients in the enfuvirtide plus background regimen arm compared to -0.73 log<sub>10</sub> c/mL for patients receiving only the background regimen (P<0.0001). As expected, patients with two or more active antiretrovirals, based on history and genotype, in their background regimen were more likely to achieve a viral load <400 c/mL [Henry, et al. 14th Int Conf AIDS 2002, July 7-12:14, Abstract LbOr19B; Clotet, et al. 14th Int Conf AIDS 2002 Jul 7-12:14, Abstract LbOr19A].

**COMMENTS:** Efavirtide offers clinicians an effective new antiretroviral class for the management of treatment-experienced patients. A clear advantage of enfuvirtide is the lack of cross-resistance with currently available antiretrovirals. However, as with other antiretrovirals and as seen in clinical trials (TORO 1 and TORO 2), therapy for treatment-experienced patients with enfuvirtide is only as good as the background regimen with which it is combined. Continued use of enfuvirtide in the face of virologic failure appears to result in mutation that confer resistance with T-1249 (a future fusion inhibitor in the pipeline) [Miralles, et al. CROI 2003, Abstract 14LB]. Due to its high cost and expected shortages, national committees are currently working on guidelines on the proper use of enfuvirtide.

**PACKAGE INSERT:** <http://www.rocheusa.com/products/fuzeon/pi.pdf>



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