

Primary Care of Veterans with HIV

Office of Clinical Public Health Programs
for the Public Health Strategic Health Care Group
Office of Public Health and Environmental Hazards
Veterans Health Administration
U.S. Department of Veterans Affairs

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IMPORTANT NOTICE

The editors of this manual are committed to providing accurate information on HIV-related care. However, please be aware that therapy options and protocols continue to change. Readers are invited to check for updates to drug information at Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>) and to treatment guidelines at AIDS Info (<http://aidsinfo.nih.gov/>).

We hope that you will send feedback and suggestions for future editions to: publichealth@va.gov.

Table of Contents

Contributors	v
Introduction	ix
Abbreviations	xii
Behavior and Prevention	
Alcohol Misuse	3
Cancer Screening.....	17
Immunizations.....	37
Prevention for Positives.....	39
Smoking Cessation.....	53
Substance Use.....	69
Organ Systems and Metabolic	
Anal Dysplasia.....	83
Androgen Deficiency.....	89
Asthma	97
Chronic Obstructive Pulmonary Disease (COPD).....	107
Dermatologic Conditions	115
Diabetes	127
Dyslipidemia.....	143
Gastroesophageal Reflux Disease (GERD).....	155
Hypertension	171
Liver Disease and Cirrhosis.....	185
Osteoarthritis.....	203
Renal Disease.....	211
Urology.....	227
Women’s Health	
Women’s Health.....	249
Neurology, Psychiatry, and Pain	
Depression	271
Low Back Pain.....	285
Peripheral Neuropathy	295
Drug Tables	
Common Medications: ARV Interactions.....	307
Food and Supplements: ARV Interactions.....	313
Lipid-Lowering Medications: ARV Interactions.....	315
Pain Medications: Dosage and Indications.....	321
Psychoactive Medications: ARV Interactions.....	327
Index	331

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Introduction

In many ways, veterans with HIV infection represent the future wave of the HIV epidemic. Compared with the overall HIV-infected population in the United States, veterans with HIV are older, more likely to be members of minority groups, and more likely to have a history of substance use.¹ Thus, it is not surprising that they are experiencing an increasing burden of medical and psychiatric comorbid disease.² Indeed, some data suggest that residual racial disparities in survival of individuals living with HIV may be explained in part by a greater burden of comorbid illness.³

Depending upon the study cited, approximately 60% of the deaths occurring among individuals with HIV infection are now attributed to “non-AIDS” causes.⁴⁻⁶ That does not mean those conditions are unassociated with HIV disease or its treatment. Many of the most common and serious comorbid conditions, including liver fibrosis/cirrhosis, anemia, renal insufficiency or failure, selected cancers, thrombosis, intracranial hemorrhage, and obstructive lung disease, are more likely to occur among HIV-infected individuals than among uninfected, demographically similar controls.⁷⁻¹⁰ Among persons with HIV infection, these conditions are more likely to be found in those with advanced disease. Further, the liver, renal, and bone marrow toxicities associated with antiretroviral treatment are well known and more likely to occur among persons with preexisting organ injury.¹¹ It must be recognized that HIV infection has become a complex, chronic disease, one for which there are likely multiple etiologies of any problem. Although this disease is substantially improved by antiretroviral treatment, some individuals experience substantial toxicities from treatment.^{11,12} As individuals age with HIV infection, organ injury associated with HIV infection, aging-related comorbid illnesses, and substance use and abuse likely will lead to even more “non-AIDS” mortality.

We must learn to prioritize and coordinate screening and treatment for important comorbid conditions while maintaining excellence in the care of HIV infection. Although most VA HIV providers consider themselves primary care providers for their patients with HIV infection, their degree of comfort with many of the staples of primary care screening and treatment is not as high as it is among general health care providers.¹³ This manual offers a practical approach to addressing many of these issues. Further, it attempts to appropriately tailor recommendations to the special issues facing patients who are receiving treatment for HIV infection.

Combination antiretroviral therapy has revolutionized the care of HIV infection. Randomized trial data now support continuous antiretroviral management of HIV infection, even among patients with comorbid disease.¹² Earlier data have demonstrated that many “non-AIDS” conditions improve with effective antiretroviral therapy.^{14,15} Clearly, it remains paramount to get patients started on an effective regimen and ensure that they are acceptably adherent. Yet, there are patients who will require careful attention to alcohol and drug use and depressive symptoms before they can achieve acceptable adherence.

Once adherent to an effective regimen, patients may have substantial comorbidities that require targeted screening and treatment. The approach to these conditions must be guided by the costs and benefits in our population of patients. Screening and treatment that require a life expectancy beyond 10 years, such as colon cancer screening, should be undertaken only for patients who are deemed likely to live that long. Otherwise, we will be exposing our patients to immediate potential harms (eg, risk of perforation from colonoscopy and the pain and discomfort of the preparation and the procedure) without the likelihood of future benefit.¹⁶ We also will need to think carefully about conditions for which our patients are at particularly high risk, including hepatitis C infection and alcohol and tobacco use, and target these accordingly. Finally, as more data become available, we need to consider how mechanisms of common comorbid diseases may differ among persons with HIV infection and determine the implications for management.

Thus, it is with great pleasure that I have written the introduction to what I hope will be the first of many editions of this manual, which is the brainchild of Dr. David Ross, the HIV Technical Advisory Group, and the Public Health Strategic Health Care Group. The manual, and this introduction, are dedicated to the hard work, commitment, and good will of the excellent providers who are taking care of our veterans with HIV infection.

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Abbreviations for Antiretroviral Drugs and Dosing Instructions Commonly Used in This Manual

DOSING TERMINOLOGY

BID = twice daily
IM = intramuscular
IV = intravenous
PO = orally
PRN = as needed
Q2H, Q4H, etc = every 2 hours,
every 4 hours, etc
QAM = every morning
QD = once daily
QH = every hour
QHS = every night at bedtime
QID = 4 times per day
QOD = every other day
TID = 3 times per day
TIW = 3 times per week

ANTIRETROVIRAL TERMINOLOGY

ART = antiretroviral therapy
ARV = antiretroviral
FI = fusion inhibitor
NNRTI = nonnucleoside
reverse transcriptase inhibitor
NRTI = nucleoside (or nucleotide)
reverse transcriptase inhibitor
PI = protease inhibitor

ANTIRETROVIRAL DRUGS

3TC = lamivudine
ABC = abacavir
APV = amprenavir
ATV = atazanavir
d4T = stavudine
ddC = zalcitabine
ddI = didanosine
DLV = delavirdine
DRV = darunavir
EFV = efavirenz
ENF = enfuvirtide
ETR = etravirine
FPV = fosamprenavir
FTC = emtricitabine
IDV = indinavir
LPV/r = lopinavir/ritonavir
MVC = maraviroc
NFV = nelfinavir
NVP = nevirapine
RAL = raltegravir
RTV = ritonavir
/r = ritonavir, low dose
SQV = saquinavir
TDF = tenofovir
TPV = tipranavir
ZDV = zidovudine

Behavior and Prevention

Alcohol Misuse

KEY POINTS

- Alcohol misuse is common among HIV-infected patients.
- It is the third leading preventable cause of death in the United States.
- Screening, followed by brief counseling interventions or treatment, can decrease drinking and improve health outcomes.
- At the initial visit and at least annually thereafter, all patients should be screened for alcohol misuse with the AUDIT-C questionnaire.
- Evaluate and treat at-risk and disordered alcohol drinkers with the 4 A's: Ask, Assess, Advise, and Assist.
- Consider referrals to Alcoholics Anonymous, cognitive-behavioral therapy, addiction specialists, and detoxification programs.
- Consider giving the pharmacologic abstinence adjunct naltrexone at 100 mg QD for 3-4 months to assist with continued abstinence. Monitor LFTs closely.
- Evaluate and treat comorbid psychiatric and substance use disorders.



BACKGROUND

Definitions

Alcohol misuse refers to the spectrum from risky drinking to alcohol dependence.

Risky drinking refers to drinking beyond **recommended drinking limits** (see below).

Alcohol abuse and **alcohol dependence** (also called “**alcohol use disorders**”) refer to diagnoses based on problems patients experience as a result of drinking, and are defined by the DSM-IV-TR. Both abuse and dependence are

Veterans with HIV*

Alcohol use disorder: 33%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to this condition

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

maladaptive patterns of alcohol use that lead to clinically significant impairment or distress.

Alcohol abuse is a maladaptive pattern of use associated with 1 or more of the following:

- Failure to fulfill work, school, or social obligations
- Recurrent alcohol use in physically hazardous situations
- Recurrent legal problems related to alcohol use
- Continued alcohol use despite alcohol-related social or interpersonal problems

Alcohol dependence is defined as a maladaptive pattern of use associated with 3 or more of the following:

- Tolerance
- Withdrawal
- Alcohol taken in larger quantity than intended
- Persistent desire to cut down or control use
- Time is spent obtaining, using, or recovering from alcohol
- Social, occupational, or recreational tasks are sacrificed
- Alcohol use continues despite physical and psychological problems

Recommended drinking limits:

Based on the accumulated epidemiological evidence, individuals who drink beyond the following levels are at increased risk of adverse consequences of drinking (National Institute for Alcohol Abuse and Alcoholism [NIAAA]):

- An average of 2 drinks daily (14 drinks per week) for younger men; an average of 1 drink daily (7 drinks per week) for women or older adults (≥65 years)
- A maximum of 4 drinks on any occasion for men; a maximum of 3 drinks on any occasion for women or older adults

Definition of a standard drink:

12 g of alcohol

Roughly equivalent to:

- 12 oz beer
- 5 oz wine
- 1.5 oz distilled spirits (80 proof)

Note that safe drinking limits may be substantially lower for some patients, depending on factors such as comorbidities (eg, liver disease), pregnancy, and interacting medications.

A great number of people drink more than the recommended limits but do not meet criteria for alcohol dependence. These nondependent drinkers account for the majority of alcohol-related morbidity and mortality in the general population. All patients who misuse alcohol should receive focused medical attention and intervention.

Epidemiology

- 35-40% of HIV-infected patients in primary care settings have documented diagnoses of alcohol use disorder; many more probably drink above recommended levels in ways that pose health risks.
- Alcohol misuse causes substantial morbidity and mortality. Medical conditions associated with alcohol misuse include alcohol withdrawal syndrome, hepatitis, cirrhosis, pancreatitis, thiamine deficiency, neuropathy, cardiomyopathy, hypertension, depression, and cancers of the oropharynx, larynx, and esophagus.
- Excessive alcohol consumption is the third leading preventable cause of death in the United States.
- Alcohol use is associated with:
 - 40% of all traffic fatalities (2000)
 - 20-37% of emergency department trauma cases (1990)
 - 66% of all drownings
 - 50% of all deaths from cirrhosis
- Alcohol use compounds the liver damage associated with hepatitis C and hepatitis B, and accelerates progression to cirrhosis.
- Concomitant use of alcohol and hepatotoxic drugs (including some ARVs) may increase the risk of early and severe liver damage.
- The risk of pancreatitis caused by ddl is higher among patients who use alcohol chronically.



EVALUATION



SCREENING

Alcohol Misuse Screening

At the initial visit and at least annually thereafter: Screen all patients for alcohol misuse. Ask drinkers the AUDIT-C questions.

The VHA recommends universal screening to identify patients who misuse alcohol. Screening followed by brief counseling interventions or treatment has been shown to decrease drinking and improve health outcomes.

- Ask all patients whether they currently drink alcohol. Ask about past alcohol use, and about family history of alcohol-related problems.
- For drinkers, use the AUDIT-C screening questionnaire (see below) to assess for risky drinking (see above for recommended drinking limits).
- For drinkers, ask more specific questions to determine whether they fulfill criteria for alcohol abuse or dependence (see DSM-IV-TR criteria, above) and whether they have signs or symptoms of liver disease, psychiatric comorbidities, behavioral complications such as violent episodes, or other substance abuse.
- Goals for evaluation:
 - Determine whether the patient is drinking above safe levels.
 - Determine whether the patient has loss of control over the use of alcohol.
 - Determine whether tolerance, dependence, or abuse is present.
 - Determine whether adverse consequences of excessive drinking have occurred.

The AUDIT-C: Alcohol Use Disorder Identification Test – Consumption Questions

The AUDIT-C is a validated 3-question screening tool for alcohol misuse and alcohol use disorders (including alcohol abuse or dependence). It is the required screening tool for alcohol misuse in the VHA.

It can identify patients with alcohol misuse who would benefit from counseling to decrease their drinking and those who use alcohol and need referral to treatment services.

1. **How often have you had a drink containing alcohol in the last year? Consider a “drink” to be a 12 oz can or bottle of beer, a glass of wine, a wine cooler, or 1 cocktail or shot of hard liquor (such as scotch, gin, or vodka).**

Never (0 points); monthly or less (1); 2-4 times/month (2); 2-3 times/week (3); ≥ 4 times/week (4)

2. **How many drinks containing alcohol did you have on a typical day when you were drinking in the last year?**

I do not drink (0 points); 1-2 drinks (0); 3-4 drinks (1); 5-6 drinks (2); 7-9 drinks (3); ≥ 10 drinks (4)

3. **How often in the last year have you had 6 or more drinks on one occasion?**

Never (0 points); less than once a month (1); monthly (2); weekly (3); daily or almost daily (4)

Scoring: AUDIT-C scores range from 0 (no alcohol use) to 12. Higher scores indicate higher likelihood that the patient's health and safety are at risk. AUDIT-C scores of ≥ 4 for men and ≥ 3 for women suggest alcohol misuse, whereas scores of ≥ 5 require brief follow-up alcohol counseling. An AUDIT-C score of ≥ 8 indicates a high probability of current dependence; a score of ≥ 5 for a patient with a history of alcohol treatment indicates high risk of current dependence.

Rx MANAGEMENT

Brief counseling with specialty referral as indicated can be effective in reducing hazardous drinking. Patients with alcohol use disorders may require comprehensive treatment programs that include the services of medical providers, psychiatrists to assist with comorbid psychiatric conditions, social workers, housing counselors, case managers, and substance abuse counselors.

- **Short-term goals:** treating alcohol withdrawal as needed; encouraging abstinence and attendance at Alcoholics Anonymous or other counseling programs for the first 3 months; engaging family and community support; ensuring adequate resources for housing, food, and income
- **Long-term goals:** sustained abstinence from alcohol use; recovery of self-esteem, health, and social functioning

Simple, office-based interventions can be made using the 4-A approach: **Ask, Assess, Advise, and Assist.**

- **Ask** about alcohol use, using AUDIT-C (see above)
- **Assess** for alcohol use disorders (see below)
- **Advise** all patients, even those with no reported heavy drinking, to stay within healthy drinking limits, keeping comorbidities in mind. Particularly for those with liver disease, there is no known “safe” level of alcohol consumption, and alcohol may be particularly dangerous for patients with HIV/HCV coinfection.
- **Assist** patients with brief interventions, pharmacotherapy, and referral for treatment services
 - Brief (<5 min) alcohol intervention (BAI) can be extremely effective for alcohol misuse. Useful information on BAI can be found at <http://www.hepatitis.va.gov/vahep?page=prtop03-wp-01-res>. Key components:
 - Aim to reach agreement on a drinking goal.
 - Let the patient lead the discussion; for example, ask patients (rather than tell them) how they think alcohol use affects their health.
 - Aim for a nonjudgmental atmosphere, using open-end questions and eye contact.
 - Give choices in the discussion rather than force topics on the patient. For example, ask about stressors and how alcohol use fits in with these.

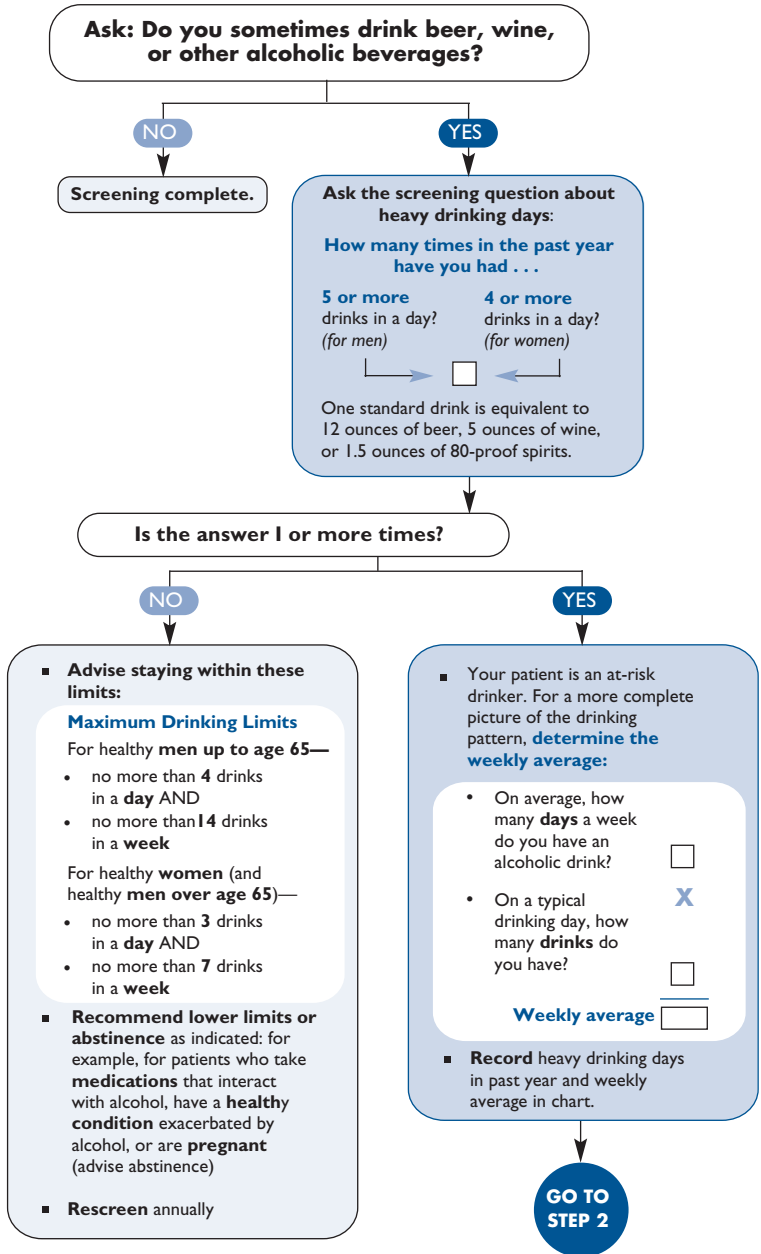
- Remember that patients vary in their degree of readiness to change.
- Patients need to understand the importance of change, to have a sense of confidence about their ability to change, and to have a support system.
- Avoid lecturing or cheerleading; if it happens, take a step back and ask an open-end question such as “What do you think of this?”
- Referral to Alcoholics Anonymous is helpful to many patients; AA meetings are held worldwide, and information is available at <http://www.aa.org>.
- Patients at risk of withdrawal should be referred to detoxification programs; those in withdrawal should be referred to an emergency department.

■ **Reinforce and reevaluate intervention messages at each visit.**

The following is an algorithmic representation of screening and intervention using this approach from the NIAAA.

HOW TO SCREEN FOR HEAVY DRINKING

STEP 1 Ask About Alcohol Use



National Institute on Alcohol Abuse and Alcoholism. A Pocket Guide for Alcohol Screening and Brief Intervention. Rockville, MD: NIAAA; 2005

HOW TO ASSESS FOR ALCOHOL USE DISORDERS

STEP 2 Assess For Alcohol Use Disorders

Next, determine if there is a *maladaptive pattern of alcohol use*, causing *clinically significant impairment or distress*.

Determine whether, in the past 12 months, your patient's drinking has **repeatedly** caused or contributed to

- risk of bodily harm** (drinking and driving, operating machinery, swimming)
- relationship trouble** (family or friends)
- role failure** (interference with home, work, or school obligations)
- run-ins** with the law (arrests or other legal problems)

If yes to **one or more** → your patient has **alcohol abuse**.

In either case, proceed to assess for dependence symptoms.

Determine whether, in the past 12 months, your patient has

- not been able to cut down or stop** (repeated failed attempts)
- not been able to stick to drinking limits** (repeatedly gone over them)
- shown tolerance** (needed to drink a lot more to get the same effect)
- shown signs of withdrawal** (tremors, sweating, nausea, or insomnia when trying to quit or cut down)
- kept drinking despite problems** (recurrent physical or psychological problems)
- spent a lot of time drinking** (or anticipating or recovering from drinking)
- spent less time on other matters** (activities that had been important or pleasurable)

If yes to **three or more** → your patient has **alcohol dependence**.

Does patient meet criteria for abuse or dependence?

NO

GO TO
STEPS 3 & 4
for
AT-RISK
DRINKING

YES

GO TO
STEPS 3 & 4
for
ALCOHOL USE
DISORDERS

HOW TO CONDUCT A BRIEF INTERVENTION

FOR AT-RISK DRINKING (no abuse or dependence)

STEP 3 Advise and Assist

- **State your conclusion and recommendation clearly** and relate them to medical concerns or findings.
- **Gauge readiness to change drinking habits.**

Is patient ready to commit to change?

NO

- **Restate your concern.**
- **Encourage reflection.**
- **Address barriers to change.**
- **Reaffirm your willingness to help.**

YES

- **Help set a goal.**
- **Agree on a plan.**
- **Provide educational materials.** (See <http://www.niaaa.nih.gov/guide>.)

STEP 4 At Followup: Continue Support

REMINDER: Document alcohol use and review goals at each visit.

Was patient able to meet and sustain drinking goal?

NO

- **Acknowledge that change is difficult.**
- **Support positive change** and address barriers.
- **Renegotiate goal and plan;** consider a trial of abstinence.
- **Consider engaging significant others.**
- **Reassess diagnosis** if patient is unable to either cut down or abstain.

YES

- **Reinforce and support continued adherence** to recommendations.
- **Renegotiate drinking goals** as indicated (e.g., if the medical condition changes or if an abstaining patient wishes to resume drinking).
- **Encourage to return** if unable to maintain adherence.
- **Rescreen** at least annually.

HOW TO CONDUCT A BRIEF INTERVENTION

FOR ALCOHOL USE DISORDERS (abuse or dependence)

STEP 3 Advise and Assist

- **State your conclusion and recommendation clearly** and relate them to medical concerns or findings.
- **Negotiate a drinking goal.**
- **Consider evaluation by an addiction specialist.**
- **Consider recommending a mutual help group.**
- For patients who have dependence, **consider**
 - the need for **medically managed withdrawal** (detoxification) and treat accordingly.
 - prescribing a **medication** for alcohol dependence for patients who endorse abstinence as a goal.
- **Arrange followup appointments**, including medication management support if needed.

STEP 4 At Followup: Continue Support

REMINDER: Document alcohol use and review goals at each visit.

Was patient able to meet and sustain drinking goal?

NO

- **Acknowledge that change is difficult.**
- **Support efforts** to cut down or abstain.
- **Relate drinking to ongoing problems** as appropriate.
- **Consider** (if not yet done):
 - consulting with an **addiction specialist**.
 - recommending a **mutual help group**.
 - engaging **significant others**.
 - prescribing a **medication** for alcohol-dependent patients who endorse abstinence as a goal.
- **Address coexisting disorders**—medical and psychiatric—as needed.

YES

- **Reinforce and support continued adherence.**
- **Coordinate care** with specialists as appropriate.
- **Maintain medications** for alcohol dependence for at least 3 months and as clinically indicated thereafter.
- **Treat coexisting nicotine dependence.**
- **Address coexisting disorders**—medical and psychiatric—as needed.



WHEN TO REFER

Most patients with moderate or severe alcohol misuse should be referred to specialized alcohol or substance use disorder treatment services. Patients with comorbid conditions that are adversely affected by alcohol, such as HCV infection or depression, may need treatment even if they do not meet typical criteria for alcohol use disorders.

Patients in withdrawal (tremors, sweats, anxiety, disorientation, or visual, auditory, or tactile hallucinations) should be referred to an emergency department for immediate evaluation and treatment, and should be referred to a detoxification program if available.

Pharmacotherapy for Relapse Prevention

Although pharmacotherapy may help to prevent relapse, multimodal treatment that includes medical therapy with or without behavioral therapy may be more effective.

Note: Caution should be used, as no trials have demonstrated the safety of these medications in HIV-infected patients who are receiving ARVs. Although it is expected that the efficacy of these medications will be similar in patients with and without HIV infection, increased monitoring for adverse effects should be exercised until more data are available.

A randomized controlled trial involving HIV-uninfected patients compared various combinations of medical management, medication, and behavioral therapy for treatment of alcohol dependence in recently abstinent patients. The study showed that:

- All treatment groups had substantial increases in the percentage of days abstinent from alcohol.
 - The highest percentage of days abstinent (77-80%) was seen in 3 treatment groups: patients who received naltrexone (100 mg QD) + medical management (9 sessions with a health care professional), naltrexone + medical management + a combined behavioral intervention (CBI) (20 sessions), or medical management + CBI + placebo pills.
 - Patients who received CBI alone (no medical management or pills [whether placebo or naltrexone]) had the lowest abstinence rates.
 - Acamprosate was no more effective than placebo.
 - Treatment effects largely dissipated after 1 year; thus ongoing monitoring is important, and treatment of relapse may be necessary.

Medication	Standard Dosage	Comments
Naltrexone (oral)	50-100 mg QD for ≥ 3 months <ul style="list-style-type: none"> • Start upon cessation of alcohol use • Optimal duration of therapy not known; most study subjects treated for 3-4 months; treatment effects tend to wane after therapy is stopped 	<ul style="list-style-type: none"> • Pure opioid receptor antagonist • Avoid in patients who use opioids (precipitates withdrawal symptoms) • Avoid in patients with liver failure • Possible adverse effects: nausea, vomiting, headache, insomnia, hepatotoxicity • Check LFTs before and after treatment
Naltrexone (IM)	190 mg IM monthly for ≥ 3 months <ul style="list-style-type: none"> • Start upon or just after cessation of alcohol use; greater benefit may be seen in patients who achieve some duration of alcohol abstinence (eg, 2-4 days) before the initial injection of naltrexone • Useful for patients with adherence issues • See PBM Criteria for Use at http://www.pbm.va.gov/CriteriaForUse.aspx 	<ul style="list-style-type: none"> • Pure opioid receptor antagonist • Possible adverse effects: nausea, vomiting, headache, hepatotoxicity, injection site reactions • Avoid in patients who use opioids (precipitates withdrawal symptoms) • Avoid in patients with liver failure • 380 mg dose has been standard but does not confer more abstinence advantage and causes more side effects
Disulfiram (Antabuse)	250 mg QD as adjunct during outpatient treatment period <ul style="list-style-type: none"> • Start ≥ 12 hours after last alcohol consumption 	<ul style="list-style-type: none"> • Disulfiram acts as an acetaldehyde dehydrogenase inhibitor • Concurrent alcohol consumption increases plasma acetaldehyde concentrations 5-10 times, causing flushing, tachycardia, hypotension, nausea, vomiting, vertigo, and anxiety within 15 minutes • Other possible adverse effects include delirium, hepatotoxicity (monitor LFTs before treatment and every 3 months during treatment), neuropathy

		<ul style="list-style-type: none"> • Do not administer to patients who take ARV syrups or other medications that contain alcohol or propylene glycol (eg, RTV, LPV/r, and FPV liquid formulations) • Patients must avoid OTC medications containing alcohol (eg, cough syrup), as well as sauces, vinegars, and foods containing alcohol • Multiple other drug interactions, including with phenytoin, rifampin, isoniazid, and warfarin
Acamprosate	<p>666 mg TID for 3 months</p> <ul style="list-style-type: none"> • See PBM Criteria for Use at http://www.pbm.va.gov/criteria/AcamprosateCriteria.pdf • Should only be used in patients with at least 4 days of abstinence and only mild withdrawal symptoms who are in a comprehensive management program including appropriate behavioral interventions • Start as soon as possible after abstinence is established and continue through relapses • Adjust dosage for renal failure: CrCl 30-50: 333 mg TID CrCl <30: contraindicated 	<ul style="list-style-type: none"> • GABA analogue; decreases excitatory glutamergic neurotransmission during withdrawal • Patients should be closely monitored for depression or suicidal thinking • Other possible adverse effects: diarrhea, somnolence • COMBINE study did not show that acamprosate was more effective than placebo



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Cancer Screening

KEY POINTS

- General recommendations from the United States Preventive Services Task Force (USPSTF) regarding cancer screening include the following:
 - Men and women at average risk should be screened for **colorectal carcinoma** (CRC) starting at age 50, using fecal occult blood testing (FOBT), flexible sigmoidoscopy with or without FOBT, colonoscopy, or double-contrast barium enema. Office-based digital rectal examination (DRE) plus FOBT should not be used.
 - Women aged 40 and older at average risk should be screened every 1-2 years for **breast cancer** using mammography.
 - Sexually active women should be screened every 3 years for **cervical cancer** using the Papanicolaou (“Pap”) smear.
 - There is not adequate evidence to recommend for or against screening men for **prostate cancer**.
- These recommendations may be applied to HIV-infected patients with CD4 counts of >350 cells/μL or completely suppressed HIV RNA. For patients with lower CD4 counts, screening should be discussed in the context of the patient’s prognosis, preferences, and health goals.



BACKGROUND

- HIV-infected persons are at higher risk than HIV-uninfected persons of developing the following cancers:

Anal squamous cell carcinoma	Non-small-cell lung carcinoma
Cervical carcinoma	Melanoma
Colorectal carcinoma	Non-Hodgkin lymphoma
Hepatocellular carcinoma	Oropharyngeal cancer
Hodgkin lymphoma	Vaginal cancer
Kaposi sarcoma	

In addition, HIV-infected patients with chronic HBV or HCV infection may be at much higher risk of developing hepatocellular carcinoma (see **Liver Disease**, p. 185).

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- Of the cancers on this list, the USPSTF has issued screening recommendations regarding cervical and colorectal cancers, which are presented in this chapter. In addition, this chapter includes USPSTF recommendations on screening for breast cancer and prostate cancer. Additional screening recommendations can be found in other chapters (see **Anal Dysplasia**, p. 83; **Liver Disease**, p. 185; **GERD**, p. 155, and **Women's Health**, p. 249).
- Because most cancer screening requires a 5- to 10-year life expectancy to show a favorable cost/benefit ratio, it is reasonable to screen HIV-infected persons for cancer if they have a CD4 count of >350 cells/ μ L or a suppressed HIV viral load. Screening patients with more advanced HIV disease is unlikely on average to extend life expectancy or be cost-effective, and should be discussed with patients in the context of their prognosis, preferences, and health goals. However, screening for cervical carcinoma is recommended for all HIV-infected women, regardless of CD4 count.
- For cancers in which there is a hereditary component of risk, the following definitions of degree of relatedness are used:
 - 1st degree relative: a parent, sibling, or child
 - 2nd degree relative: a grandparent, uncle, or aunt
 - 3rd degree relative: a great-grandparent or cousin

Colorectal Cancer

Summary

Most CRC arises from adenomatous polyps, which grow relatively slowly; polyps and colorectal tumors can be detected with varying degrees of sensitivity by any one of several screening techniques, including FOBT, endoscopic visualization and biopsy (flexible sigmoidoscopy and colonoscopy), and barium enema. The incidence of CRC increases with age. **The USPSTF and the VA/DoD recommend that persons at average risk be screened for CRC starting at age 50.** In persons at above-average risk, screening should start at an earlier age. The choice of screening procedure (see **Table 1**) depends on patient preferences and availability of procedures at particular facilities.

HIV-infected persons are at increased risk of CRC compared with HIV-uninfected persons. A low nadir CD4 count is associated with an increased risk, whereas ART is associated with a decreased risk.

Epidemiology/Pathogenesis

- Most colon cancers develop from adenomatous polyps; polyps >1 cm in size carry a higher risk than smaller polyps of development of CRC.
- Prevalence of adenomatous polyps increases with age.
- Average lifetime risk of developing colon cancer in the United States is 6%.

- The following confer a higher-than-average risk of developing CRC:
 - History of CRC in a 1st degree relative
 - Family history of large polyps before age 60
 - Ulcerative colitis or Crohn disease
 - Polyps >1 cm in size
- Patients with specific genetic predisposition to CRC such as familial adenomatous polyposis (FAP) or hereditary nonpolyposis colon cancer (HNCC) are at extremely high risk of developing CRC.

Screening Methods

- **FOBT:** Detection of blood in a stool specimen, usually done by smearing a stool specimen onto absorbent paper impregnated with guaiac, followed by application of hydrogen peroxide; any blood present in the specimen will catalyze the oxidation of guaiac by peroxide, producing a rapid color reaction. Samples blood loss from any point in the GI tract. Specimens can be prepared at home using commercial test cards.
- **Flexible sigmoidoscopy:** Examination of the colon from the rectum to the splenic flexure, a region in which the majority of malignant lesions arise, with a 60 cm flexible fiberoptic endoscope with biopsy capability.
- **Colonoscopy:** Examination of the entire colon with a 100-160 cm flexible fiberoptic endoscope with biopsy capability.
- Efficacy of screening methods is shown in **Table 1**.

Recommendations for CRC Screening

- 80% of CRCs occur in people at average risk.
- Multiple recommended screening methods for average-risk patients (see **Table 1**).
- Screening recommendations for higher-risk patients are shown in **Table 2**.
- Screening recommendations for persons at very high risk (individuals with, or relatives of persons with, familial colon cancer syndromes such as FAP or HNCC) are beyond the scope of this chapter; consultation with GI or Oncology is recommended.
- FOBT on specimens obtained by DRE is **not** recommended.
 - DRE is not sensitive and ↓ FOBT specificity
 - If performed, a positive result should be followed up with colonoscopy
- Fecal immunochemical test (FIT) and stool DNA test (sDNA) have not been recommended by the VHA.
- Virtual colonoscopy is under investigation but is not yet recommended.

Table I. Recommended Screening Methods for Persons at Average Risk of Developing CRC

Screening Method Recommended by USPSTF	Accuracy and Effectiveness	Comments/ Limitations/Risks
Home FOBT every year	<ul style="list-style-type: none"> • ↓ mortality 15-33%, depending on frequency of screening • Positive predictive value (percentage of patients with positive test result who have cancer or large polyp): <ul style="list-style-type: none"> • Rehydrated specimens: 6-8% • Unrehydrated specimens: 20-40% • Rehydration before adding developer: <ul style="list-style-type: none"> • ↑ sensitivity from 40% to >50% • ↓ specificity from 98% to 90% • Leads to more colonoscopies • Annual screening found 49% of cancers; 38% of patients tested required colonoscopy • Screening every 2 years found 39% of cancers; 28% of patients tested required colonoscopy 	<ul style="list-style-type: none"> • Patient submits three 2-window cards, 1 card each from 3 consecutive stools collected at home. • Do not use DRE to collect specimens. • The American Gastrointestinal Association (AGA) recommends against rehydrating specimens. • If result is positive in any card window, obtain colonoscopy. • FOBT itself is extremely low risk, but leads to many colonoscopies being performed, with associated risks of bleeding and perforation.
Flexible sigmoidoscopy every 5 years	<ul style="list-style-type: none"> • ↓ mortality 59% for cancers within reach of sigmoidoscope • Sensitivity: 70-80% • Specificity difficult to define 	<ul style="list-style-type: none"> • Complete or partial bowel prep required. • Misses lesions proximal to the splenic flexure. • Proximal lesions more common in women than men. • Estimated to find 80% of patients with abnormal findings, as distal abnormalities will prompt examination of entire colon with colonoscopy.

		<ul style="list-style-type: none"> • In one study, sigmoidoscopy alone would have missed 65% of women with advanced lesions detected by colonoscopy. • In another study, 52% of patients with advanced proximal lesions (by colonoscopy) had no distal lesions. • Presence of an adenoma generally necessitates full colonoscopy. Controversy exists regarding presence of small tubular adenomas, though many providers would perform colonoscopy. • Complication rate: <ul style="list-style-type: none"> • Perforation: <0.01% • Bleeding: 2.5-5.5%
FOBT + flexible sigmoidoscopy every 5 years	<ul style="list-style-type: none"> • In one study, rigid sigmoidoscopy + 3-card FOBT (hydrated) detected 76% of advanced lesions vs 70% for sigmoidoscopy alone; 24% of advanced lesions were missed; incidence of death from cancer decreased by approximately 50% in sigmoidoscopy + FOBT group vs sigmoidoscopy alone • Studies of adding flexible sigmoidoscopy to FOBT show doubling of diagnostic yield 	<ul style="list-style-type: none"> • Positive FOBT result necessitates full colonoscopy, so perform FOBT before sigmoidoscopy. • Complete or partial bowel prep required before flexible sigmoidoscopy.
Colonoscopy every 10 years	<ul style="list-style-type: none"> • ↓ mortality >50% • Sensitivity: <ul style="list-style-type: none"> • 90% for polyps >1 cm • 75% for polyps <1 cm 	<ul style="list-style-type: none"> • Complete bowel prep required. • Colonoscopy can visualize entire colon. Suspicious lesions can be removed for biopsy and as treatment.

	<ul style="list-style-type: none"> • Colonoscopy has been the reference standard against which FOBT and sigmoidoscopy have been studied 	<ul style="list-style-type: none"> • Greater yield of colonoscopy (most sensitive test for polyps) must be weighed against risks of perforation, bleeding, and conscious sedation, as well as inconvenience of full colonic preparation and conscious sedation. • Risk of screening colonoscopy <ul style="list-style-type: none"> • Any major complication: 0.3% • Perforation: 0.05% • Bleeding: 0.15-0.18% • Risk of colonoscopy as therapeutic procedure is higher <ul style="list-style-type: none"> • Perforation: 0.07-0.72% • Bleeding: 0.2-2.7% • Risks of procedure are greater in persons >70 years of age, but so are benefits, as proximal lesions are more common in this population.
Double-contrast barium enema	<ul style="list-style-type: none"> • Has low sensitivity compared with colonoscopy: <ul style="list-style-type: none"> • 32% for polyps <0.5 cm • 53% for polyps 0.6-1 cm • 48% for polyps >1 cm 	<ul style="list-style-type: none"> • Complete bowel prep required. • Option for patients who refuse colonoscopy.

Table 2. Screening Recommendations for Persons at Increased Risk of CRC*

Risk Factor	Increase in Risk	Screening Recommendations
1st degree relative with CRC or AP diagnosed ≥60 years of age OR	1st degree relative: ↑ 2- to 3-fold	Screen as for person at average risk (see Table 1), but start at age 40.

Two 2nd degree relatives with CRC or AP at any age	2nd or 3rd degree relative: ↑ 1.5-fold (2- to 3-fold if >1 relative)	
1st degree relative with CRC or AP diagnosed <60 years of age OR Two 1st degree relatives with CRC or AP diagnosed at any age	1st degree relative aged ≤60: ↑ 3- to 4-fold 1st degree relative: ↑ 2- to 3-fold	Screening colonoscopy every 5 years, starting at age 40, or 10 years before age at which relative was diagnosed, whichever comes first.
2nd or 3rd degree relative(s) with CRC	↑ 1.5- to 3-fold	Screen as for person at average risk (see Table 1).
Inflammatory bowel disease (UC or CD)	↑ 2.4-fold in UC (if disease widespread) ↑ up to 5.6-fold in CD, depending on location	Colonoscopy every 1-2 years with biopsies for dysplasia. Younger age at diagnosis of CD seems to increase risk, as does distal (colon) vs proximal (ileum) disease.
Personal history of CRC		Patients with CRC should undergo high-quality perioperative colonoscopy to detect synchronous lesions. Colonoscopy should be performed 1 year after the resection (or 1 year following the colonoscopy that confirmed absence of synchronous disease). If the examination performed at 1 year is normal, then the next examination should be performed in 3 years. If that colonoscopy is normal, then the interval to the subsequent examination should be 5 years. Following the examination at 1 year, the intervals between subsequent examinations may be shortened if there is evidence of HNCC or if adenoma findings warrant earlier colonoscopy. If an obstructing tumor prevents high-quality colonoscopy at the time of resection, examination for synchronous tumors can be performed by double-contrast barium enema or CT colonography.

After low anterior resection of rectal cancer, periodic examination of the rectum may be considered to identify local recurrence. This usually is performed at 3- to 6-month intervals for the first 2 or 3 years.

* **Not including characterized familial colon cancer syndromes**

Adapted from Levin et al. See **References**.

Abbreviations: AP = adenomatous polyp; CD = Crohn disease; UC = ulcerative colitis

Reminders

CPRS reminder definition and resolution options for CRC screening may differ among VA Medical Centers, depending on local decisions and procedure availability. An example of a typical CPRS reminder for CRC screening is shown.

Reminder Resolution: COLORECTAL CANCER SCREEN

Screening for colorectal cancer can be accomplished by one of two options, fecal occult blood detection or colonoscopy. Each method satisfies this screen for different time periods—see below. Testing usually begins at age 50 in the general population. This institution has decided that for general screening, fecal occult blood detection will be the test of first choice.

A. FECAL OCCULT BLOOD TEST— satisfies reminder for one year

Most recent FOBT done:

OCCELD1: comment	11/24/1999@12:42	feces
OCCELD2: comment	11/24/1999@12:42	feces
OCCELD3: comment	11/24/1999@12:42	feces

Click here to order Fecal Occult Blood test X 3

Patient's Colorectal Cancer screening is being done by a non VA provider; the most recent FOBT was performed outside this medical center.

B. COLONOSCOPY:

C. REFUSALS:

D. SCREENING NOT MEDICALLY INDICATED DUE TO:

Clear Clinical Maint Visit Info < Back Next > Finish Cancel

<No encounter information entered>

* Indicates a Required Field

What to do with a positive result

- A positive screening result should be followed by a full colonoscopy, unless contraindicated.
- Patients with negative screening but with symptoms suggestive of CRC or polyps should be offered a full colonoscopy.

Breast Cancer

Summary

Breast cancer is the most common cancer diagnosed among women in the United States. Incidence of breast cancer increases with age, and there is evidence that mammographic screening reduces mortality due to breast cancer. Most cases of breast cancer are detected by mammography. Whereas the benefits of starting screening for women older than 50 are well established, increasing evidence points to a protective effect of starting to screen women at age 40. It is important to note that the rate of false-positive screening tests in women 40-50 years of age is high and that the benefits of screening need to be weighed against the potential for emotional distress and additional testing caused by false-positive screening results. **Nevertheless, the USPSTF and VA/DoD recommend screening women ≥ 40 years of age with mammography every 1-2 years.** Clinical breast examination (CBE) and breast self-examination (BSE) may be part of screening, depending on patient and provider preference. There is no clear evidence that HIV infection increases the risk of breast cancer or alters treatment outcomes.

Epidemiology

- Lifetime risk of invasive breast cancer in U.S. women is approximately 12.5%; breast cancer is the most common cancer among women in the United States, and the second most common cause of cancer death among women in the United States (after lung cancer).
- Women at increased risk of breast cancer are those with:
 - Family history of breast cancer in a 1st degree relative
 - Risk higher if multiple 1st degree relatives with breast cancer
 - Risk higher if affected relatives were <40 years of age when diagnosed
 - Women with a specific mutation conferring risk of breast cancer, such as BRCA1 or BRCA2
 - History of atypical hyperplasia on previous breast biopsy
 - History of first pregnancy after age 30
 - Increased estrogen exposure
 - Early menarche or late menopause
 - Hormone replacement therapy
 - Older age
 - 0.4% annual incidence at age 30-39
 - 1.5% annual incidence at age 40-49
 - 2.8% annual incidence at age 50-59
 - 3.6% annual incidence at age 60-70

- Breast cancer in women <40 years of age appears to be less common but more aggressive. Thus, screening may have less of a protective effect than it does for older women. The increased density of breast tissue in younger women also may reduce the ability of mammography to detect abnormalities.

Screening methods

- Mammography involves low-dose radiography of the breasts. It should be performed at an accredited, certified facility, with interpretation by an appropriately trained and certified radiologist.
- CBE involves physical examination of the breast by a health care provider for signs of malignancy (eg, masses, induration, discharge) or other abnormalities.
- BSE involves monthly examination of the breast by the patient for signs such as redness, dimpling, or other abnormalities.

Effectiveness of screening

- Mammography is less reliable (lower sensitivity, specificity, and positive predictive value) in younger women than in older women.
- Mammography is relatively sensitive for breast cancer, but sensitivity declines with time from mammogram:
 - 71-96% sensitivity for cancers diagnosed within 1 year of screening
 - 56-86% sensitivity for cancers diagnosed within 2 years of screening
- Specificity of one-time mammogram is 94-97%.
- Positive predictive value of one-time mammography:
 - 2-22% of women with an abnormal result will require further workup
 - 12-78% of women with an abnormal result will require biopsy
- Mammography reduces breast cancer-specific mortality as much as 32% depending on the study; metaanalysis finds a reduction in disease-specific mortality of about 15%, including among women <50 years of age.
- CBE has an estimated sensitivity of 40-69%, specificity of 86-99%, and positive predictive value of 4-50%. There is no evidence at present that CBE reduces breast cancer-specific mortality.
- BSE has an estimated sensitivity of 26-41%; its specificity has not been defined. There is no evidence at present that BSE reduces breast cancer-specific mortality.

Recommendations for breast cancer screening

- Screening mammography every 1-2 years for women 40-69 years of age.
- Providers should discuss screening with women aged 70 and older, taking into account estimated life expectancy and presence of comorbid disease.
- CBE and BSE may be incorporated into screening, according to patient and provider preference.

- VA facilities with certified mammography sites are listed at <http://vaww1.va.gov/Radiology/page.cfm?pg=3>. A listing of non-VHA certified mammography sites can be accessed at <http://vaww1.va.gov/Radiology/page.cfm?pg=108>.
- Further information on mammography is available through the VHA Mammography Office at <http://vaww1.va.gov/Radiology/page.cfm?pg=1>.

Reminders

CPRS reminder definition and resolution options for mammography may differ among VA Medical Centers, depending on local decisions. An example of a typical CPRS reminder for annual mammography is shown.

Reminder Resolution: --MAMMOGRAM 50-69

--Women between the ages of 50-69 should be screened for Breast Cancer with a mammogram every 2 years.

--Order Mammogram

--Mammogram performed elsewhere Location:

Date: * ... Results:

--Patient DECLINES Mammogram Comment:

--Mammogram NOT applicable due to Bilat Mastectomy

Comment:

=====

IF YOU HAVE IDENTIFIED THAT THIS PATIENT HAS AN INCORRECT DIAGNOSIS ON FILE. SELECT THE BOX BELOW TO SEND A CONSULT TO PBS FOR CHART CORRECTION.

=====

<---CLICK here to request correction of an incorrect diagnosis!

Clear Clinical Maint Visit Info < Back Next > Finish Cancel

CLINICAL REMINDER ACTIVITY

---MAMMOGRAM 50-69:

Mammogram request order placed.

--Mammogram performed elsewhere

Date: January 14, 2002

Health Factors: DAY INCORRECT DM DX - 14DAY INACTIVATE, DAY MAMMOGRAM DONE ELSEWHERE (Historical), DAY MAMMOGRAM N/A BILAT MASTECTOMY, DAY MAMMOGRAM REFUSED

Orders: MAMMOGRAM REQUEST, PBS DIAGNOSIS REMOVE

What to do with a positive result

- Results should be communicated to the patient as soon as possible. Generally, a lay summary will be sent to the patient by the interpreting radiologist. However, the ordering provider should ensure that results have been communicated to the patient within a reasonable time frame.
- Patients with an abnormal result should be referred to the appropriate service (Women’s Health, Gynecology, or General Surgery, depending on the facility) as soon as possible for evaluation and possible biopsy.

Cervical Cancer

Summary

Although there are no randomized controlled trials showing the effectiveness of cervical cancer screening, numerous observational studies have found an association between screening and reductions in the incidence of cervical cancer and disease-specific mortality.

HIV-infected women are at elevated risk of cervical dysplasia and cervical cancer. Cervical cancer is highly associated with type 16 and 18 human papillomavirus (HPV) infection (high-risk subtypes). HPV prevalence is higher among HIV-infected women than among HIV-uninfected women, and HIV-infected women have increased persistence of HPV and greater likelihood of infection with high-risk types of HPV. Although the time between diagnosis of carcinoma in situ (CIS) and development of invasive disease is shorter among HIV-infected women who are not on ART than among HIV-uninfected women, ART has not been shown consistently to prevent or alter the course of cervical dysplasia in HIV-infected women. Women with advanced immunosuppression (CD4 count of <200 cells/ μ L) are at higher risk of cervical abnormalities than women with CD4 counts of >200 cells/ μ L.

The USPSTF and VA/DoD recommend cervical cancer screening using Pap smear or liquid-based cytology in sexually active women with a cervix. Screening should be started at age 21 or within 3 years of starting sexual activity, whichever comes first. For HIV-uninfected women, the Pap test should be repeated every 3 years. For HIV-infected women, most authorities recommend more frequent screening, typically at the time of HIV diagnosis and again 6 months later. Women with normal cytology and CD4 counts of >200 cells/ μ L can then be screened annually, and women with CD4 counts of <200 cells/ μ L are screened every 6 months.

Epidemiology/pathogenesis

- Cervical cancer is associated with genital HPV infection; cancer is preceded by identifiable neoplastic changes (cervical intraepithelial neoplasia, or CIN) in the transformation zone of the cervix. Localized cervical cancer is highly curable (5-year survival of 92%), whereas disseminated disease is not (5-year survival of 13%). HIV-infected women progress from CIS to invasive disease faster than HIV-uninfected women. Cervical cancer is an AIDS-defining condition.
- Women at increased risk of cervical cancer include those with:
 - Immunosuppression (including HIV infection)
 - Tobacco use (smoking)
 - Increased risk of HPV infection, such as:
 - Earlier onset of sexual intercourse
 - Multiple sexual partners
 - Sexual partners who have had multiple sexual partners

Screening methods

- Pap smear: Cervical epithelial cells, collected by brush and spatula, are either smeared directly on a slide and fixed, or suspended in a liquid fixative and spun onto a slide. The smear should be examined by an experienced cytopathologist.
- Cervical detection of HPV has higher sensitivity but lower specificity than traditional Pap smear for cervical cancer. The USPSTF does not currently recommend HPV testing as a screening method.

Effectiveness of Screening and Screening Interval

- Sensitivity of a single Pap smear for high-grade CIN is 60-80%; specificity is approximately 98%.
- Effectiveness of cervical cancer screening on incidence and mortality of cervical cancer has not been studied prospectively. Nevertheless, data from good-quality case-control and ecological studies show a strong association between screening and reductions in cervical cancer incidence and disease-specific mortality.

Screening recommendations

- Screen HIV-infected women at the time of diagnosis and 6 months thereafter.
- If initial results are normal, rescreen annually if CD4 count is >200 cells/ μ L or every 6 months if CD4 count is <200 cells/ μ L.
- HIV-infected women also should be screened annually for anal carcinoma using Pap smears (see **Anal Dysplasia**, p. 83).
- Because of the increased risk of vaginal cancer associated with HIV infection, HIV-infected women with a history of high-grade CIN or invasive cervical cancer should be screened with regular vaginal cuff Pap smear following hysterectomy.

Reminders

Because the frequency of recommended screening for cervical cancer differs between HIV-infected and HIV-uninfected women, the standard CPRS reminder for cervical cancer screening generally is not applicable to the former. HIV providers should work with the local Information Resource Management Service to construct HIV-specific reminders for cervical cancer screening.

What to do with a positive result

- Most experts recommend more aggressive management of HIV-infected women than HIV-uninfected women, while some recommend the same management regardless of HIV serostatus.
- The following recommendations are based largely on the 2006 consensus guidelines of the American College of Obstetrics and Gynecology for management of cervical abnormalities, regardless of HIV serostatus (see **Table 3**):

- ASCUS, LSIL, and HSIL refer to cytologic grade of cervical abnormality.
- CIN refers to histologic grades of cervical abnormality. CIN 2 and CIN 3 are considered high-grade precursors of cervical cancer.

(Table 3 refers to the management of adult women only, and not to adolescents, pregnant women, or the elderly.)

Table 3. Management of Women with Abnormal Cervical Cytology on Screening

Cytology Result	Next Step	Comments
Atypical Squamous Cells of Undetermined Significance (ASCUS)	<ul style="list-style-type: none"> • Refer for colposcopy <p>Could consider:</p> <ul style="list-style-type: none"> • HPV testing for oncogenic subtypes <p>OR</p> <ul style="list-style-type: none"> • Repeat cytology (Pap) 	<p>There is controversy about management of ASCUS in HIV-infected women:</p> <ul style="list-style-type: none"> • Many authorities recommend that all HIV-infected women with ASCUS be referred for colposcopy. • In HIV-infected women, there are insufficient data to recommend HPV DNA testing for oncogenic HPV types as part of management of ASCUS. • If colposcopy is chosen, and no CIN is found, repeat cytology at 12 months. • If HPV testing is chosen, reflex HPV testing of samples collected during cytologic screening is preferred, for patient's convenience. This requires liquid-based cytology or samples collected specifically for HPV testing and held. Otherwise, HPV testing requires another Pap smear. <ul style="list-style-type: none"> • If HPV negative, repeat cytology at 12 months. • If HPV positive, manage as for LSIL (below). • If repeat cytology is chosen, repeat at 6-month intervals until 2 consecutive negative tests, then return to normal screening interval. If repeat shows ASCUS or higher, refer for colposcopy.

Atypical Squamous Cells/ cannot exclude HSIL (ASC-H)	<ul style="list-style-type: none"> Refer for colposcopy 	If no CIN 2 or 3 is found on colposcopy, perform cytology at 6 and 12 months, or HPV testing at 12 months. If above are negative, return to regular cytologic screening schedule.
Low-Grade Squamous Intra-epithelial Lesion (LSIL)	<ul style="list-style-type: none"> Refer for colposcopy 	If no CIN 2 or 3 is found on colposcopy, perform cytology at 6 and 12 months, or HPV testing at 12 months. If above results are negative, return to regular cytologic screening schedule.
High-Grade Squamous Intra-epithelial Lesion (HSIL)	<ul style="list-style-type: none"> Refer for colposcopy or loop electrosurgical procedure (LEEP) 	<p>If no CIN 2 or 3 is found, multiple options include: colposcopy and cytology every 6 months for 1 year as long as colposcopy is adequate and cytology is negative; excisional diagnostic procedure.</p> <p>If colposcopy is chosen, excisional procedure is indicated if repeat colposcopy shows HSIL or is unsatisfactory. If repeat colposcopies are negative, return to routine cytologic screening.</p>

Adapted from Wright et al. See **References**.

See also **Women’s Health**, p. 249.

Prostate Cancer

Summary

In contrast to screening for colorectal, breast, and cervical cancer, there is controversy over whether to screen men for prostate cancer. **The VA/DoD and USPSTF do not recommend routine screening; the American Cancer Society (ACS) and the American Urological Association (AUA) favor annual screening for all men at age 50, and for higher-risk men at age 45, as long as they have a life expectancy ≥ 10 years.** Although screening is effective at detecting prostate cancer in its early stages, it is not clear that screening reduces disease-associated or overall mortality. Likewise, the effect of treating prostate cancer in its early stages on overall mortality is not clear, and treatment, whether by prostatectomy or radiation, carries a substantial risk of side effects such as urinary incontinence and sexual dysfunction (see below).

The rate of prostate cancer increases over time in HIV-infected men, as it does in HIV-uninfected men. When corrected for age, HIV-infected men seem to be at lower risk of prostate cancer than HIV-uninfected men, for reasons that are unknown.

Epidemiology

- Lifetime risk of developing prostate cancer is 16% among men in the United States.
- 10-year risk of developing prostate cancer increases with age, from 0.17% at age 40 to 6.46% at age 60.
- Lifetime risk of death caused by prostate cancer is 3% among men in the United States.
- Most deaths resulting from prostate cancer occur at age >65.
- Disease confined to the prostate gland at diagnosis carries a better prognosis than disease extending beyond the gland.
- Incidence of disease and mortality are greater among African American men than among white men in the United States, and among men with a 1st degree relative with prostate cancer.

Screening methods

- Screening for prostate cancer includes measurement of serum prostate-specific antigen (PSA) combined with DRE.
- Prognosis is associated with degree of differentiation of tumor cells (Gleason score) on biopsy and whether disease is confined to the gland or is extraprostatic. Higher Gleason scores (indicating less-differentiated cells) and extraprostatic disease confer a worse prognosis.
- Elevated PSA is associated with prostate cancer, and with benign prostate abnormalities such as benign prostatic hyperplasia (BPH), prostatitis, and trauma to the gland.
- The higher the PSA, the higher the likelihood of prostate cancer, and the higher the likelihood that the cancer has spread beyond the prostate gland:
 - **PSA ≤4 ng/mL** is classified as “normal.” Although up to 27% of men with a PSA <4 ng/mL will have cancer, most of these will have disease confined to the gland.
 - **PSA >4 ng/mL** is classified as “elevated.” Approximately 1 in 3 men with elevated PSA will actually have cancer. For **PSA 4-10 ng/mL**, 1 in 4 men will have cancer. Most of these cancers will be confined to the gland, but the low positive predictive value of the test means that many men will undergo unnecessary biopsy. For **PSA >10 ng/mL**, up to two thirds of men will have cancer and more than half of those cancers will be extraprostatic.

Treatment for early prostate cancer: Side effects and benefits

- Treatment consists of active surveillance (watchful waiting), prostatectomy, or radiation therapy.
- Risk of persistent (at least 12 months in duration) side effects from radical prostatectomy:

- Impaired sexual function: 20-70%
- Urinary incontinence: 15-50%
- Risk of persistent (at least 12 months in duration) side effects from external-beam radiation therapy:
 - Impaired sexual function: 20-45%
 - Urinary incontinence: 2-16%
 - Bowel problems: 6-25%
- When compared with watchful waiting, radical prostatectomy following *clinical* detection of moderately to well-differentiated prostate cancer confined to the gland decreases disease-specific mortality. The effect on overall mortality is less clear. Whether this applies to cancer detected by *screening* is also not clear.

Effectiveness of Screening

- When analyzed properly, the one randomized trial of screening with PSA and DRE vs no screening showed no mortality benefit from screening.
- Additional prospective trials of screening effectiveness are ongoing.

Screening recommendations

- Patients should be counseled annually regarding the risks and benefits of screening for prostate cancer by PSA and DRE; screening may be performed if desired by the patient.
- Depending on Veterans Integrated Service Network (VISN), facility, and clinician decision making, prostate cancer screening may be offered to patients deemed to be at increased risk.

Reminders

CPRS reminder definition and resolution options for prostate cancer counseling and screening may differ among VA Medical Centers, depending on local decisions. An example of a typical CPRS reminder for annual prostate cancer counseling and screening is shown.

Reminder Resolution: ---PROSTATE COUNSELING

--There is controversy about whether men over the age of 50 should undergo routine testing each year for early detection of prostate cancer.

Patient advised of the risks and benefits of screening for prostate cancer with PSA blood test. (PSA education handout given to patient)
 Level of Understanding: (None selected) [v]
 Comment: []

Patient requests PSA Test. (place lab order for PSA test)
 Patient declines PSA test at this encounter.

Patient received prostate counseling previously at another facility.
 Date: * January [v] 14 [v] 2002 [v] ... [v] Comment: []
 Location: [v]

Patient declined prostate counseling at this encounter.
 Comment: []

IF YOU HAVE IDENTIFIED THAT THIS PATIENT HAS AN INCORRECT DIAGNOSIS ON FILE. SELECT THE BOX BELOW TO SEND A CONSULT TO PBS FOR CHART CORRECTION.

<---CLICK here to request correction of an incorrect diagnosis!

Clear Clinical Maint Visit Info < Back Next > Finish Cancel

CLINICAL REMINDER ACTIVITY
 ---PROSTATE COUNSELING:
 Patient advised of the risks and benefits of screening for prostate

Patient Educations: PROSTATE COUNSELING-DISCUSSED
 Health Factors: DAY INCORRECT DM DX - 14DAY INACTIVATE.DAY PROSTATE COUNSELING DONE

What to do with a positive result

- Refer to urologist for transrectal ultrasound (TRUS) and biopsy for:
 - Elevation in PSA (PSA >4 ng/mL)
 - Prostatic abnormality (asymmetry, nodule, or induration of the gland) on DRE



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Immunizations

KEY POINTS

- All HIV-infected patients should be offered hepatitis B, pneumococcus, and inactivated influenza vaccination as recommended.
- Other vaccines may be indicated for some HIV-infected patients (see **Immunization Schedule** on next page).
- Live virus vaccines should not be administered to HIV-infected patients, with the possible exception of MMR and varicella immunizations.



BACKGROUND

- Immunization is a cost-effective, low-risk intervention to prevent morbidity and mortality in HIV-infected patients.
- The current recommendations regarding immunization of HIV-infected individuals are available at <http://aidsinfo.nih.gov>; the most recent schedule is shown on the next page.
- All HIV-infected individuals should be offered 23-valent pneumococcus and hepatitis B vaccination (if not already immune to HBV); vaccination with the inactivated trivalent influenza vaccine should be offered annually during influenza season.
- Other vaccines should be offered based on specific risk factors; see next page.
- Live virus vaccines generally should not be administered to HIV-infected patients; however, administration of MMR, varicella, and zoster vaccines may be appropriate for some patients.

Veterans with HIV*

Influenza vaccination: 60%

Pneumococcus vaccination: 68%

Hepatitis B vaccination: 40%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who received the indicated immunizations

Immunization Schedule for HIV-Infected Adults

Vaccine ▼	Age Group ►	19-49 Years	50-64 Years	≥65 Years
Influenza (trivalent inactivated)*		1 dose annually		
Pneumococcus (polysaccharide)		1 dose		
Hepatitis B*		3 doses (0, 1-2, 4-6 months)		
Tetanus, diphtheria, pertussis (Td/Tdap)*		1 dose Td booster every 10 years		
		Substitute 1 dose of Tdap for Td		
Human papillomavirus (HPV)*		For women aged 15-26 [#]		
		HPV quadravalent vaccine 0.5 mL IM months 0, 2, and 6		
Measles, mumps, rubella (MMR)*		Do not administer to severely immunosuppressed persons		
Varicella*		Do not administer to severely immunosuppressed persons		
Hepatitis A*		2 doses (0, 6-12 months, or 0, 6-18 months)		
Meningococcus*		1 or more doses		

* Covered by the Vaccine Injury Compensation Program

[#] Effective in preventing HPV infection and high-grade CIN associated with vaccine-related HPV types among young HIV-seronegative women. There are no data on the safety, tolerability, immunogenicity, or efficacy in HIV-infected women, or in HIV-infected men.

For all persons in this category who meet the age requirements and who lack evidence of immunity (eg, lack documentation of vaccination or have no evidence of prior infection)

Recommended if some other risk factor is present (eg, on the basis of medical, occupational, lifestyle, or other indication)

Adapted from the Advisory Committee on Immunization Practices (ACIP) Adult Immunization Schedule. For detailed information on immunizations against influenza, pneumococcal disease, hepatitis B, human papillomavirus, varicella, and hepatitis A, refer to the **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents** (http://aidsinfo.nih.gov/contentfiles/Adult_OI.pdf). For information on immunizations against tetanus, diphtheria, pertussis, measles, mumps, rubella, and meningococcal disease, refer to recommendations of the ACIP (<http://www.cdc.gov/vaccines/pubs/ACIP-list.htm>).



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Adult Prevention and Treatment of Opportunistic Infections Guidelines Working Group. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents [DRAFT]; June 18, 2008; p. 208. Available at http://aidsinfo.nih.gov/contentfiles/Adult_OI.pdf. Accessed December 8, 2008.

Prevention for Positives

KEY POINTS

- HIV prevention should be a focus of routine HIV primary care.
- Prevention interventions should emphasize patients' own health and the health of their partners.
- Assessment of sexual and substance-use behaviors and discussion of risk reduction interventions can be brief: 5-10 minutes per visit over a series of visits.
- Elements of the prevention evaluation and intervention include:
 - A detailed HIV transmission risk assessment, including the patient's sexual practices with each partner, and needle-use practices, if applicable
 - Screening and testing for STDs
 - Pregnancy screening and testing
 - Identification and correction of misconceptions
 - General prevention messages
 - Individualized interventions
 - Referrals
 - Periodic reevaluation



BACKGROUND

Basic Epidemiology of HIV Transmission in the United States: The Role of Prevention for Positives

There are an estimated 56,000 new HIV infections each year in the United States, almost all attributable to risky sexual and drug-use behaviors. Each new infection originates with someone already infected with HIV, and nearly all are preventable. Assessing patients' behaviors and promoting healthy changes can decrease the risk of HIV transmission. This chapter will focus on performing sexual risk assessment

Veterans with HIV*

Alcohol use disorder: 33%

Illicit drug use: 30%

Other and unspecified drug use: 22%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to these conditions

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

and making simple interventions to prevent transmission of HIV infection; this, in turn, can protect patients and their sexual and drug-sharing partners from other sexually transmitted and bloodborne pathogens, and possible HIV superinfection.

Transmission route for HIV/AIDS cases diagnosed in the United States in 2006:

- **Men:** 67% sex with other men; 16% high-risk heterosexual contact; 12% injection drug use (IDU)
- **Women:** 80% heterosexual sex; 19% IDU

Source: CDC, 2008. Based on data from 33 states with long-term, confidential name-based HIV reporting. See **References**.

Helping Patients Adopt and Maintain Safer Sexual Behaviors

The HIV clinic is an important setting for prevention efforts, to help patients decrease the risks of:

- Transmitting HIV to others via sexual or IDU behaviors
- Acquiring and transmitting an STD
- Acquiring a bloodborne infection (for injection drug users)
- HIV superinfection (note: this appears to occur rarely, but can adversely affect clinical status and treatment options)
- Unintended pregnancy

Nevertheless, studies have shown that many HIV providers do not assess transmission risks with or provide prevention messages to their patients.

For some patients, decreasing HIV transmission risks requires them to make small changes in sexual and drug-use behavior; for others, significant changes are needed. Although behavior changes can be difficult to make and to maintain, they should be encouraged. Several studies have shown that assessment of HIV transmission risk followed by brief prevention interventions initiated by the care provider can be effective, at least in the short term. Various risk reduction interventions in primary care and STD clinics have resulted in:

- Increased condom use
- Safer IDU practices
- Fewer STDs

As with any behavior change intervention (eg, smoking cessation, dietary modification), HIV prevention interventions need to be reevaluated and reinforced regularly. Over time, primary care providers can have a significant impact on their patients' behaviors. Clinicians often underestimate how seriously patients take their recommendations.

Addressing patients' health behaviors, particularly in the realms of sex and drug use, can be challenging or uncomfortable for some medical providers. Learning how to conduct a partner-by-partner risk assessment can reduce this discomfort. Given the preventable nature of HIV infection, HIV risk assessment and the delivery of individualized prevention messages should be routine and ongoing aspects of HIV care that are performed at the initial evaluation and periodically thereafter.

Clinicians can greatly affect patients' risks for transmission of HIV to others via the following actions:

- Performing a brief screening for HIV transmission risk behaviors
- Communicating prevention messages
- Discussing sexual and drug-use behavior
- Positively reinforcing changes to safer behavior
- Referring patients for services such as substance abuse treatment
- Facilitating partner notification, counseling, and testing
- Identifying and treating other STDs

These measures also may decrease patients' risks of acquiring other STDs and blood-borne infections (eg, viral hepatitis).

Adapted from CDC, HRSA, NIH, and HIVMA. See **References**.

Doing prevention work with HIV-infected patients can be divided into evaluation steps and management steps.

Evaluation:

1. Establish rapport and conduct a quick, detailed behavioral risk assessment.
2. Assess for the presence of STDs.

Management:

1. Locate patient's risk behavior along the risk continuum.
2. Correct misinformation, answer questions, and educate.
3. Assess patient's readiness for behavior change.
4. Work toward risk reduction with an individualized prevention message based on the patient's risk behaviors and readiness to change.
5. Treat STDs and supply medications, condoms, and lubricant if needed.
6. Agree on what patient will do to reduce risk.
7. Agree to address prevention at future visits.

The rest of this chapter will focus on these steps in more detail.



HIV transmission risk assessment should be performed at the initial evaluation and periodically thereafter. For patients with significant ongoing risk factors for HIV transmission, it should be part of every visit, if possible.

Sexual risk assessment

- Should include an evaluation of risks of HIV transmission and risks of acquisition and transmission of other STDs (including HBV and HCV infections).

Drug and alcohol risk assessment (see also **Alcohol Misuse**, p. 3; and **Substance Use**, p. 69)

- Illicit drug use (particularly methamphetamine use) and alcohol misuse are associated with unsafe sex practices, and with STD and HIV acquisition and transmission.
- Sharing of nonsterile injection equipment can itself cause transmission of HIV and other bloodborne pathogens (including HBV and HCV).

Mental health assessment (see also **Depression**, p. 271)

- Serious mental illness, posttraumatic stress disorder, and depression increase the likelihood of risky sexual and drug- and alcohol-use behaviors.

STD screening/testing

- The presence of an STD indicates risky sexual practices and increased risk of HIV transmission, and of acquisition of different HIV strains.
- Coinfection with an STD (eg, gonorrhea, chlamydia, syphilis, chancroid, herpes simplex virus [HSV], and, in women, trichomoniasis) can increase HIV transmission risk and is deleterious to the patient's own health.

Sexual risk assessment: In order to provide appropriate and specific recommendations, it is important to understand the patient's risk behaviors and why he or she is engaging in them. A basic assessment should include questions about a variety of topics (see box below). *Because a patient's sexual activities may vary substantially with different partners or in different circumstances, asking follow-up questions to explore the circumstances of unsafe behaviors is crucial to targeting specific risk behaviors for intervention.* One very helpful way of organizing an efficient but detailed risk assessment is to ask patients to make a mental list of their most recent partners, and then explore their risk behaviors with each partner (see **Table 1** below for questions to ask).

Note: Veterans may be particularly reluctant to acknowledge same-sex sexual activities or IDU.

When interviewing patients, it is important to establish rapport in order to elicit truthful and complete responses and to establish a context for behavioral interventions. It often is helpful to normalize the questions as a routine part of primary care, and these topics should be discussed openly in a nonjudgmental manner.

Providers often find that systematically evaluating risk in a partner-by-partner fashion makes the risk assessment more clinical, less emotionally charged, and more comfortable for them and their patients.

Reassuring patients about the confidentiality of their responses to questions about risky behavior is a key component for establishing rapport and trust and obtaining truthful responses. The confidentiality of HIV-related information in the VA system is explicitly and specifically protected by federal law; for more information, see <http://www.hiv.va.gov/vahiv?page=prtop03-ov-01>; it may be helpful at a patient's initial visit to clarify his or her confidentiality rights.

Table 1. Components of a Detailed Risk Assessment

- | | |
|---|---|
| <ul style="list-style-type: none">• Number of recent sex partners• Sex of each partner• Type of relationship with each partner (eg, main, casual, anonymous)• HIV status of each partner• Whether patient discloses his/her HIV status to partners or potential partners• Type of sexual activity engaged in with each partner• Safer and less-safe sexual activities engaged in with each partner• Use of any risk reduction techniques (eg, condoms, serosorting,* disclosure)• Consider asking questions such as:<ul style="list-style-type: none">• “What made it more difficult for you to use condoms during this sexual encounter/with this partner?”• “What made it easier for you to use condoms during this sexual encounter/with this partner?” | <ul style="list-style-type: none">• Substance use (including alcohol) associated with sex• Circumstances of risky sex behaviors (eg, while intoxicated or high, with anonymous partners, in particular settings)• Risky drug-use practices (eg, sharing injection equipment or nasal straws)• Barriers to “safer” sex (and drug-use) practices• STD symptoms• Women: current pregnancy, desire or intention for pregnancy, contraception• Men with female sex partners: intentions for conception or fathering, contraception |
|---|---|

* Serosorting, whereby an HIV-infected person has unprotected sex only with HIV-infected partners, reduces HIV transmission. Serosorting does not affect the risk of acquiring other STDs, including HBV and HCV infections, or the risk of reinfection with drug-resistant or more pathogenic strains of HIV.

For a more complete risk assessment questionnaire, see the Risk Assessment Battery (University of Pennsylvania and Philadelphia Veterans Administration Medical Center), reproduced in the *VA Prevention Handbook*; see **References**.

How to start the conversation

Sometimes, the hardest part of doing prevention for positives is simply starting the conversation. The CDC HIV Prevention Guidelines present **examples of screening and follow-up questions** that may be used in interviewing patients:

Open-end question by clinician, similar to one of the following:

- “What are you doing now that you think may present a risk of transmitting HIV to a partner?”
- “Tell me about the people you’ve had sex with recently.”
- “Tell me about your sex life.”

Screening questions* (checklist; should take approximately 4 minutes):

- “Since your last checkup here,” or, if first visit, “Since you found out you are infected with HIV ...”
- “Have you been sexually active; that is, have you had vaginal, anal, or oral sex with a partner?”
If yes:
“Have you had vaginal or anal intercourse without a condom with anyone?”
If yes:
“Were any of these people HIV negative, or are you unsure about their HIV status?”
“Have you had oral sex with someone?”
If yes:
(For a male patient) “Did you ejaculate into your partner’s mouth?”
- “Have you had a genital sore or discharge, discomfort when you urinate, or anal burning or itching?”
- “Have you been diagnosed or treated for an STD, or do you know whether any of your sex partners have been diagnosed or treated for an STD?”
- “Have you shared drug-injection equipment (needle, syringe, cotton, cooker, water) with others?”
If yes:
“Were any of these people HIV negative, or are you unsure about their HIV status?”

These questions may be used in a face-to-face interview, or with a self-administered questionnaire.

*Adapted from CDC, HRSA, NIH, and HIVMA. See **References**.

STD Screening

- The presence of an STD suggests behaviors that may result in HIV transmission.

- In addition to the morbidity associated with the STD itself, the presence of an STD increases the risk of HIV transmission; diagnosis and treatment of STDs may therefore decrease HIV transmission, as well as prevent transmission of the STD.
- Screen all patients at baseline and regularly thereafter, depending on their risk factors (eg, every 3-6 months in patients with a new sex partner or a partner who is an injection drug user); do specific tests according to sites of possible exposure; see below.
- Routinely ask patients whether they have symptoms of an STD; perform diagnostic testing for all symptomatic patients, and treat as indicated.

Table 2. Screening for STDs

STD	Screening Test
Syphilis	Nontreponemal tests: rapid plasma reagin (RPR); Venereal Disease Research Laboratory test (VDRL)
Chlamydia	Urogenital infection: Nucleic acid amplification test (NAAT) on first-void urine (men and women), or cervical (women) or urethral (men) swab specimen Rectal infection: NAAT of rectal swab* (for all who report engaging in anal receptive sex)
Gonorrhea	Urogenital infection: NAAT on first-void urine (men and women), or cervical (women) or urethral (men) swab specimen; culture of male urethral or female endocervical swab specimen (for men with symptoms of urethritis, Gram stain of urethral specimen may be done) Pharyngeal infection: NAAT or culture of oral swab* (for all who report engaging in oral receptive sex) Rectal infection: NAAT or culture of rectal swab* (for all who report engaging in anal receptive sex)
Trichomoniasis	Wet-mount examination or culture of vaginal secretions (for all women)
HSV	Serologic testing for HSV-2; recommended by some experts (for patients not previously diagnosed with HSV)

Adapted from CDC. Sexually Transmitted Disease Treatment Guidelines – 2006. See **References**.

* NAAT is not currently approved for this indication by the FDA. There is evidence that NAAT can accurately diagnose pharyngeal and rectal gonorrhea and rectal chlamydia, however, and many local public health departments have obtained Clinical Laboratory Improvement Amendment (CLIA) waivers to perform NAAT on pharyngeal and rectal swabs.

Pregnancy Screening

Screen all women who have a possibility of pregnancy based on sexual history, as well as those with missed menses or other signs or symptoms of pregnancy.

Information and education are important: Many patients have an incomplete or inaccurate understanding of how HIV is transmitted, the risks of various behaviors, and methods to prevent infection of sex partners or needle-sharing partners.

- Patient education may increase knowledge and provide motivation.
- Providers may identify and correct misconceptions.
- It is worth specifically mentioning that ART has not been proven to make patients noninfectious.
- However, information alone is not adequate to change patients' behavior.

Brief, tailored interventions and prevention messages delivered by clinicians may help patients reduce their risks of transmitting HIV.

- These are more effective in achieving behavior change than patient education alone.

There are a number of models for health behavior change and various counseling techniques or programs based on those models (for further information, see the *VA HIV Prevention Handbook* and **References**, below). Most involve:

- Assessing the patient's level of awareness and concern
- Helping the patient to better understand his or her potentially harmful behavior
- Determining the patient's readiness for change (see **Stages of Change**, below)
- Working with the patient to target a particular behavior for change
- Helping the patient bring about the desired change (this may require developing new skills [eg, negotiation])
- Working toward further specific goals as the patient is ready

(Adapted from AIDS Institute, New York State Department of Health. *HIV and Primary Care: Putting Prevention into Practice*; 1998.)

In working with patients, it is important to assess their risk, readiness, motivation, and skills around specific behavioral changes and to work with them to prepare for these changes.

Risk Continuum

In interviewing patients, assess their positions on a continuum of risk of HIV transmission (see **Table 3**, below). Again, note that the degree or type of risk each person engages in may differ, depending on specific circumstances. Focus on specific behaviors.

Table 3. Relative Risk of HIV Acquisition (per act)

Risk Factor	Relative Risk of Acquisition
Sexual Activity (some popular terms)	
Insertive fellatio (“getting head, being blown/sucked”)*	1#
Receptive fellatio (“giving head, blowing/sucking”)*	2
Insertive vaginal sex	10
Insertive anal sex (“topping”)	13
Receptive vaginal sex	20
Receptive anal intercourse (“bottoming”)	100
Condom Use	
Yes	1
No	20

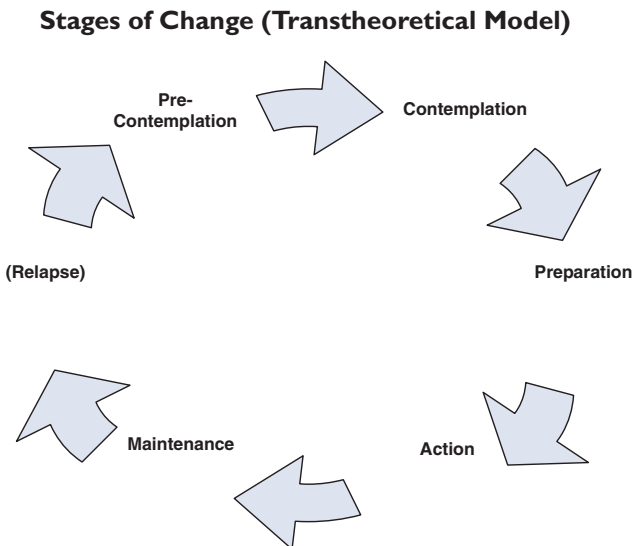
* Best-guess estimate

Referent category

Adapted from Varghese B, Maher JE, Peterman TA, et al. Reducing the risk of sexual transmission: quantifying the per-act risk for HIV infection based on choice of partner, sex act, and condom use. *Sex Transm Dis* 2002;29:38-43. Also adapted from CDC, HRSA, NIH, and HIVMA. Incorporating HIV Prevention into the Medical Care of Persons Living with HIV. *MMWR* 2003;52:RR-12.

Assess readiness for change

Using the Stages of Change model (below), identify the patient’s readiness to change risky sexual behaviors (for more on stages of change, see **Alcohol Misuse**, p. 3; **Substance Use**, p. 69; and **Smoking Cessation**, p. 53).



Work toward risk reduction: Many people may not want, or may not be willing, to adopt behaviors that entirely eliminate the risk of HIV transmission (eg, abstinence); for most, the goal is to move from riskier activities to less-risky activities (see **Table 3**, above). Patients may do this in increments, with the support of clinicians, as they are ready and able.

Interventions may be as brief as 5-10 minutes per session. They should be repeated, refined, and reinforced at follow-up visits. For more extensive support, refer within and outside the VHA (eg, for counseling, psychiatric treatment, and substance misuse treatment).

Individualize prevention messages and interventions. Based on the risk assessment, the clinician can help patients identify behaviors that are less risky, and can target them for intervention. The intervention should be tailored to the individual, and the goal should be attainable. Risk reduction could include:

- Disclosing one's HIV status
- Asking about partner's HIV status
- Monogamy
- Reducing the number of sex partners
- Using condoms (male or female), particularly for anal or vaginal intercourse
- Having sex only with other HIV-infected partners (serosorting)
- Not having sex while intoxicated or under the influence of drugs or alcohol
- Using adequate lubrication to avoid trauma to genital or rectal mucosa
- ART with maximal suppression of HIV viremia; adherence to ART
- Regular STD testing
- Referring partners for HIV and STD testing and counseling
- For drug users: using clean injection equipment; not sharing injection equipment

Using the risk continuum (see **Table 3**, above), help the patient identify ways toward less-risky behaviors.

An example of an intervention, based on the Stages of Change theory, is the following:

Responses to Risk-Behavior Questions, Corresponding Stages of Behavior Change, and Possible Interventions

Type of Answer	Stage of Behavior Change	Possible Intervention
<p>“I don't think about it.”</p>	<p>Precontemplative Either unaware of risk or has no intention to change.</p>	<p>Contemplation of resistance by the patient. Education may enhance such awareness.</p>
<p>“I worry about it, but I don't really know what to do, if anything.”</p>	<p>Contemplative Considers change but has no specific plan.</p>	<p>Education as to options. Assessment of barriers to change and discussion of benefits of change, resources, and intervention options.</p>
<p>“I've thought about it. I guess I'd like to try something.”</p>	<p>Prepared Ready for change. Planning for change and may have taken some initial action.</p>	<p>Discuss options for initiating change.</p>
<p>“I've started using condoms, but not all the time.” OR “I've started cleaning my works.” OR “I'm in a treatment program.” OR “I've been clean for 3 months.”</p>	<p>Action Initiated change.</p>	<p>Identify and acknowledge successful actions. Explore resources and referrals. Problem solve to help increase behavior changes.</p>
<p>“I've been using a condom now for about 6 months, nearly all the time.” OR “I've started using a syringe exchange program.” OR “I found out about a drug treatment program.”</p>	<p>Maintenance Adopted a new behavior.</p>	<p>Evaluate factors supporting and potentially discouraging maintenance.</p>
<p>“I was really good for a long time, but then I started seeing somebody new and I just stopped. I'm not sure it was the right thing to do.” OR “I went cold turkey for a while, but I ran into some old friends who were using, and I picked up again.”</p>	<p>Relapse Time or changing factors result in discontinuing adopted behavior.</p>	<p>Evaluate the need for reinitiating behavior. Discuss factors influencing cessation of desired behavior.</p>

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Providers should give information, education, and support regarding ways to reduce risk.

Practical Supports

Prescribe condoms (male and female condoms are available on the VHA National Formulary). Refer to drug treatment programs as needed, and needle-exchange programs if available.

Refer patients, as needed, to VHA or community resources, for:

- More intensive risk reduction counseling and intervention
- Instruction on practical skills (eg, correct condom use, negotiation skills)
- Substance abuse treatment
- Mental health treatment
- Assistance with social problems (eg, lack of money or housing)
- Case management, social services
- Support around other problems that contribute to risky behaviors

Follow Up:

- At each visit, briefly reassess HIV transmission risks
- Identify and correct misconceptions
- Answer the patient's questions
- Reinforce focused prevention messages
- Give encouragement and positive reinforcement for positive changes in risk behaviors
- Identify next steps for further risk reduction
- For patients who continue risky behaviors, elicit their beliefs and attitudes about their behaviors; offer counseling and develop further intervention, based on their motivation and their current stage on the change continuum



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Smoking Cessation

KEY POINTS

- Smoking is the leading cause of preventable death and disease in the United States, accounting for approximately 440,000 deaths each year. It is a chronic, relapsing disorder that often requires repeated interventions and multiple attempts to quit.
- Patient interest in smoking cessation is high (>66% in most surveys).
- HIV-infected patients are 2-3 times more likely to be smokers than their age-matched HIV-uninfected counterparts.
- HIV-infected smokers face traditional tobacco-related risks, such as cardiac disease, stroke, COPD, and osteoporosis. These conditions are likely to become more prevalent with the aging of the HIV-infected population on effective ART. Smoking and HIV infection substantially increase the risks of respiratory tract infection, including acute bronchitis, bacterial pneumonia, PCP, and TB.
- HIV-infected smokers also are at higher risk of several tobacco-related cancers, and may be at increased risk of poorer immunologic and virologic responses to ART.
- Asking patients about smoking is an important part of primary care management. Current users should be asked about smoking at every visit.
- Brief (<3 min) tobacco dependence interventions are effective, and every tobacco user should be offered treatment.
- Counseling and medication are effective when used by themselves for treating tobacco dependence. The combination of counseling and medication, however, is more effective than either alone.
- Evidence-based treatment options include behavioral counseling and support, nicotine replacement therapy, bupropion, and varenicline.

Note: Current information on VHA smoking and tobacco use cessation policy and tools can be found online at <http://www.publichealth.va.gov/smoking/>.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.



- Smoking is a cause of cancers of the bladder, cervix, esophagus, kidney, larynx, lung, oral cavity, pancreas, and stomach; of leukemia; of peripheral atherosclerosis, cerebrovascular disease, and coronary artery disease; of COPD, decreased lung function, and lung infections; of pregnancy complications; and of peptic ulcer disease.
- HIV-infected patients are 2-3 times more likely to be smokers than their age-matched HIV-uninfected counterparts.
- In the United States, 30-65% of patients in HIV primary care clinics are smokers.
- HIV-infected smokers have higher rates of certain diseases (compared with HIV-uninfected smokers and HIV-infected nonsmokers), such as lung cancer, head and neck cancers, anal and cervical cancers, oral candidiasis, and oral hairy leukoplakia.
- HIV infection increases the risk of respiratory tract infections, and smoking further increases the risks of acute bronchitis, bacterial pneumonia, PCP, and TB.
- Smoking may decrease the immunologic and virologic response to ART. In a cohort of HIV-infected women, smokers had lower CD4 cell counts and higher HIV viral loads compared with age-matched HIV-infected female nonsmokers after initiation of ART.
- Smoking is the leading cause of preventable death and disease in the United States. Tobacco use is a chronic, relapsing disorder that often requires repeated interventions and multiple attempts to quit.
- Most smokers are interested in quitting. Surveys have found that two thirds of HIV-infected smokers want to quit.
- Smoking cessation programs for HIV-infected smokers are effective. For example, among patients who were given a 10-week supply of nicotine patches, self-help booklets, and initial physician counseling plus (by randomization) 8 counseling phone calls or no calls, 37% of those in the counseling group were not smoking at a 3-month follow-up, compared with 10% of those who did not receive the counseling phone calls.

Veterans with HIV*

Tobacco Use: 38%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to this condition



The 5 A's

These strategies are designed to be brief (<3 minutes of direct clinician time). They need not be delivered by the same clinician; for example, a clinic nurse may ask about tobacco use, whereas a prescribing clinician (eg, MD, PA, or NP) may advise, assess, and assist, with referral to another provider for counseling services.

ASK ...

- All patients about tobacco use at every clinic visit:
 - If a patient has never used, you do not need to ask again.
 - If a patient quit years ago, congratulate and check in periodically.
 - Consider making it a part of your office practice to ask about and record tobacco use while patients are having vital signs recorded.



ADVISE ...

- Smokers with clear, strong, and personalized suggestions:
 - **Clear:** “I think it is important that you quit smoking. I can help.”
 - **Strong:** “Quitting smoking is one of the most important things you can do to protect your health.”
 - **Personalized:** Associate smoking with something that is important to the patient, such as exposure of children to tobacco smoke, the expense of cigarettes, or pulmonary and cardiovascular comorbidities. “Remember the time you had that terrible pneumonia?” “Do you realize that you can save almost \$2,000 a year on cigarette expenses if you quit?”



ASSESS ...

- Smokers' readiness to quit within 30 days: “Are you willing to give quitting a try in the next 30 days?”
- If not ready, consider using motivational interviewing to increase patient's readiness to quit (see the **5 R's for Patients Unwilling to Quit**, below*).
- If ready, **assist** and **arrange** (following).



ASSIST ...

- A patient's preparations for quitting:
 - **Setting a quit date.** Ideally, the quit date should be within 2 weeks.
 - **Telling family, friends, and coworkers about quitting, and requesting understanding and support.**
 - **Anticipating challenges to the upcoming quit attempt, particularly during the critical first few weeks.** These include nicotine withdrawal symptoms.
 - **Removing tobacco products from the environment.** Before quitting, avoiding smoking in places where a lot of time is spent (eg, work, home, car). Making the home smoke free.
- Offer nicotine replacement or, if appropriate, bupropion, varenicline, or other medication (see below for more details on medication options).
- Provide practical counseling (problem-solving/skills training; see below).
- Offer intensive treatment options (smoking cessation intervention programs and groups).
- Offer readily available counseling and support services: phone support, clinic counselors.



ARRANGE ...

- Enrollment in a VHA-based smoking cessation clinic, if the patient wishes.
- Referral to appropriate counseling services.
- Referral to evidence-based cessation program in the community or to phone quit lines if VHA-based interventions are not convenient for the patient or if the patient is interested (800-QUIT-NOW is a national portal for state programs).
- Follow-up contact during the first week after quit date (in person or by phone).
- Follow-up visit 1 month after quit date.
- Subsequent follow-up visits; congratulate upon success in quitting; anticipate further support with relapses (approximately 35-40% patients relapse 1-5 years after quitting).

Adapted from Fiore et al. See **References**.

* For more detailed suggestions on how to conduct motivational interviewing with smokers, see Fiore et al. Chapter 3, Section B (see **References**).

Current tobacco users who are not ready to quit:

Continue to encourage smoking cessation.

The 5 R's for Patients Unwilling to Quit

- **Relevance:** Explain to patients why cessation is personally relevant (eg, comorbidities, cost).
- **Risks:** Ask patients to explain their perceived potential risks of smoking; discuss these risks with them (eg, sexual dysfunction, infertility, fetal harm, CV and pulmonary disease, malignancies, secondhand smoke). Explain that:
 - 20 minutes after quitting, heart rate and blood pressure drop
 - 12 hours after quitting, carbon monoxide levels drop to normal
 - 2 weeks to 3 months after quitting, circulation and lung function improve
 - 1 year after quitting, risk of coronary heart disease is cut in half
 - 5 years after quitting, stroke risk is the same as for nonsmokers
 - 10 years after quitting, lung cancer risk is cut in half
- **Rewards:** Ask patients to explain what they might gain from cessation (eg, breath smells better, stained teeth get whiter, bad odor of clothes goes away, food tastes better, sense of smell returns to normal, everyday activities do not result in shortness of breath, skin tone gets better, health improves, worries about secondhand smoke lessen, respiratory symptoms improve, lung function improves).
- **Roadblocks:** Ask patients to identify barriers to quitting (eg, fear of failure, weight gain, depression) and offer options to address those barriers.
- **Repetition:** Discuss these issues with patients at each visit.

Adapted from Fiore et al. See **References**.

Current tobacco users who are ready to quit:

- Offer smoking cessation treatment at every visit to every patient who smokes.
- Even minimal (<3 minute) intervention can yield benefit, including simply advising a patient to quit.
- For patients with symptoms suggestive of COPD, particularly shortness of breath, consider pulmonary function testing, including spirometry, lung volume, and diffusion studies, and provide medication to support a quit attempt (see **COPD**, p. 107).
- Patients who are informed of abnormal pulmonary function test results may be more likely to quit.
- If applicable, discuss challenges patients have encountered during previous attempts to quit and tailor current recommendations to what patients can accomplish.

- Research strongly supports treatment in the form of behavioral counseling (even brief sessions [<3 minutes]) and first-line smoking cessation medications. Specifically, U.S. Public Health Service's 2008 update of the Clinical Practice Guideline on Treating Tobacco Use and Dependence (see **References**, Fiore et al.) finds strong evidence in favor of:
 - Using medications to assist in smoking cessation
 - Combining medication with behavioral counseling
 - Providing multiple counseling sessions as opposed to single counseling sessions
- Pharmacologic interventions included in the table below are first-line therapies found to be effective by the USPHS. All were found to be more effective than placebo at assisting in cessation. A list of 7 monotherapies is provided, along with 4 combination therapies. Not all therapies listed in the Guideline are considered first-line by the VHA (see below). Combination therapies may be particularly effective at blunting nicotine withdrawal symptoms, but may cost more and may expose the patient to a wider range of side effects.
- Two components of counseling have been found to be particularly effective: working with patients to develop **problem-solving skills** and strategies, and delivering **social support** as part of counseling.

Examples of Problem-Solving Skills	
Type of Skill	Examples
Identifying situations that endanger smoking cessation	<ul style="list-style-type: none"> • Negative stressors • Being around smokers • Alcohol • Smoking cues • Availability of cigarettes
Identifying coping skills	<ul style="list-style-type: none"> • Learning to anticipate and avoid tempting situations • Cognitive strategies for improving mood, decreasing stress • Changing routines that expose the patient to smoking cues
Identifying feelings that can threaten cessation	<ul style="list-style-type: none"> • A single puff increases the risk of relapse • Withdrawal symptoms peak 1-2 weeks after quitting but may persist for months • Withdrawal symptoms can include negative mood, urges to smoke, difficulty concentrating

Adapted from Fiore et al. See **References**.

Examples of Social Support

Type of Support	Examples
Encouragement to quit	<ul style="list-style-type: none"> • Effective treatments are available • Half of people who have ever smoked have been able to quit • Communicate belief in patient's ability to quit
Communicate caring and concern	<ul style="list-style-type: none"> • Ask how patient feels about quitting • Express willingness to help as often as needed • Ask about patient's fears and ambivalence about quitting
Encourage patient to talk about the quitting process	<ul style="list-style-type: none"> • Why does patient want to quit? • What are patient's concerns about quitting? • What success and difficulties in quitting has patient had in past?

Adapted from Fiore et al. See **References**.

- Continue to encourage cessation even if the patient relapses. Relapse does **not** mean that the patient will not quit successfully on a future attempt.
- Counsel patients on potential nicotine withdrawal symptoms. Note that 25% of smokers who quit do **not** have these symptoms. Nicotine withdrawal symptoms include:
 - Depressed mood
 - Insomnia
 - Irritability
 - Anxiety
 - Difficulty concentrating
 - Restlessness
 - Decreased heart rate
 - Increased appetite and weight gain (10% of patients gain >13 kg after smoking cessation)

Pharmacologic Interventions

Key points:

- Nicotine replacement therapies (NRTs), such as nicotine patch, gum, and lozenges, do not interact with ARVs and have low toxicity at recommended dosages, even in patients with cardiovascular disease.
- All forms of NRT are equally efficacious.
- Varenicline is **not** considered first-line therapy for smoking cessation by the VHA; see the Varenicline Criteria for Prescribing at <http://www.pbm.va.gov/CriteriaForUse.aspx>.

VHA Formulary Choices for Pharmacotherapy of Smoking Cessation

	Bupropion	Nicotine Transdermal Patch	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge	Varenicline
Formulations	Bupropion SR 150 mg, 300 mg Bupropion IR 100 mg	(Nicoderm/Habitrol) 21 mg, 14 mg, 7 mg (Nicotrol) 15 mg, 10 mg, 5 mg	2 mg, 4 mg	2 mg, 4 mg	0.5 mg, 1 mg
Start instructions	1-2 weeks before quit date		On quit date		1 week before quit date
Recommended regimen	Bupropion SR 150 mg QD for 3 days, then 150 mg BID (8 hours apart) Reduce dosage for patients with cirrhosis: 150 mg QOD Bupropion IR 100 mg QD for 3 days, then 100 mg TID; reduce dosage for patients with cirrhosis: 75 mg QD	High dependence# High-dose patch for 4-6 weeks, then medium-dose patch for 2 weeks, then low-dose patch for 2 weeks Low dependence medium-dose patch for 6-8 weeks, then low-dose patch for 2 weeks	High dependence# 4 mg Q1-2H for 6 weeks, then Q2-4H for 4 weeks, then Q4-6H for 2 weeks Low dependence 2 mg Q1-2H for 6 weeks, then Q2-4H for 3 weeks, then Q4-6H for 3 weeks Maximum: 24 pieces/24 hours	High dependence# 4 mg Low dependence 2 mg Suck 1 lozenge Q1-2H for 6 weeks, then 1 lozenge Q2-4H for 3 weeks, then 1 lozenge Q4-8H for 3 weeks Maximum: 20 lozenges/24 hours or 5 lozenges/6 hours	Initial: 0.5 mg QD on days 1-3, then 0.5 mg BID on days 4-7, then 1 mg BID for total duration of 12 weeks Reduce dosage for CrCl <30: maximum dosage 0.5 mg BID; end-stage renal disease or hemodialysis: 0.5 mg QD

<p>Administration comments</p>	<ul style="list-style-type: none"> • Start 1-2 weeks before quitting smoking (to achieve steady-state levels) • Continue treatment for 7-12 weeks (if no progress is made by week 7, consider discontinuing therapy) • If insomnia, take evening dose in afternoon 	<ul style="list-style-type: none"> • Usually worn 16-24 hours; remove overnight • Apply between neck and waist • Rotate sites • Takes 2-3 days for effect after application of first patch 	<ul style="list-style-type: none"> • Chew slowly (about 10 chews) until peppery taste is released, then “park” between teeth and gums until flavor dissipates; repeat process on and off for 30 minutes per piece • Has been studied in combination with patch 	<ul style="list-style-type: none"> • Allow lozenge to dissolve slowly over course of 20-30 minutes, shifting in mouth occasionally • Do not chew or swallow (increased risk of GI side effects) • Avoid acidic beverages within 15 minutes of use (eg, citrus juices, soft drinks); these decrease absorption 	<ul style="list-style-type: none"> • Start 1 week before quit date • Take drug after eating and with 8 oz of water • Instruct patient or caregiver to report depression, suicidal ideation, unusual changes in behavior, or worsening of preexisting psychiatric illness • An additional 12 weeks of treatment in patients who have successfully stopped smoking may increase likelihood of long-term abstinence 	<p>18.5-23% (12-week course) vs 4-10% with placebo</p> <p>43.6% (with additional 12-week course) vs 37% with placebo</p>
<p>1-year abstinence rates[§]</p>	<p>10-30% (up to 35% when combined with patch)</p>	<p>16-30% (dose dependent); high-dose patch: 30%</p>	<p>20-30%</p>	<p>15-20%</p>	<p>18.5-23% (12-week course) vs 4-10% with placebo</p> <p>43.6% (with additional 12-week course) vs 37% with placebo</p>	

	Bupropion	Nicotine Transdermal Patch	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge	Varenicline
ARV interactions	Metabolized by the cytochrome P450 system; EFV and TPV may ↓ bupropion levels 40-50%; when using with these ARVs, monitor for depression and titrate to clinical effect; RTV may ↑ bupropion levels		None		Does not interact with the cytochrome P450 system; no ARV interactions identified to date
Time to peak blood concentrations	3 hours (half life = 21 hours)	4-10 hours	15-30 minutes	No data	3-4 hours
Absorption	20%	75-90%	30%	30%	High; virtually complete absorption
Advantages (+)	(+) Good adherence; ease of use; can be combined with patch; consistent rate of exposure; helps with withdrawal symptoms	(+) Best adherence; easy to use; consistent rate of exposure; unobtrusive	(+) Helps prevent sudden urges; can titrate to adjust for cravings; oral substitute for cigarettes; slow release of nicotine reduces addiction potential	(+) Easy to use; discreet; higher immediate levels; can titrate to adjust for cravings; reduces self-reported withdrawal symptoms	(+) Good adherence; ease of use; consistent rate of exposure; higher rate of abstinence compared with bupropion and placebo
Disadvantages (-)					

<p>(-) Many drug interactions resulting from metabolism by CYP 2B6; CNS side effects; must be adjusted for hepatic insufficiency; increased risk of seizures</p>	<p>(-) Less effective than gum for cravings; difficult to control titration; absorption increased at elevated temperatures; should abstain from smoking while using NRT</p>	<p>(-) Difficult for those with poor dentition or dentures; must learn proper chewing technique; should abstain from smoking while using NRT; must abstain from drinking/eating during gum use; swallowing nicotine causes GI side effects (hiccups, diarrhea or constipation, flatulence, belching)</p>	<p>(-) Must abstain from drinking/eating during lozenge use; should abstain from smoking while using NRT</p>	<p>(-) Potential for serious neuropsychiatric side effects, particularly in patients with underlying psychiatric disease; dosage adjust for renal insufficiency (CrCl <30); high incidence of nausea; not studied in patients with underlying mental illness</p>
<p>Adverse effects</p> <ul style="list-style-type: none"> • Anxiety • Disturbed concentration • Dizziness • Insomnia • Constipation • Dry mouth • Nausea • Seizures (risk: 1:1,000) 	<ul style="list-style-type: none"> • Sleep disturbances • Local skin irritation • Bone pain • Headache • Nausea 	<ul style="list-style-type: none"> • Local mouth irritation • Jaw pain • Hiccups • Dyspepsia • Rhinitis • Nausea 	<ul style="list-style-type: none"> • Local mouth irritation/tingling • Heartburn, indigestion, nausea (if chewed) • Headache • Nausea, diarrhea • Flatulence 	<ul style="list-style-type: none"> • Dream disorders • Headache • Insomnia • Abnormal behavior • Agitation • Depressed mood • Suicidal thoughts • Constipation • Flatulence • Nausea, vomiting <p>Consider dosage reduction for patients sensitive to adverse effects (eg, nausea, headache, insomnia)</p>

	Bupropion	Nicotine Trans-dermal Patch	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge	Varenicline
VHA National Formulary restrictions	None	None	None	Restricted to patients who cannot tolerate gum (eg, dentures, missing teeth, TMJ), previous head or neck surgery)	Must meet criteria for use (http://www.pbm.va.gov/CriteriaForUse.aspx) Restricted to patients without active mental health disorders or with clinically stable mental health disorders who have had > 1 relapse on NRT or bupropion
VHA cost** and average cost per day based on above regimens	SR: \$0.48/tablet \$0.96/day IR: \$0.28/tablet \$0.84/day	14 mg patches: \$2.50/patch \$2.50/day	2 mg gum: \$12.62/50 pieces \$20.12/110 pieces \$0.18-\$0.25/piece \$2.20-\$6/day 4 mg gum: \$13.70/50 pieces \$25.69/110 pieces \$0.23-\$0.27/piece \$2-\$6.50/day	2 mg or 4 mg lozenges: \$29.45/72 lozenges \$0.41/lozenge \$5-8/day	0.5 mg and 1mg tablets: \$1.17/tablet \$2.34/day

<p>Contraindications and relative contraindications</p>	<p>Contraindications:</p> <ul style="list-style-type: none"> • History of seizures • Predisposition to seizures (eg, severe head trauma, CNS tumor, cirrhosis) • Abrupt withdrawal from heavy, daily alcohol or other sedative • MAO inhibitor within 14 days • Bulimia, anorexia nervosa <p>Relative contraindications:</p> <ul style="list-style-type: none"> • Hypersensitivity • Pregnancy category B 	<p>Relative contraindications:</p> <ul style="list-style-type: none"> • Hypersensitivity • Pregnancy category D • Use within 14 days post MI, or in patients with serious or worsening angina • Patients should be advised not to smoke while on NRT 	<p>Relative contraindications:</p> <ul style="list-style-type: none"> • Serious neuropsychiatric disorders (including suicidal and homicidal ideation) • History of suicidal, homicidal, or assaultive behavior in the past 12 weeks • Untreated or unstable mental disorder such as psychotic disorder, bipolar disorder, major depressive disorder, and PTSD • Severe renal impairment • Pregnancy category C
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	Bupropion	Nicotine Transdermal Patch	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge	Varenicline
Comments	<ul style="list-style-type: none"> • Use with caution in patients with liver, kidney failure • Avoid in patients on MAO inhibitors 	<ul style="list-style-type: none"> • In combination with behavioral program, patch doubles the quit rate • Durability of cessation is better with 21 mg patches than with 14 or 7 mg patches • Using the 21 mg patch yields roughly 40-50% the plasma nicotine levels of smoking 1.5 packs per day 	<ul style="list-style-type: none"> • In combination with an intensive behavioral program, nicotine gum can double the quit rate • Using 2 mg ad lib yields roughly 40% plasma nicotine levels of smoking 1 pack per day 	<ul style="list-style-type: none"> • In combination with an intensive behavioral program, nicotine lozenges can increase the quit rate 	<ul style="list-style-type: none"> • Not first-line therapy for smoking cessation • Ask patients about any psychiatric history before prescribing varenicline • Monitor for signs/symptoms of psychiatric illness during use • Monitor serum creatinine levels; as renal function decreases (as seen in elderly patients), dosage reductions may be necessary

* Remove nicotine patch at bedtime.

High dependence: in general, >20 cigarettes per day or use of first cigarette within 30 minutes of awakening.

§ All NRTs have been shown to double 6- to 12-month abstinence rates compared with placebo.

** Cost based on FSS or BIG4 pricing as listed on PBM website (<http://www.pbm.va.gov/PBM/prices.htm>).

Note: Two additional prescription products, a nicotine inhaler and nicotine nasal spray, are FDA approved for NRT; however, these products are not available on the VHA National Formulary. For more information on these products, visit the American Lung Association Smoking Cessation Support website at <http://www.lungusa.org/>.

Combinations of Pharmacologic Therapies Found to Be Effective

Therapy	Dosage and Duration	Comments
Preferred Combinations		
Patch + gum	<ul style="list-style-type: none"> • Studies used patch for >14 weeks • Use standard dosages and durations of each component drug 	<ul style="list-style-type: none"> • Coadministration with RTV ↑ bupropion levels: use cautiously, especially at high dosages.
Patch + bupropion SR		
Alternative Combinations		
Patch + (venlafaxine or paroxetine or nortriptyline)	Studies used highest-dose patch (21 or 22 mg) for 6-8 weeks plus either Paroxetine 20 mg daily for 9 weeks OR Venlafaxine 22 mg daily for 21 weeks OR Nortriptyline 75-100 mg daily for 8-52 weeks	<ul style="list-style-type: none"> • Nortriptyline and other tricyclic antidepressants are CYP 2D6 substrates: consider reducing dosage when given with RTV. Monitor serum levels. Serum levels in smoking cessation studies (in HIV-uninfected patients) ranged from 55 ng/mL to 69 ng/mL. • FPV and DRV decrease paroxetine levels.

Preventing or Addressing Relapse with Patients Who Have Quit

- Congratulate patients at each visit and discuss the benefits and challenges of quitting.
- Use open-end questions relevant to the topics below to discover whether the patient wishes to discuss issues related to quitting:
 - The benefits, including potential health benefits, the patient may derive from cessation
 - Any success the patient has had in quitting (eg, duration of abstinence, reduction in withdrawal)
 - The problems encountered or anticipated threats to maintaining abstinence (eg, depression, weight gain, alcohol, other tobacco users in the household, significant stressors)
 - If the patient is still taking medication, assess effectiveness, side effects, and other medication issues
- Interventions to address barriers to maintaining cessation:
 - **Lack of support:** Refer patients to a group, schedule follow-up phone calls, help identify potential sources of support (individuals, community or religious organizations).
 - **Prolonged withdrawal symptoms:** Prolong pharmacologic interventions or consider combination therapy.
 - **Depressed mood:** Consider using antidepressants and initiating psychotherapy.

- **Weight gain:** Reassure patients that weight gain is common and self-limited, encourage patients to increase exercise, counsel on a healthy diet (avoid strict dieting), preferentially use pharmacologic interventions that cause less weight gain (eg, bupropion, nicotine gum).
- **Flagging motivation:** Reassure patients that flagging motivation is common, check to see if patients might be using tobacco periodically, and counsel that taking even a single puff will increase urges and make quitting more difficult.
- **Smoking lapses:** Suggest continued use of medications, which can reduce the likelihood that a lapse will lead to a full relapse. Encourage another quit attempt or a recommitment to total abstinence. Reassure that quitting may take multiple attempts, and use the lapse as a learning experience. Provide or refer for intensive counseling.



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Substance Use

KEY POINTS

- Substance use disorders (SUDs) are common among people who are HIV infected: 40% of HIV-infected individuals in the United States are associated with injection drug use (IDU), either directly or by having an IDU sex partner.
- Among injection drug users in the United States, 40-45% are HIV infected.
- Substance use is a significant cause of morbidity and mortality in itself, and it is associated with HIV transmission and acquisition.
- Ask all patients about any current or recent use of illicit drugs or alcohol, or misuse of prescription drugs. Ask specifically about injection drugs, opioids, methamphetamines, cocaine, and “club drugs.”
- At each visit, ask the patient directly about his or her substance use. Ask patients about their perceptions of **IMPORTANCE** of the issue and their **CONFIDENCE** in making any kind of change.
- A comprehensive treatment program includes the care of medical providers, psychiatrists to assist with comorbid psychiatric conditions, social workers, housing counselors, case managers, and substance abuse counselors. Group therapy with peer support also may be important.
- Treatment options exist along a continuum and include detoxification, treatment of comorbid conditions, maintenance of treatment, and prevention of relapse.



BACKGROUND

- Substances frequently abused in the United States include alcohol, nicotine, cannabis, prescription medications (narcotics, sedatives, and many others), cocaine, heroin, methamphetamines, tranquilizers, hallucinogens, anabolic steroids, inhalants, and “club drugs.”

Veterans with HIV*

Alcohol use disorder: 33%

Illicit drug use: 30%

Other drug use: 22%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to these conditions

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- Club drugs include methylenedioxymethamphetamine (MDMA, or ecstasy), flunitrazepam (Rohypnol), gamma-hydroxybutyrate (GHB), and ketamine.
- The focus of this chapter is on recognition and management of abuse involving heroin, other opiates, and methamphetamine. Abuse of cocaine, cannabis, and club drugs will be addressed briefly.
- Alcohol misuse and cigarette smoking are discussed in separate chapters (see **Alcohol Misuse**, p. 3 and **Smoking Cessation**, p. 53).

Definitions

Addiction: a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over substance use, compulsive use, continued use despite harm, and craving.

Physical dependence: a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, or administration of an antagonist.

Tolerance: a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

Substance dependence: a maladaptive pattern of substance use, leading to clinically significant impairment or distress, manifested as tolerance (need for increased amounts of the substance or decreased effect with the same amount) or withdrawal symptoms.

Substance abuse: a maladaptive pattern of substance use that has become socially, legally, or occupationally problematic for an individual.

SUD: a more general term comprising substance dependence or abuse.

IDU: includes IV drug use, IM drug use, and skin popping. IDU can involve opiates, methamphetamines, cocaine, sedatives/tranquilizers, or other drugs.

Epidemiology

- Drug abuse is closely associated with HIV infection in the United States: 40-45% of injection drug users are HIV infected, and 25-30% of noninjection drug abusers are HIV infected.
- About 40% of people who are HIV infected are associated with IDU, either directly or by having an IDU sex partner.
- In the United States, 60% of injection drug users are men, 45% are white, 43% have completed high school, and 53% are employed.
- Comorbidities are common: 30% of injection drug users in the United States are PPD positive, 80-90% are infected with hepatitis C, 40% are infected with hepatitis B, and 60% use alcohol.

- Drug abusers are at high risk of unsafe sex practices. For example, cocaine abusers are more likely to involve themselves in prostitution and unsafe sex in order to obtain money for drugs.
- At least one third of drug abusers have an overt psychiatric comorbidity.

Substance Abuse, HIV Infection, and ART

- Cocaine use decreases CD4 cell production by as much as 3- to 4-fold and increases the rate of HIV viral replication by up to 20-fold.
- Methamphetamine binges are associated with interruptions in ART adherence.
- In a prospective cohort study, active drug use was strongly associated with underutilization of ART, nonadherence, and inferior virologic and immunologic responses to ART, compared with former drug use and nonuse of drugs.
- A recent national survey showed that 23% of health providers for HIV-infected patients have a negative attitude score toward treating HIV-infected IDU patients. These providers are less likely to prescribe ARVs to their IDU patients even when the patients meet criteria for starting ART.



EVALUATION

Although there are many reasons to identify patients who abuse substances, and to try motivating them toward treatment, there is little evidence from primary care settings that screening and brief interventions alone are effective. Approaches that focus on the effects of substance abuse on the patient's own health (eg, in terms of poor ARV adherence, acquisition of infections) may be useful. See also **Prevention for Positives**, p. 39.



SCREENING

At initial visit and at least annually thereafter: Ask all patients about any current or recent use of illicit drugs (in addition to alcohol and nicotine), including IDU, opioids, methamphetamines, cocaine, club drugs, and illegally obtained prescription drugs. Check for comorbid psychiatric illnesses.



MANAGEMENT

- Goals for patients: Return to productive functioning.
- Goals for providers: Reduce stigma and treatment bias.
- Treatment includes helping the patient accept the role of having an illness, detoxification, treatment of comorbid conditions, maintenance of treatment, and relapse prevention.

- Treatment ideally involves a comprehensive program of behavioral interventions, though many patients may not accept referral.
- Comprehensive treatment may reduce drug abuse by 40-60%, reduce associated crime by 40-60%, and increase employment prospects by 40%.
- A comprehensive treatment program incorporates the expertise of medical providers, psychiatrists to assist with comorbid psychiatric conditions, social workers, housing counselors, case managers, and substance abuse counselors. Group therapy with peer support also is an important component of treatment.
- Drug therapy alone for treatment of addiction is successful with only 10% of patients.
- For patients unwilling to enter treatment, continue to address their substance use, focusing on reducing use or increasing readiness for drug cessation.

Brief Interventions

At each visit, ask the patient directly about substance abuse. A useful technique for facilitating a patient-centered conversation about the readiness to change is to ask questions about the patient's perception of **IMPORTANCE** of the issue and his or her **CONFIDENCE** in making any kind of change.

Raise Importance

Ask: "On a scale of 1-10, how **IMPORTANT** is it for you to change your substance use?"

"Why did you give it (number) and not a (lower number)?"

"What would it take for you to give it a (higher number)?"

Raise Confidence

Ask: "On a scale of 1-10, how **CONFIDENT** are you that you can change successfully?"

"Why did you give it (number) and not a (lower number)?"

"What would it take for you to give it a (higher number)?"

Management of Specific Substance Use Disorders

Illicit Drug	Behavioral Interventions	Pharmacologic Interventions
<p>Heroin and other opioids</p>	<ul style="list-style-type: none"> • In addition to brief primary care provider interventions suggested above, refer for specialty evaluation and treatment, or to substance abuse counselors in community-based organizations, rehabilitation facilities, and methadone maintenance sites. • Specific psychosocial interventions for opioid use have not demonstrated consistent efficacy. • Opioid agonist therapy is the gold standard for heroin addiction treatment. • If the patient is in withdrawal, or at high risk of withdrawal, refer for detoxification or to an emergency department. If unstable (medically or psychiatrically), refer to an emergency department. • For local (non-VA) substance abuse resources: 800-662-HELP. • Narcotics Anonymous provides group support: http://www.na.org. • Counsel on safe injection practices, including reducing risk of transmission of HIV and other bloodborne pathogens. 	<ul style="list-style-type: none"> • Treat comorbid psychiatric conditions. • Methadone is a full opioid agonist used for opioid agonist therapy in opioid treatment programs. • Methadone maintenance programs typically start with a dose of ≤ 30 mg and adjust to the lowest effective dose that suppresses withdrawal signs and symptoms. Typical dosage is between 60 mg and 120 mg QD. • Adverse effects include constipation, weight gain, drowsiness, excessive sweating, and changes in libido. • Can increase QT interval, precipitating torsade de pointes and other arrhythmias. Avoid use in patients with baseline prolonged QTc; use with caution if coadministered with other medications that prolong QT. • Methadone levels may be lowered by various ARVs; see Potential ARV Interactions, below, and Common Medications, p. 307. • Buprenorphine is a partial mu-opioid agonist and weak kappa antagonist with 25-50 times the analgesic potency of morphine. It has a pharmacologic “ceiling,” and lower risk of overdose and abuse than full opioid agonists. • Buprenorphine use is controlled nationally and within the VHA; physicians are able to prescribe buprenorphine only with special training and a specific DEA certificate. See PBM Criteria for Use at http://www.pbm.va.gov/criteria/Buprenorphine.pdf. • It is administered sublingually. • At high dosages, it may block the effects of full opioid agonists, leading to withdrawal. Therefore, patients should stop taking short-acting opioids 12-24 hours before starting buprenorphine and reduce their

		<p>methadone use to a maximum of 30-40 mg/day.</p> <ul style="list-style-type: none"> • In the United States, buprenorphine is coformulated with naloxone. Naloxone is poorly absorbed sublingually; however, if the tablet is crushed and injected parenterally, the naloxone precipitates opiate withdrawal. • Buprenorphine has been approved for use in office-based opioid dependence treatment. • Buprenorphine is induced over the first 3 days of treatment, with an initial daily dosage of 4-8 mg, increased by 4-8 mg QD until relief from withdrawal symptoms is achieved. The maximum recommended dosage is 32 mg QD. • Side effects include disturbed sleep, drowsiness, sweating, headaches, nausea, constipation, and reduced libido. Mild increases in ALT have been reported. • Buprenorphine may interact with PIs and with EFV; see Potential ARV Interactions, below. • In acute pain episodes, buprenorphine can be used Q8H for analgesic effects. • Naltrexone: opioid antagonist. Precipitates opiate withdrawal; appropriate only for patients with >7 days of abstinence. • Not recommended because compliance is poor; consider as component of substance abuse program for highly motivated patients.
<p>Methamphetamine</p>	<ul style="list-style-type: none"> • If unstable (medically or psychiatrically), refer to an emergency department or hospitalize. • Behavioral interventions are the mainstay of treatment; no pharmacologic agents have proven efficacy. • Refer to outpatient or inpatient behavioral counseling: 	<ul style="list-style-type: none"> • Treat comorbid psychiatric conditions. • Dextroamphetamine “replacement therapy” has not shown greater efficacy than placebo. • Ongoing studies suggest that bupropion may be useful as an adjunct to behavioral therapies. • RTV inhibits amphetamine metabolism and can lead to a 2- to 3-fold increase

	<p>motivational interviewing and cognitive-based therapy (eg, Matrix Model).</p> <ul style="list-style-type: none"> • Refer to harm reduction programs. • Consider referral to contingency management programs that provide vouchers of escalating value for successive urine samples documenting abstinence. • For local (non-VA) substance abuse resources: 800-662-HELP. • Narcotics Anonymous provides methamphetamine-specific groups: http://www.na.org. • Crystal Meth Anonymous: http://www.crystalmeth.org. • Ask about ART adherence at each visit, as methamphetamine users frequently go on binges that lead to interruptions in ART adherence. • Methamphetamine use is associated with unsafe sexual behaviors. Explore risk behaviors, screen for STDs, and counsel on safer sex options; see Prevention for Positives, p. 39. • Provide written or illustrated instructions that can be processed <i>visually</i>, as methamphetamine users often have impaired auditory memory. 	<p>in amphetamine levels. Patients should be educated about this interaction.</p>
<p>Cocaine</p>	<ul style="list-style-type: none"> • Refer to cognitive-behavioral therapy tailored to substance abusers. • For local substance abuse resources: 800-662-HELP. • Narcotics Anonymous also provides cocaine-specific groups: http://www.na.org. 	<ul style="list-style-type: none"> • Treat comorbid psychiatric conditions. • Consider the pharmacologic adjunct naltrexone at 50 mg QD for 12 weeks in combination with participation in relapse prevention programs.

Club drugs
(see below)

- Refer to cognitive-behavioral therapy tailored to substance abusers.
- For local substance abuse resources: 800-662-HELP.
- Narcotics Anonymous also provides group support for club drug users: <http://www.na.org>.
- Treat comorbid psychiatric conditions.
- RTV increases MDMA levels 5- to 10-fold and can increase the risk of fatal heatstroke and dehydration.
- RTV also increases GHB levels, leading to increased risk of seizures, respiratory depression, and loss of consciousness.

**POTENTIAL ARV INTERACTIONS****Methadone:**

- The following may ↓ methadone levels. Monitor for signs of opiate withdrawal. Dosage adjustment of methadone may be needed.
 - NRTIs: ABC
 - NNRTIs: EFV, NVP
 - PIs: ATV, DRV, FPV/r, LPV/r, NFV, SQV/r, TPV/r
- DLV may ↑ methadone levels. Start methadone at low dosage, monitor for methadone toxicity.
- Methadone may ↓ ddl levels. Dosage adjustment not established.

Buprenorphine:

- PIs: May ↑ buprenorphine levels and ↑ risk of adverse effects.
- EFV: May ↓ buprenorphine levels; monitor for signs of opiate withdrawal.
- Dosage adjustment of buprenorphine may be needed.

Cannabis and Club Drugs

The effects of club drugs are less well-characterized. Here is an overview of the effects of cannabis and some common club drugs:

Illicit Drug	Effects	Notes
Cannabis (marijuana) Also known as chronic, pot, weed, grass, Mary Jane, spliff, ganja, hash, skunk, puff, herb, and many other names	Intoxicant, stimulant, psychedelic (mild hallucinogenic), relaxant	<ul style="list-style-type: none"> • Very few people develop physical dependence, but psychological dependence is common. A chronic heavy user can appear apathetic and unmotivated, and may perform poorly at work or school. • Other health risks include increased incidence of respiratory infections, as well as toxicities from adulterants (eg, formaldehyde).

<p>MDMA</p> <p>Also known as ecstasy, E, X, XTC, rolls, beans, Adam</p>	<p>Stimulant, hallucinogenic amphetamine</p>	<ul style="list-style-type: none"> • MDMA is one of the most popular recreational psychoactive drugs, most commonly sold in the form of “ecstasy” tablets. It is known for its empathogenic, euphoric, and stimulant effects. • Physical effects are similar to those of amphetamines. • Between 300 and 400 deaths have been reported from MDMA use and overheating. • Concurrent use with amphetamines, cocaine, or alcohol increases the risk of overheating. • RTV increases MDMA levels 5- to 10-fold and can increase the risk of fatal heatstroke and dehydration.
<p>Flunitrazepam (Rohypnol)</p> <p>Also known as roofies, “date-rape” drug</p>	<p>Benzodiazepine sedative-hypnotic</p>	<ul style="list-style-type: none"> • Flunitrazepam has been used in many “date rapes” in the United States, with cases also reported in Europe and Australia. • 10 times more potent in sedative-hypnotic effects than diazepam. • Causes paralysis, unconsciousness, and short-term amnesia. • Onset occurs within 10 minutes after being taken; the effects peak in 8 hours and last 12 hours. • Mixing with alcohol at higher doses can lead to unconsciousness for several days.
<p>Gamma-hydroxybutyrate (GHB)</p> <p>Also known as liquid ecstasy, GBL (a pro-drug), BDO, GBH, Blue Nitro, Midnight Blue, RenewTrient, Reviar-ent, SomatoPro, Serenity, Enliven</p>	<p>Sedative depressant, anesthetic</p>	<ul style="list-style-type: none"> • GHB is popular on the rave scene. It has effects of alcohol-like intoxication and sexual disinhibition. • Higher doses can lead to disorientation, blurred vision, nausea, vomiting, impaired physical coordination, and muscle spasms. • Onset occurs within minutes; overdose can lead to unconsciousness within 30 minutes. The risk of coma and death is potentiated by concurrent alcohol use. • RTV increases GHB levels, leading to increased risk of seizures, respiratory depression, and loss of consciousness.

<p>Ketamine hydrochloride</p> <p>Also known as K, Special K, Dorothy, cat tranquilizer, tekno, green</p>	<p>Dissociative anesthetic, hallucinogenic (same class as phencyclidine, or PCP)</p>	<ul style="list-style-type: none"> • Ketamine was developed as a veterinary and human anesthetic, but it has become popular in club and rave scenes. • Initial effects are of stimulation and euphoria, followed by sedation and hallucination (out-of-body sensations). Physical effects include nausea and vomiting, slurred speech, lack of coordination, and numbness. • Physical risks include injury resulting from the anesthetic effects. Overdoses can lead to respiratory compromise. • Used chronically, ketamine can increase the risk of drug-induced hepatitis.
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Pain Management in Patients with an SUD

- The prevalence of self-reported pain among HIV-infected patients ranges from 28-97%.
- HIV-infected patients with an SUD are more likely to be untreated or under-treated for pain.
- Pain management in SUD patients may be complicated by opiate tolerance.
- Clinician concerns about pain management in patients with an SUD include:
 - Drug seeking by patients
 - Diversion
 - Relapse to substance abuse
 - Legal repercussions
 - Inadequate knowledge or skills on the part of the clinician
 - Unavailability of specialists
- SUD patient concerns about pain management include:
 - Relapse to substance abuse
 - Anticipated physical discomforts (eg, thinking that medicines will be injected; fearing side effects)
 - Fearing accusations of malingering
 - Perceived “weakness” in taking medications for pain
- Appropriate evaluation of pain in the HIV-infected SUD patient includes:
 - An accurate and complete pain history, including results of previous evaluations; distinguishing between neuropathic and nonneuropathic pain may help guide therapy

- Use of a numeric pain scale to assess and follow severity and response to therapy
- Appropriate and complete evaluation to identify correctable causes of pain (eg, use of ddl or other neurotoxic medication in a patient complaining of painful neuropathy)
- Accurate and complete documentation of findings via CPRS
- Principles of pain management in the HIV-infected SUD patient include:
 - Having a single provider prescribe all pain medications
 - Accurate and complete documentation of the rationale for the treatment used, including dosage, dose interval, amount prescribed, and refill procedures
 - If a patient has an active SUD, referral to a treatment program
 - Agreement with the patient on goals of therapy:
 - In cases of acute pain, elimination of pain is a reasonable goal, with agreement on when the need for therapy will end
 - For chronic pain, the goal should be reasonable relief of pain with a maximum level of functioning
 - Use of specific rules (“contract”) that addresses reports of lost medications, missed appointments etc, to promote accountability and decrease the risk of diversion or drug-seeking behavior; an example of such a contract is available at http://www.painmed.org/pdf/controlled_substances_sample_agrmt.pdf
 - Pretreatment agreement to random urine toxicology screens
 - Use of a stepwise approach to analgesia (see **Pain Medications**, p. 321)
 - Use of nonpsychotropic pain medications, when possible, to achieve pain relief
 - When opiates are indicated, use the minimum dosage needed to relieve pain
 - Around-the-clock dosing is more effective than use as needed
 - Ensuring that adequate pain relief is obtained to prevent self-medication: Increasing dosages may be required if the underlying cause of pain (eg, malignancy) progresses or tolerance develops
 - Referral to a pain specialist for complex management issues or concerns over drug-seeking behavior



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Organ Systems and Metabolic

Anal Dysplasia

KEY POINTS

- HIV-infected patients are at much higher risk of developing squamous cell cancer of the anus (SCCA) than the general population and have a poorer 5-year survival rate once it is diagnosed.
- At-risk populations include all HIV-infected men and women, particularly MSM (with or without HIV infection), any patient with a history of anogenital condyloma, and women with abnormal cervical or vulvar histology.
- All at-risk men and women should be screened for anal cancer at baseline and annually thereafter by digital rectal examination (DRE). Some specialists recommend an anal Pap smear, if available, at baseline and annually thereafter.
- All patients with abnormal cytology of any degree should be referred for high-resolution anoscopy (HRA) and biopsy.



BACKGROUND

- Anal dysplasia denotes precancerous changes in the squamous cells lining the anus. It is associated with human papillomavirus (HPV) infection. Neoplastic changes begin in the basal cell layer of the anal squamous epithelium, at the transformation zone. If untreated, anal dysplasia may progress over time to SCCA.
- Anal HPV infection and dysplasia are analogous to cervical HPV infection and dysplasia; much of the model for evaluation and management of SCCA is based on cervical cancer screening and management. However, no large studies to date have shown that detection and treatment of precancerous anal lesions prevent anal cancer.
- HIV infection is associated with increased rates of anal HPV infection, anal dysplasia, oncogenic HPV types, and SCCA.
- The relative risk of SCCA among HIV-infected individuals compared with the general population ranges from 33 to 222, depending on the cohort.

Veterans with HIV*

Squamous cell cancer of the anus: 1%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to this condition

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- The rate of SCCA is 2 times higher in HIV-infected MSM than in HIV-uninfected MSM.
- Rates of anal HPV infection and abnormal cytology increase with decreasing CD4 counts.
- HIV-infected persons with SCCA are an average of 10 years younger at presentation than HIV-uninfected persons with SCCA.
- HIV-infected persons with SCCA have poorer responses to treatment: the 5-year survival rate is 47-60%, compared with 70-80% in the general population.
- Studies comparing survival rates among patients with SCCA in the years before and after the availability of effective ART in the United States show conflicting results; there is no clear indication that ART improves SCCA outcomes.
- The long lead time between HPV infection and the development of cancer allows for screening and intervention. The value of screening and treatment of anal dysplasia is under investigation.



EVALUATION

Risk factors	<p>Populations of HIV-infected persons at highest risk of HPV infection and anal dysplasia include:</p> <ul style="list-style-type: none"> • MSM • Persons with a history of anal receptive intercourse • Persons with a history of anogenital condylomas • Women with abnormal cervical or vulvar histology • Smokers
Symptoms	<ul style="list-style-type: none"> • Rectal bleeding is present in 45% of patients with SCCA. • Sensation or pain associated with a rectal mass is present in 30% of patients with SCCA; pain may occur with defecation or with receptive anal intercourse. • Pruritus or anal discharge is present in 25% of patients with SCCA. • Approximately 20% of patients with SCCA have no tumor-related symptoms. • Dysplasia usually is asymptomatic.
Physical examination	<ul style="list-style-type: none"> • Check perianal skin for external lesions. • Conduct DRE to check for masses and other lesions. • Check inguinal lymph nodes for enlargement suggesting spread (hard, fixed, progressive).



Summary of Evaluation for Anal Dysplasia

At baseline and annually:

- Ask about symptoms (eg, mass or rectal bleeding).
- Examine perianal skin and inguinal lymph nodes.
- Screen for dysplasia: anal Pap test (where available) using smear or liquid cytology (see below).
- Screen for cancer: DRE

Note: Anal Pap smears should be performed before conducting DRE to avoid contamination of Pap smear with lubricant.

- Routine screening for anal neoplasia is not yet universally adopted for a number of reasons:
 - There is a lack of randomized controlled trials demonstrating that early diagnosis and treatment of anal intraepithelial neoplasia (AIN) leads to decreased rates of anal cancer.
 - Infrastructure for reading anal Pap smears, and for evaluating and treating abnormal anal findings, is not available in many clinics.
 - The sensitivity and specificity for anal Pap smears has been variable. The sensitivity of anal Pap smears has ranged from 69% to 93% and the specificity has ranged from 32% to 59%, compared with diagnosis by HRA-directed biopsy samples.
 - Treatments for HIV-related anal dysplasia have shown mixed efficacy.
- However, accumulating evidence and clinical experience support screening for and treatment of precancerous lesions.
 - Cohort studies show that early detection of anal dysplasia may be beneficial because identification and treatment of small, localized lesions lead to better morbidity and mortality outcomes.
 - A recent analysis of SCCA outcomes in the general population showed that the 5-year survival rate for patients with local disease was 78%, compared with 56% for those with regional disease and 18% for those with distant disease.
 - One small study showed that early detection of anal dysplasia with anal Pap smears was cost-effective.

Anal Pap tests: Currently, there are no universally adopted guidelines for anal dysplasia screening. Many specialists recommend screening all at-risk men and women at baseline and (if normal) annually thereafter.

Anal Pap Test Procedure

- Moisten and insert a Dacron (polyester) swab into the anal canal about 4-5 cm (past the anal sphincter and transformation zone), rotate around the anus to collect cells while removing the swab, while maintaining gentle pressure against the anal canal. Proceed to slide or liquid prep:
 - **Glass slide prep cytology:** Rotate the swab on labeled glass slide, apply fixative, and allow it to dry.
 - **Liquid prep cytology:** Insert the swab into the liquid fixative, swirl around for 15 seconds, remove, and cap the jar. This method avoids drying artifacts.

Note: An anal Pap test must be performed before insertion of lubricant into the anus, because lubricating jelly interferes with smear interpretation. In addition, patients should refrain from using enemas or engaging in receptive anal intercourse for 24 hours before an anal Pap test is performed.

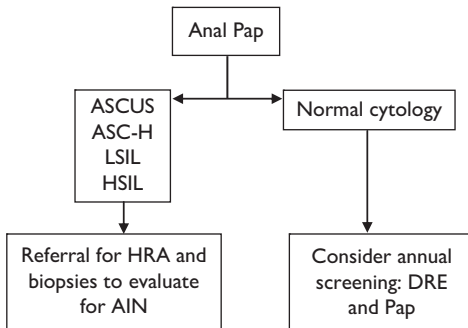
Anal Pap smears should be read by a pathologist trained in their interpretation. Anal cytology is generally graded using Bethesda 2001 criteria, which are ordered as follows:

- Negative for intraepithelial lesion or malignancy
- Atypical squamous cells of undetermined significance (ASCUS)
- Atypical squamous cells, cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
- High-grade squamous intraepithelial lesion (HSIL)
- SCCA

LSIL is sometimes referred to as grade I anal intraepithelial neoplasia (AIN I), whereas HSIL may be referred to as AIN 2 or 3, carcinoma in situ, or Bowen disease.

Rx MANAGEMENT

Management of Abnormal Pap Results



- Any patient with abnormal cytology (ASCUS,ASC-H, LSIL, HSIL) should be referred to GI or General Surgery for HRA and biopsy of visible lesions.
- Note that ASCUS and LSIL findings on cytology do not rule out the presence of HSIL or cancer; follow-up evaluation with HRA is important.
- If HRA is not available at a local VA facility, one option is to refer the patient to a local non-VA provider on a fee basis; a list of anal dysplasia specialists in the United States can be found at <http://www.analcancerinfo.ucsf.edu/resources/index.html>.
 - If HRA cannot be obtained, regular anoscopy can be performed to look for visible lesions. Biopsy should be performed on lesions to determine the degree of histologic changes and rule out invasive cancers. Note that anoscopy is likely to be insensitive.

Treatment

There currently are no consensus treatment guidelines. The treatment options presented here are based on expert opinion.

The focus of treatment is on high-grade, precancerous lesions, particularly HSIL. Lower-grade lesions typically are monitored.

Cytologic Findings	Treatment Options
Condylomata, ASCUS, and LSIL	<ul style="list-style-type: none"> • Monitor via HRA every 6 months until normal twice in succession, then annual Pap smear • Patients with LSIL may opt to receive topical treatment (see below) for symptoms such as bleeding, itching, or burning; or for discrete lesions <p>Follow-up HRA should be done every 6-12 months</p>
HSIL,ASC-H (high probability of AIN grades 2-3)	<p>Topical therapy</p> <p>For small lesions (<1 cm² at the base):</p> <ul style="list-style-type: none"> • Local application of bichloroacetic acid or 80-90% trichloroacetic acid (well-tolerated but occasionally painful) • Liquid nitrogen <p>Other topical, self-applied options studied in small cohorts include:</p> <ul style="list-style-type: none"> • Topical imiquimod applied for 6-10 hours then washed off, TIV for 16 weeks • Topical 5% 5-fluorouracil applied BID for 16 weeks • These sometimes are used to treat diffuse lesions <p>Infrared coagulation (office based)</p> <ul style="list-style-type: none"> • For lesions too large for topical therapy • Followed by debridement of destroyed tissue using biopsy forceps • Note: this treatment is not yet FDA approved

	<p>Surgery and laser ablation</p> <ul style="list-style-type: none"> • For large (>1 cm²) or extensive lesions, or for patients unable to receive infrared coagulation • Surgical excision with a scalpel for discrete lesions with or without laser ablation • Large lesions may require multiple, staged procedures to reduce risk of bleeding, anal stenosis, sphincter compromise, and infection • Referrals should be made to surgical centers with experience in treating anal dysplasia <p>Follow-up HRA should be done every 6 months</p>
SCCA	<p>Full discussion of anal cancer is beyond the scope of this chapter, but special points are noted below:</p> <ul style="list-style-type: none"> • Clinical staging consists of physical examination and biopsy of the primary tumor; palpation of the groin, CT of the chest, and CT or MRI of the abdomen and pelvis • Staging is based on size of tumor (T1-4) and node positivity (N0-3 for nodal metastases) and correlates with 5-year survival rate • First-line treatment consists of chemoradiotherapy rather than surgery

Prevention

The efficacy of HPV vaccines in preventing anal HPV infection is under investigation.



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Androgen Deficiency

KEY POINTS

- Androgen deficiency is relatively common among HIV-infected individuals, although its prevalence has decreased as ART use has increased.
- Symptoms of HIV-associated androgen deficiency can include loss of muscle mass, fatigue, depression, decreased libido, difficulty concentrating, and reduced functional status.
- Testosterone replacement can alleviate these symptoms to varying degrees.
- Men with low-normal serum testosterone but symptoms of androgen deficiency may benefit from replacement therapy.
- Most HIV-infected men with androgen deficiency will have the hypogonadotropic variant rather than testicular failure; measuring follicle-stimulating hormone (FSH) and luteinizing hormone (LH) can help distinguish the two types.
- The use of testosterone replacement in women with HIV-associated wasting remains under study.



BACKGROUND

- Androgen deficiency is defined as sub-normal testosterone production with associated symptoms. Hypogonadism is a more general term that refers to deficient sex hormone production; in men, it refers to defective testosterone production, whereas in women, it refers to defective estrogen production.
- This chapter will address testosterone deficiency in HIV-infected adults; for information on female hypogonadism, see **Women's Health**, p. 249.
- Mechanisms may be *primary* (testicular) or *secondary* (hypothalamic/pituitary).
 - Primary (hypergonadotropic) androgen deficiency: low testosterone (free, bioavailable, or total) + elevated FSH and/or LH.

Veterans with HIV*

Male androgen deficiency: 2%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to this condition

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- Secondary (hypogonadotropic) androgen deficiency: low testosterone (free, bioavailable, or total) + low or normal FSH and/or LH.
- Most HIV-infected men (up to 75%) with decreased testosterone levels have secondary (hypogonadotropic) androgen deficiency.
- Up to 50% of men with AIDS-related wasting had abnormally low testosterone levels in studies done before the availability of effective ART. Many HIV-infected women also have subnormal androgen levels (note that normal testosterone levels in women are approximately one tenth those in men).
- Prevalence of androgen deficiency has declined with the use of ART, but remains substantial: Up to 20% of men on ART with less-than-ideal body weight have abnormally low free testosterone.
- Manifestations in men include reduced muscle mass, decreased strength, fatigue, depression, difficulty concentrating, decreased libido, oligospermia, reduced functional status, and bone loss.
- Manifestations in women are less studied, but include fatigue, decreased libido, and wasting.
- Treatment of hypogonadal HIV-infected men with testosterone can lead to increased muscle mass and quality of life, and improvements in depression. In women, treatment has shown increase in weight and social functioning.
- Among HIV-infected men ≥ 49 years of age, very low total testosterone is associated with viral load $>10,000$ copies/mL, and is inversely associated with African American race.

Possible causes of androgen deficiency in HIV-infected men include:

- HIV infection (mechanism unclear)
- Cirrhosis
- Medications/drugs (eg, opiates, glucocorticoids, ketoconazole, anabolic steroids, megestrol, or testosterone)
- Tumors, infection, or infiltration of the hypothalamus or pituitary gland
 - In addition to endocrine abnormalities, symptoms may include headaches, seizures, visual disturbances (temporal field cuts, diplopia)
 - Prolactinoma
 - Metastatic disease
 - Granulomatous disease
 - Abscess
- Radiation therapy, chemotherapy
- Trauma
- Malnutrition



Symptoms	<p>Note: Onset can be subtle and symptoms may be attributed to other causes (“getting older,” primary depressive disorder, anxiety, chronic illness)</p> <ul style="list-style-type: none"> • Loss of libido • Weight loss, especially of lean muscle mass • Erectile dysfunction • Oligospermia/decreased ejaculate volume • Depressive symptoms, poor concentration • Fatigue • Infertility
Physical examination	<p>To include assessment of muscle mass, secondary sexual characteristics, visual fields. Check for:</p> <ul style="list-style-type: none"> • Small or soft testes (size smaller than approximately 4.5-6.5 cm long × 2.8-3.3 cm wide; suggests atrophy) • Testicular masses (roll each testicle between thumb and 1st two fingers, feeling for fixed or firm masses, which may not be tender) • Gynecomastia; suggests primary androgen deficiency if FSH or LH is elevated
Laboratory evaluation	<p>The measurement of testosterone is less than optimal. Total testosterone usually reflects all circulating testosterone components: free (unbound) testosterone + testosterone bound (loosely) to albumin and (tightly) to sex hormone-binding globulin (SHBG). Only free testosterone and albumin-bound testosterone are bioavailable. SHBG can increase with old age, liver disease, and androgen deficiency itself, thus increasing the total testosterone measured while potentially decreasing the amount of unbound (active) testosterone.</p> <p>Initial evaluation:</p> <ul style="list-style-type: none"> • Serum testosterone: morning blood sample for total testosterone <ul style="list-style-type: none"> • Average serum testosterone levels decrease with age, and there is no absolute cutoff dividing normal from subnormal serum testosterone. One approach defines normal as >2.5 standard deviations below the mean serum total testosterone of healthy young males (approximately 319 ng/dL, per the American Association of Clinical Endocrinologists [AACE]).

- If total testosterone level is below or near normal, most authorities recommend rechecking total testosterone and measuring free testosterone (by equilibrium dialysis or by free testosterone concentration) or bioavailable testosterone. The analog method of measuring free testosterone is not sufficiently accurate.
- FSH, LH to distinguish primary from secondary androgen deficiency.

Other tests:

- Other pituitary hormone levels (prolactin, growth hormone, TSH), if hypopituitarism (hormone levels low) or pituitary adenoma (hormone levels high) is suspected.
- Sperm count and motility, if fertility is an issue.
- Consider MRI if workup suggests hypothalamic or pituitary mass or other abnormality (eg, abnormal pituitary hormone levels, visual field lesions, or neurologic signs).
- Testicular ultrasound if testicular masses are detected on examination.

Rx MANAGEMENT


- Evaluate and treat potential reversible causes of androgen deficiency (see above).
- Testosterone is the preferred treatment for men with documented androgen deficiency (signs and symptoms with abnormal total testosterone usually <200-320 ng/dL, or free testosterone usually <6.5 ng/dL).
- Some authorities recommend testosterone replacement therapy in men with symptoms of androgen deficiency (see **Symptoms**, above), but low-normal testosterone levels.
- Typical recommended dosages for men (note that testosterone is classified as a Schedule III drug by the U.S. Drug Enforcement Agency):
 - IM testosterone (cypionate or enanthate):
 - 100 mg IM every 7 days
 - 200 mg IM every 14 days
 - 300 mg IM every 21 days
 - Longer dosing intervals with higher dosages are more convenient, but risk higher peak levels and greater fluctuations in testosterone level.
 - Transdermal (patch) testosterone: 1 patch (5 mg) applied daily
 - Testosterone gel: 5 mg applied daily to trunk and shoulders
 - Transscrotal testosterone: 6 mg patch applied daily
- For women with HIV-associated wasting and subnormal serum testosterone, twice weekly transdermal testosterone (5 mg twice weekly) for 6 months has been studied as a treatment. This treatment resulted in an increase in muscle

mass with no significant side effects. There are no firm guidelines for testosterone use in women.

- **Testosterone is absolutely contraindicated in men with prostate cancer**; it should be used with extreme caution in men with benign prostatic hypertrophy, and only after urologic consultation.
- **Testosterone is absolutely contraindicated in pregnant women because of adverse effects on the fetus.**
- Testosterone therapy usually is well tolerated. Potential adverse effects of testosterone therapy include:
 - Testicular atrophy
 - Hirsutism
 - Gynecomastia
 - Prostatic enlargement
 - Acne
 - Mood swings (especially with high doses of IM testosterone)
 - Polycythemia (more common with IM testosterone)
 - Elevations in ALT,AST
 - Dyslipidemia
 - Skin irritation at patch site
 - Sleep apnea (rare)
 - In women, testosterone may also cause virilization; start with low doses and monitor closely for adverse effects
- Follow up 2-3 months after starting replacement:
 - Measure serum testosterone response to check for efficacy of dosage:
 - IM testosterone: measure serum testosterone at midpoint between doses
 - Patch: measure 4-8 hours after application
 - Gel: timing not critical, as blood levels are constant
 - Assess for side effects and check hepatic transaminases and hemoglobin/hematocrit.
 - In case of adverse effects, discontinue or lower the dosage of testosterone.
 - With the IM formulation, may consider switching to a transdermal formulation, which gives more even dosing and avoids high peak testosterone levels. May also consider switching from high-dose/less-frequent administration to lower-dose/more-frequent administration.
 - Testosterone therapy may unmask cryptic prostate cancer. Examine the prostate every 6-12 months, looking for prostatic enlargement; check serum prostate-specific antigen (PSA) in older men.

- If significant enlargement on therapy develops, masses or nodules are detected, or PSA becomes abnormally elevated, discontinue testosterone and refer to Urology for evaluation.

Note: Other anabolic steroids such as oxandrolone, an orally available alkylated androgen, are not recommended in place of testosterone, as they do not have the same effects in the body and may convey higher risk of adverse effects, such as hepatic toxicities (peliosis hepatis, hepatoma, cholestatic jaundice) and lipid derangements. Nandrolone, a parenteral androgen with more anabolic properties than testosterone, is no longer available in the United States.

 WHEN TO REFER	
Endocrinology	<ul style="list-style-type: none"> • Lack of symptomatic improvement • Diagnostic uncertainty, especially if secondary androgen deficiency remains in the differential diagnosis • Evidence of hypothalamic or pituitary mass
Urology	<ul style="list-style-type: none"> • Testicular masses • Prostatic enlargement, masses, or nodules, or elevated PSA

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Asthma

KEY POINTS

- Asthma is characterized by airway hyperresponsiveness, inflammation, and reversible obstruction.
- Stepwise, multimodal treatment of asthma may decrease symptoms.
- Patients should know their baseline peak expiratory flow rate (PEFR) measurements and their PEFR thresholds for seeking medical care.
- Drug-drug interactions between PIs and certain medications may affect treatment.



BACKGROUND

- Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning.
- These symptoms are associated with airflow limitation that typically is reversible and responsive to bronchodilator therapy, unlike chronic obstructive pulmonary disease (COPD) (see **COPD**, p. 107).
- In asthma, airflow limitation is secondary to airway hyperresponsiveness and narrowing (increased resistance to flow) caused by inflammation and edema. In contrast, in COPD (particularly in the case of emphysema), airflow limitation is primarily caused by lung tissue destruction and loss of recoil, and is largely irreversible.
- Asthma is best distinguished from COPD (emphysema and chronic bronchitis) by clinical features such as:
 - Marked variability in symptoms
 - No history of cigarette smoking (although some asthmatics may smoke)
 - Onset early in life (although asthma may present in adulthood)
 - History of allergies such as hay fever

Because COPD may demonstrate partially reversible airflow obstruction, the response to a bronchodilator, particularly a single administration in the pulmonary function laboratory, may not reliably distinguish asthma and COPD.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

Epidemiology

- The prevalence of asthma in the United States is approximately 6-11%, depending on the population surveyed (higher prevalence among people living in the inner city).
- 75% of patients with asthma are diagnosed before the age of 7, although asthma may develop at any age.
- A small cross-sectional study of 83 HIV-infected children and young adults showed that 34% of the subjects carried a clinical diagnosis of asthma, and 42% were using rescue bronchodilators.

Veterans with HIV*

Asthma: 6%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to this condition



EVALUATION

Clinical Signs and Symptoms

Risk factors	<ul style="list-style-type: none"> • Atopy • Passive smoking • Upper respiratory tract infections • Beta-blockers (including ophthalmic formulations) 	
History	Favoring diagnosis of asthma	Favoring other diagnosis (especially COPD)
	<ul style="list-style-type: none"> • Wheezing • Cough often worse at night • Shortness of breath • Chest tightness • Episodic symptoms: hours to days • Triggers: exercise (after 10-15 minutes), cold air, exposure to allergens (dust, molds, furry animals, cockroaches, pollens), GERD, aspirin or NSAIDs • Personal or family history of atopy (including allergic rhinitis) • Asthmatic symptoms as a child 	<ul style="list-style-type: none"> • Onset of symptoms at age >50 • History of cigarette smoking • Sputum production • Lack of marked improvement after beta-agonist inhaler or oral steroids
Physical examination	<ul style="list-style-type: none"> • Normal between exacerbations • Wheezes (nonspecific, and may not be present) • Rhonchi • Prolonged expiration 	

	<ul style="list-style-type: none"> • In severe exacerbations (status asthmaticus): <ul style="list-style-type: none"> • Use of accessory muscles • Tachypnea • Tachycardia • Prolonged expiratory phase • Disappearance of wheezing as airflow diminishes (suggests impending respiratory arrest)
Imaging	<ul style="list-style-type: none"> • Chest X ray usually normal; may show hyperinflation in severe disease
Pulmonary function tests	<ul style="list-style-type: none"> • Spirometry (see below) • Peak flow rate assessment (see below)
Differential diagnosis	<ul style="list-style-type: none"> • COPD • Diffuse bronchiectasis • Allergic bronchopulmonary aspergillosis • Constrictive bronchiolitis • Eosinophilic bronchitis • Postviral bronchiolitis (usually reversible with time but not bronchodilators) • Upper airway obstruction (tumors) • Congestive heart failure

Pulmonary Function Testing

Definitions

- **Irreversible airflow obstruction:** a post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio of <0.70 (note: may be less specific in older people).
 - **Reversible airflow obstruction:** increase in post-bronchodilator FEV_1 of ≥ 200 mL or $>12\%$ of predicted value.
 - **Partially reversible airflow obstruction:** post-bronchodilator $FEV_1/FVC <70\%$ of predicted value despite significant bronchodilator responsiveness.
- **Spirometry:** Measure FEV_1 , FVC, and bronchodilator response.
 - **PEFR:** Measure brief, forceful exhalation on a peak flow meter. Peak flow meters are inexpensive, provide objective, reproducible assessments of airflow, and may be ordered through a facility's Prosthetics Service for home use by patients.

The test can be performed with the patient sitting or standing. Instruct the patient to breathe in maximally, put meter to mouth, seal lips around mouthpiece, and blow as hard and as fast as possible into meter.

- Record patients' personal best PEFR when they feel well and have had a number of good trials on the meter.

- **Normal peak flow range is 80-100% of the personal best PEF.**
- Normal variability in PEF is 15-20%. Unchanged PEF in the presence of symptoms suggests a diagnosis other than asthma.
- Average PEFs vary by age, sex, and height.

If initial pulmonary function test (PFT) results are normal or unobtainable, but asthma is still suspected:

- Have the patient record serial PEF measurements and symptoms in a diary to determine whether there is evidence of intermittent airflow limitation that correlates with symptoms such as dyspnea, chest tightness, or cough.
- Repeat evaluation when patient is symptomatic.
- Consider performing serial measurements before and after bronchodilator treatment (this is helpful only if there is baseline airflow limitation at the time of testing).
- To diagnose occupational asthma, test before and after occupational exposures; this can be done with spirometry or PEF. Taking repeated PEF measurements and keeping a symptom diary are simple to do and may provide more useful information.
- Consider performing bronchoprovocation testing (methacholine or exercise challenge) for patients with atypical symptoms, such as chronic (rather than intermittent) cough or with normal baseline pulmonary function. Provocative testing should not be performed in patients who have typical asthma symptoms.

Rx MANAGEMENT

Chronic Asthma

Goals

- ≤ 2 episodes/week of symptoms requiring treatment with short-acting beta-agonist (SABA) medication
- Prevent exacerbations and need for emergency department visits
- Minimize limitations on activity
- Minimize toxicities

Monitoring and Intervention

- **Patients with asthma who use tobacco should be counseled to stop.** (See **Smoking Cessation**, p. 53.)
- At each visit, ask patients whether asthma has woken them from sleep, necessitated more rescue bronchodilator use than usual, necessitated urgent care or emergency room visits, or limited participation in usual activities.
- Ask about control of triggers.
- Instruct patients to perform serial PEF measurements at home and workplace.

- Determine each patient’s baseline PEFR.
- Determine each patient’s PEFR threshold and symptom threshold for escalating therapy or seeking medical evaluation; see **Acute Asthma Exacerbation**, below. Patients should know their baseline PEFRs and their PEFR thresholds. Written plans based on symptoms or PEFR thresholds improve disease control.
- Review and instruct on correct use of inhalers with spacers. Patients who are unable to use spacers properly may need a nebulized formulation of a SABA.
- Use of SABA >2 times per week generally indicates inadequate chronic control and may necessitate a “step-up” in treatment. See below.

Maintenance Treatment according to Severity of Symptoms

Severity	Classification Criteria	Treatment
Intermittent	<ul style="list-style-type: none"> • Symptoms ≤ 2 days/week • Nighttime awakenings ≤ 2/month • SABA use ≤ 2 days/week • No interference with normal activity • $FEV_1 > 80\%$ predicted or PEFR $> 80\%$ personal best; FEV_1/FVC normal • 0-1 exacerbations requiring oral steroids per year 	<p>Step 1:</p> <ul style="list-style-type: none"> • SABA, as needed
Mild Persistent	<ul style="list-style-type: none"> • Symptoms > 2 days/week • Nighttime awakenings 3-4/month • SABA > 2 days/week but not daily • Minor limitation with normal activity • FEV_1 or PEFR $\geq 80\%$; FEV_1/FVC normal • ≥ 2 exacerbations requiring oral steroids per year 	<p>Step 2:</p> <ul style="list-style-type: none"> • Low-dose inhaled corticosteroid (ICS)* • SABA, as needed <p>Alternatives: cromolyn, leukotriene receptor antagonist (montelukast, zafirlukast), nedocromil, theophylline</p>
Moderate Persistent	<ul style="list-style-type: none"> • Symptoms daily • Nighttime awakenings > 1/week but not daily • SABA daily • Some limitation with normal activity • FEV_1 or PEFR $> 60\%$ and $< 80\%$, or FEV_1/FVC reduced 5% 	<p>Step 3:</p> <ul style="list-style-type: none"> • Low-dose ICS* and long-acting beta-agonist (LABA) (eg, salmeterol or formoterol) <p>OR</p> <ul style="list-style-type: none"> • Medium-dose ICS*

	<ul style="list-style-type: none"> • ≥ 2 exacerbations requiring oral steroids per year 	<ul style="list-style-type: none"> • Consider short course of oral steroids (eg, prednisone 40 mg QD for 5 days) when initiating treatment • SABA, as needed <p>Alternatives: low-dose ICS* with leukotriene receptor antagonist, theophylline, or zileuton</p>
Severe Persistent	<ul style="list-style-type: none"> • Symptoms throughout the day • Nighttime awakenings daily • SABA several times per day • Extreme limitation with normal activity • FEV_1 or PEFr $< 60\%$, or FEV_1/FVC reduced $> 5\%$ • ≥ 2 exacerbations requiring oral steroids per year 	<p>Step 4:</p> <ul style="list-style-type: none"> • High-dose ICS* and LABA <p>Step 5 (add to above):</p> <ul style="list-style-type: none"> • Consider omalizumab for patients with allergies, as evaluated by an immunologist

*There are important interactions between some inhaled corticosteroids and certain ARVs. See **Potential ARV Interactions** below.

WHEN TO REFER

- Disease severity moderate persistent or greater: refer to Pulmonary
- Atypical symptoms: refer to Pulmonary
- Elevated IgE levels: refer to Pulmonary or Allergy/Immunology

Acute Asthma Exacerbation

Treatment according to Severity of Symptoms

Severity	Signs and Symptoms	Treatment
Mild	<ul style="list-style-type: none"> • Dyspnea with activity or • $PEFR \geq 70\%$ personal best/ predicted 	<ul style="list-style-type: none"> • Can be managed at home • SABA • Possible short course of oral systemic corticosteroids (5 days)
Moderate	<ul style="list-style-type: none"> • Dyspnea limits usual activity or 	<ul style="list-style-type: none"> • Usually requires emergency department or office visit

	<ul style="list-style-type: none"> • PEFR 40-69% personal best/predicted 	<ul style="list-style-type: none"> • Frequent SABA • Oral steroids (40-80 mg QD) until PEFR >70% personal best/predicted
Severe	<ul style="list-style-type: none"> • Dyspnea at rest, or lack or response to treatments for moderate-severity acute asthma <p>or</p> <ul style="list-style-type: none"> • PEFR <40% personal best/predicted 	<ul style="list-style-type: none"> • Usually requires emergency department or office visit • Frequent nebulized SABA • Oral steroids (40-80 mg QD) until PEFR >70% personal best/predicted
Life Threatening	<ul style="list-style-type: none"> • Too dyspneic to speak <p>or</p> <ul style="list-style-type: none"> • PEFR <25% personal best/predicted 	<ul style="list-style-type: none"> • Requires emergency department visit, usually hospitalization • Nebulized SABA and ipratropium hourly or continuous • PO or IV steroids • Consider magnesium sulfate infusion (2 g), heliox delivered albuterol • Consider intubation in patients with persistent hypercapnia, exhaustion, depressed mental status

Medications and Other Therapies

For acute symptoms and exacerbations	
SABA (eg, albuterol, levalbuterol)	<ul style="list-style-type: none"> • Mainstay of therapy for intermittent disease • Via nebulizer (eg, 0.083% albuterol solution) or metered-dose inhaler (MDI) (90 mcg/puff) • For symptoms: PRN • For exacerbation: 4-8 puffs every 20 min × 3, then Q1-4H PRN
Anticholinergic bronchodilators (eg, ipratropium)	<ul style="list-style-type: none"> • Adjunct to beta-agonists • Via nebulizer (0.03% solution), or MDI (18 mcg/puff, 2 puffs), 4-8 puffs every 20 minutes for up to 3 hours
Systemic corticosteroids (prednisone or equivalent)	<ul style="list-style-type: none"> • For mild exacerbation, prednisone 40-60 mg QD for 5-10 days • For more severe exacerbations, prednisone 40-80 mg QD until PEFR reaches 70% personal best/predicted • Methylprednisolone 60-125 mg IV Q6-12H for severe exacerbations

For long-term control	
Inhaled corticosteroids (ICS); in order of <i>increasing</i> potency (on mg per mg basis): <ul style="list-style-type: none"> • Triamcinolone = flunisolide • Beclomethasone = budesonide • Fluticasone 	<ul style="list-style-type: none"> • Mainstay of therapy for mild disease or greater • See http://www.pbm.va.gov/reviews/oralinhalesteroids.pdf for dosing summary • Start with beclomethasone 200 mcg BID or equivalent • Use lowest dose consistent with disease control • Adding LABA is superior to doubling ICS dose
LABA (eg, formoterol, salmeterol)	<ul style="list-style-type: none"> • Not appropriate for monotherapy; may mask exacerbation • Administer via dry powder inhaler (DPI) • Dosage: formoterol 12 mcg Q12H; salmeterol 50 mcg Q12H
Leukotriene receptor antagonists (eg, montelukast, zafirlukast)	<ul style="list-style-type: none"> • Potential alternative to low-dose ICS for patients with mild asthma unable to use MDI or DPI, or as adjunct to ICS for patients with moderate persistent asthma • Montelukast has not been shown to inhibit CYP 3A4, whereas zafirlukast may inhibit CYP 3A4 and 2C9, potentially interacting with PIs
Mast cell inhibitors (cromolyn, nedocromil)	<ul style="list-style-type: none"> • Potential alternative to low-dose ICS for patients with mild asthma unable to use MDI or DPI, or as adjunct for ICS in patients with moderate persistent asthma • Dosage: 2 puffs QID
Theophylline	<ul style="list-style-type: none"> • Use discouraged because of drug-drug interactions and narrow therapeutic index • Use only with patients who show clinical benefit • Dose using extended-release form; follow levels closely (target level 5-15 mcg/mL) • Initial dosage: 300 mg QD in 2-3 divided doses; a dose increase of 1 mg/kg will increase levels by 2 mcg/mL • Decrease by 50% in patients with liver dysfunction
Omalizumab	<ul style="list-style-type: none"> • Reserved for patients with elevated serum IgE • Use restricted to Pulmonary or Allergy/Immunology services
Oral corticosteroids	<ul style="list-style-type: none"> • 7.5-60 mg QD (or dosed QOD to decrease adrenal suppression)
For prevention of exercise-induced bronchospasm	
<ul style="list-style-type: none"> • Use SABA just before exercise; alternatively, use LABA 15 minutes (formoterol) or 30 minutes (salmeterol) before exercise 	



Inhaled Corticosteroids

Fluticasone:

- **PIs:** caution: ↑ serum fluticasone levels; can cause systemic corticosteroid side effects, including Cushing syndrome
 - Avoid (or limit) use with RTV, particularly in the LPV/r, ATV/r, and DRV/r combinations
 - Even boosting dosages of RTV (eg, 100 mg BID) may ↑ serum fluticasone C_{max} by 2,500%
 - ATV: can ↑ fluticasone levels – use with caution
 - It is unclear whether significant interactions occur between other inhaled steroids and PIs
- **NRTIs, NNRTIs:** no significant interactions expected

Long-Acting Beta Agonists

- CYP 3A4 inhibitors such as RTV may ↑ salmeterol levels

Theophylline

- RTV: ↓ theophylline AUC
- IDV: small ↑ in theophylline AUC
- Monitor and adjust theophylline dosing as needed

Leukotriene receptor antagonists

- Zafirlukast may inhibit CYP 3A4 and 2C9, potentially interacting with PIs (no formal studies); monitor clinically for adverse effects. Montelukast has not been shown to inhibit CYP 3A4.



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Chronic Obstructive Pulmonary Disease (COPD)

KEY POINTS

- COPD comprises emphysema, chronic bronchitis, or a combination of the two.
- COPD is a common cause of morbidity in HIV-infected veterans.
- Multimodal treatment may decrease symptoms and slow progression.
- For smokers, smoking cessation should be emphasized.
- Drug-drug interactions between PIs and inhaled corticosteroids may affect treatment.



BACKGROUND

COPD is:

- A general term that applies to individuals with emphysema, chronic bronchitis, or as is common clinically, a combination of the two.
- Characterized by airflow limitation that is not fully reversible.
- Usually progressive; it is associated with abnormal inflammatory response of the lung to irritants.
- Preventable and treatable.
- Diagnostically defined as a post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio of <0.70 , and lack of alternative explanation for the symptoms and airflow obstruction.

Veterans with HIV*

COPD: 11%

Emphysema: 2%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to these conditions

Epidemiology

- COPD is the fourth leading cause of chronic morbidity and mortality in the United States.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- More than 100,000 people in the United States die each year of complications from COPD.
- Underdiagnosed: Approximately 50% of patients with COPD have not been diagnosed.
- Only 15-20% of individuals with a significant smoking history are ever diagnosed with COPD. This reflects underdiagnosis as well as variability in susceptibility of smokers to the disease.
- HIV-infected subjects were 50-60% more likely than HIV-uninfected subjects to have COPD in a prospective observational study done at VA medical centers.
- After adjustment for age, race, ethnicity, pack-years of smoking, and history of intravenous drug and alcohol abuse, HIV infection has been identified as an independent risk factor for COPD.

Types of COPD

Emphysema	<ul style="list-style-type: none"> • Abnormal and permanent enlargement of the airspaces that are distal to the terminal bronchioles • Usual onset in mid-life; largely irreversible,* often progressive (particularly in smokers who continue to smoke)
Chronic bronchitis	<ul style="list-style-type: none"> • Productive cough for 3 months in each of 2 successive years in a patient for whom other causes of cough have been excluded • Usual onset in mid-life; largely irreversible; often progressive (particularly in smokers who continue to smoke)

* Irreversible airflow obstruction = post-bronchodilator $FEV_1/FVC < 70\%$



EVALUATION

Risk factors	<ul style="list-style-type: none"> • Pack-years of smoking • Increasing age • History of bacterial or <i>Pneumocystis jiroveci</i> pneumonia • History of recurrent respiratory infections • Exposure to occupational or other dust and chemicals • Exposure to environmental (secondhand) tobacco smoke • Exposure to indoor and outdoor air pollution • Low socioeconomic status
History	<p>Dyspnea</p> <ul style="list-style-type: none"> • With exertion • Progressive • Persistent

	<ul style="list-style-type: none"> • Often described as causing “gaspings,” “heaviness,” “difficulty breathing” <p>Chronic cough (may not be present)</p> <ul style="list-style-type: none"> • Intermittent or persistent • Productive or nonproductive <p>Chronic sputum production</p> <ul style="list-style-type: none"> • If present, any pattern of chronic sputum production (even of small amounts) can suggest COPD
<p>Physical examination</p>	<p>Note: Physical examination has low sensitivity and specificity.</p> <ul style="list-style-type: none"> • Vital signs, including respiratory rate (may be elevated), O₂ saturation (may be low), blood pressure, heart rate, temperature (all may be elevated in exacerbations) • Observation: tachypnea, dyspnea, accessory muscle use, hyperinflation, pursed lips • Lungs: prolonged expiratory phase, decreased lung sounds, basilar crackles, wheezes may be present (usually during an exacerbation) • CV: distant heart sounds due to hyperinflation • Extremities: clubbing, cyanosis
<p>Imaging</p>	<ul style="list-style-type: none"> • Chest X rays have low sensitivity for COPD (50%) but may establish alternative diagnoses; radiographic features associated with COPD include flattened diaphragm, increased radiolucency of the lung, long heart shadow, bullae, prominent hilar vasculature suggestive of pulmonary hypertension and cor pulmonale
<p>Pulmonary function tests (PFTs), including spirometry</p>	<p>PFTs and spirometry are the diagnostic tests of choice. Order:</p> <ul style="list-style-type: none"> • Spirometry: airflow loops and measurements • Lung volume (increased in COPD) • Diffusing capacity of the lung for carbon monoxide (D_LCO) (reduced in COPD; normal in asthma) • Consider arterial blood gas (ABG) test for patients with <50% of predicted FEV₁, severe symptoms, and documented or suspected hypoxemia (O₂ saturation by pulse oximetry <88%) • Consider bronchodilator reversibility testing for diagnosis of airway obstruction, particularly if history of asthma symptoms; may see partial but not full reversibility in COPD • Repeat spirometry if there is an increase in symptoms, or a complication
<p>Other evaluation</p>	<ul style="list-style-type: none"> • α₁-antitrypsin deficiency screening: patients of Caucasian descent who develop COPD before age 45 or have a strong family history of early COPD • Exercise tolerance may give useful information; most COPD patients can walk 500-600 meters over a 6-minute period; increases of >50 meters indicate clinically significant response to rehabilitation

Differential diagnosis (keep in mind that patients may have multiple conditions affecting pulmonary function, eg, COPD plus congestive heart failure)	Asthma (see Asthma , p. 97) <ul style="list-style-type: none"> • Reversible airway obstruction, without other features of COPD (see Asthma for distinction between reversible and irreversible airflow obstruction) • Chronic inflammatory disorder; recurrent episodes of wheezing, breathlessness, chest tightness, and coughing • Onset usually in childhood; symptoms vary daily
	Heart failure <ul style="list-style-type: none"> • Orthopnea, crackles, elevated jugular venous pulse (JVP), S3 gallop, volume restriction rather than airflow limitation on PFTs
	Bronchiectasis <ul style="list-style-type: none"> • Large volumes of purulent sputum, bronchial dilation, and wall thickening on chest X ray; high resolution CT scan is diagnostic test of choice
	Tuberculosis <ul style="list-style-type: none"> • Exposure risk, subacute fevers, weight loss, infiltrate on chest X ray
	Bronchiolitis obliterans <ul style="list-style-type: none"> • Younger age, nonsmoker, fume exposure, hypodense areas on CT scan
	Diffuse panbronchiolitis <ul style="list-style-type: none"> • Male, nonsmoker, chronic sinusitis, diffuse small centrilobular nodular opacities on CT scan

R_x MANAGEMENT

Smoking Cessation: Prevention *and* Treatment

- **Smoking cessation** is the single most effective and cost-efficient intervention for most people to reduce the risk of developing COPD and **limit** its progression.
- Brief, 3-minute periods of counseling from a provider to urge a smoker to quit result in smoking cessation rates of 5-10%.
- **For all smokers**, try to incorporate the 5 A's of brief cessation counseling at each visit:
 - **A**sk about tobacco use
 - **A**dvice to quit
 - **A**ssess willingness to make a quit attempt within the next 30 days
 - **A**ssist patients in quitting if they are ready
 - **A**rrange follow-up

See **Smoking Cessation**, p. 53, for more information.

Stable Chronic COPD

Goals: prevent progression, relieve symptoms, improve exercise tolerance, improve health status, prevent and treat complications, prevent and treat exacerbations, reduce mortality

Remember: Counsel for smoking cessation at all stages!

All Patients:


- Avoid triggers and exposures
- Receive annual influenza vaccine
- Receive pneumococcal vaccine every 5 years

Other Treatments according to Stage:

Stage	Spirometric Classification	Treatment
I: Mild	FEV ₁ /FVC <0.70 FEV ₁ ≥80% predicted	<ul style="list-style-type: none">• Short-acting bronchodilator as needed: beta-agonists such as albuterol, levalbuterol, and pirbuterol, and/or anticholinergics such as ipratropium
II: Moderate	FEV ₁ /FVC <0.70 FEV ₁ 50-79% predicted	Short-acting bronchodilator, plus: <ul style="list-style-type: none">• Long-acting bronchodilator (fixed dosing schedule): beta-agonists (eg, salmeterol, formoterol, arformoterol) and/or anticholinergics (eg, tiotropium)• Pulmonary rehabilitation
III: Severe	FEV ₁ /FVC <0.70 FEV ₁ 30-49% predicted	Each of the above, plus: <ul style="list-style-type: none">• Inhaled corticosteroid* for repeated exacerbations (steroid in order of increasing potency: triamcinolone, flunisolide, beclomethasone, budesonide, fluticasone)• For patients with significant symptoms, consider addition of theophylline: may improve symptom control
IV: Very Severe	FEV ₁ /FVC <0.70 FEV ₁ <30% predicted	Each of the above, plus: <ul style="list-style-type: none">• Oxygen supplementation if PaO₂ <60• Consider surgical procedures

Respiratory Failure	PaO ₂ <60 mmHg with or without PaCO ₂ >50 mmHg	Same as “IV:Very Severe” above
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*There are important interactions between some inhaled corticosteroids and certain ARVs. See **Potential ARV Interactions** below.

	WHEN TO REFER
<ul style="list-style-type: none"> ■ Pulmonary rehabilitation (stage II and greater) – refer to Pulmonary or Physical Therapy, depending on facility practice ■ Lung volume reduction (stage IV) – refer to Thoracic Surgery 	

Acute Exacerbations of COPD

This refers to acute increases in symptoms beyond normal daily variation, including 1 or more of the following symptoms:

- **Cough:** ↑ severity and frequency
- **Sputum production:** ↑ in volume or changes in character
- **Dyspnea:** ↑
- Among patients with an acute exacerbation of COPD and a PaCO₂ of >50 mmHg, the 6-month mortality rate is 33%.
- Precipitants include bacterial or viral infection (50-60%), air pollution exposure (10%), and temperature changes.
- In patients with COPD and advanced HIV infection, consider evaluation for respiratory opportunistic infections (eg, *P jiroveci* pneumonia) in the setting of an exacerbation.

Medications and Other Therapies

Beta-adrenergic agonists (albuterol, levalbuterol, pirbuterol)	<ul style="list-style-type: none"> • Mainstay of therapy • eg, albuterol via nebulizer (2.5 mg) or metered-dose inhaler (MDI) (180 mcg [2 puffs]) Q2H
Anticholinergic bronchodilators (ipratropium, glycopyrrolate)	<ul style="list-style-type: none"> • In addition to beta-agonists • eg, ipratropium via nebulizer (500 mcg) or MDI (34 mcg [2 puffs]) Q4H
Glucocorticoids	<ul style="list-style-type: none"> • Methylprednisolone 60-125 mg IV Q6-12H, or prednisone 40 mg PO QD • Treat for up to 14 days; studies show good outcomes with 9 days of treatment • Studies show no difference in outcomes between taper vs abrupt cessation of steroids in courses up to 14 days

Antibiotics	<ul style="list-style-type: none"> • Controversial; studies do not show convincing benefit over placebo • May consider for patients with increased sputum purulence AND increased sputum volume OR for patients with increased dyspnea alone • For patients with severe exacerbations requiring mechanical ventilation (invasive or noninvasive) • Predominant bacteria include <i>Haemophilus influenza</i>, <i>Streptococcus pneumoniae</i>, and <i>Moraxella catarrhalis</i> • For uncomplicated patients ($FEV_1 >50\%$, no antibiotics in past 3 months, <3 exacerbations in last year): doxycycline, TMP-SMX, 2nd or 3rd generation cephalosporin, or extended-spectrum macrolide • For complicated patients (cardiac disease, $FEV_1 <50\%$, antibiotics in past 3 months, ≥ 3 exacerbations in past year): amoxicillin + clavulanate or fluoroquinolone • Treat for 7-10 days
Theophylline	<ul style="list-style-type: none"> • Initial dosage of 400-600 mg/day (long-acting formulation), with target blood level of 5-12 mcg/mL
Oxygen therapy	<ul style="list-style-type: none"> • By nasal cannulae, Venturi masks, non-rebreather masks • Titrate to target pulse oxygen $>90\%$ or $PaO_2 >60-65$ mmHg
Noninvasive positive pressure ventilation (NIPPV) in hospitalized patients	<ul style="list-style-type: none"> • Such as bilevel positive airway pressure • Improves respiratory acidosis, decreases respiratory rate, severity of breathlessness, and length of hospital stay • Studies suggest that NIPPV may reduce mortality and the need for invasive ventilation • Consider in moderate to severe exacerbations with acidemia ($pH \leq 7.35$) and increased work of breathing (eg, $RR >25$); also in patients with $PaCO_2$ above baseline (note that patients with COPD may have stable chronic elevation in $PaCO_2$); compare acute value with baseline



POTENTIAL ARV INTERACTIONS

ARVs and inhaled corticosteroids

Fluticasone:

- **PIs:** Caution: ↑ serum fluticasone levels; can cause systemic corticosteroid side effects, including Cushing syndrome
 - Avoid (or limit) use with RTV, particularly in the LPV/r, ATV/r, and DRV/r combinations
 - Even boosting doses (eg, 100 mg BID) of RTV may ↑ fluticasone C_{max} by 2,500%
 - ATV: can ↑ fluticasone levels – use with caution
- It is unclear whether significant interactions occur between other inhaled steroids and PIs
- **NRTIs, NNRTIs:** no significant interactions expected

ARVs and theophylline

- RTV: ↓ theophylline AUC
- IDV: small ↑ in theophylline AUC
- Monitor and adjust theophylline dosage as needed



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Dermatologic Conditions

This chapter will focus on the diagnosis and treatment of some of the most common dermatological diseases in HIV-infected adults: seborrheic dermatitis, folliculitis, onychomycosis, psoriasis, and HPV-associated warts.

KEY POINTS

- Immunologic status strongly influences the incidence and clinical presentation of many dermatologic conditions.
- At CD4 counts of <50 cells/ μL , patterns in skin findings can become atypical and bizarre.
- In the absence of effective ART, up to 40% of HIV-infected patients and 80% of those with AIDS have seborrheic dermatitis; this condition usually improves with ART.
- Eosinophilic folliculitis is seen more commonly in patients with CD4 counts of <200 cells/ μL , and during immune reconstitution. It usually improves after 6 months on ART.
- Staphylococcal folliculitis is seen more commonly in patients with CD4 counts of <200 cells/ μL . Presumptive treatment should include coverage for MRSA.
- Onychomycosis should be confirmed by KOH preparations of nail clippings before treatment. Oral antifungals interact with many ARVs; consult dosing information before prescribing.
- Psoriasis can be severe ($>50\%$ of the body surface area) in patients with CD4 counts of <200 cells/ μL , particularly those not on effective ART.
- HPV-associated warts are difficult to treat, require multiple treatments, and may recur despite immune reconstitution with ARVs.



BACKGROUND

Epidemiology

- Dermatological diseases are common among HIV-infected persons.
- In one large population study, 69% of HIV-infected patients had cutaneous disease.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- Seborrheic dermatitis is the most common dermatologic diagnosis.
- At CD4 counts of <50 cells/ μ L, patterns in skin findings can be atypical and bizarre.
- Skin findings may represent opportunistic infections or other illnesses.

Veterans with HIV*
Number of visits to dermatology clinic: 7,098

*Veterans in the VA HIV Clinical Case Registry in care in 2007

Dermatologic Conditions according to Clinical Status

Clinical Status	Associated Dermatological Diseases
Most common at CD4 counts of <200 cells/ μ L in patients who are not on effective ART	<ul style="list-style-type: none"> • Severe psoriasis (>50% body) • Extreme photodermatitis • Prurigo nodularis • Molluscum contagiosum (see photo at end of chapter) • Adverse drug reactions • Mycobacteria: <i>tuberculosis</i>, <i>kansasii</i>, MAC • Fungal infections (eg, cryptococcus, aspergillosis) • Herpes zoster • Eosinophilic folliculitis • Bacillary angiomatosis (<i>Bartonella</i>) • Kaposi sarcoma • Lichenification • Diffuse seborrheic dermatitis
May occur at any CD4 count despite ART	<ul style="list-style-type: none"> • Eczema • Xerosis • HPV-associated warts • Kaposi sarcoma (less common at higher CD4 count and with ART) • Staphylococcal and streptococcal skin infections • Drug reactions
May emerge or worsen with immune reconstitution on ART	<ul style="list-style-type: none"> • Acne • Erythema nodosum
Associated with HIV/HCV coinfection	<ul style="list-style-type: none"> • Lichen planus • Xerosis • Leukocytoclastic vasculitis • Pruritus without apparent rash

**Seborrheic Dermatitis***

Etiology	Findings/ Distribution	Diagnostic Clues	Management
<p>May be related to skin-surface yeasts (<i>Malassezia furfur</i>) and environmental factors</p>	<p>Erythematous scaly plaques on the central face, scalp, behind ears</p> <p>Can be pruritic</p> <p>Can affect sternum, axillae, and genital region</p>	<p>More severe, atypical, and diffuse in patients with low CD4 count nadirs</p> <p>Common in patients who are not on ART: up to 40% of HIV-infected patients and 80% of AIDS patients have seborrheic dermatitis</p> <p>Should improve with immune reconstitution on ART</p>	<p>Hydrocortisone 1% ointment mixed with ketoconazole or econazole applied BID to affected area</p> <p>If very itchy: triamcinolone 0.5% ointment in nonfacial areas</p> <p>Scalp: ketoconazole, tar (T-Gel), selenium sulfide (Selsun), or zinc pyrithione (eg, Head & Shoulders) shampoo twice weekly; leave lather on for 5 minutes before rinsing</p>

* See photo at end of chapter.

Folliculitis

Etiology	Findings/ Distribution	Diagnostic Clues	Management
<p>Eosinophilic folliculitis (see photo at end of chapter)</p>	<p>Numerous, extremely itchy pustules on the face, neck, scalp, and trunk</p>	<p>Mainly seen in patients with CD4 counts of <200 cells/μL</p> <p>Can be seen during immune reconstitution in the first 3-6 months on ART</p>	<p>Itraconazole* 200-400 mg daily (for anti-eosinophilic effect)</p>

		Very pruritic, especially on face	Permethrin 5% can be used every other day from the waist up (for drying effect) Should resolve after 6 months on ART
Pityrosporum folliculitis (see photo at end of chapter)	Erythematous papules and tiny pustules along hair follicles	Looks like a milder version of bacterial folliculitis with much smaller lesions Lesions are smaller and less pruritic than eosinophilic folliculitis Commonly excoriated Less likely to form large pustules Overgrowth of tinea	Ketoconazole* 200 mg PO QD for 3 weeks Follow with maintenance therapy using ketoconazole 2% shampoo twice weekly
Staphylococcus folliculitis	Erythematous papules and pustules along hair follicles	Often excoriated Often draining pus Presents as an erythematous flare MRSA common; consider culture to guide treatment	Presumptive treatment for MRSA: <ul style="list-style-type: none"> • TMP-SMX DS BID, or doxycycline, or clindamycin; treat for 10-14 days If confirmed MRSA: <ul style="list-style-type: none"> • dicloxacillin or cephalexin
Pseudomonas folliculitis	Papular lesions appear within 8-48 hours after exposure	Associated with use of hot tub and wet suit/swimwear (lesions may be concentrated in areas covered by swimwear) In immunocompetent persons, self-limited to 7-14 days	For immunosuppressed persons or those with prolonged or severe cases, consider treating with ciprofloxacin for 10 days

*See Potential ARV Interactions, below.

Be sure to differentiate folliculitis and acne.

- Acne presents with red papules and pustules on face, neck, arms, and back.
- It is associated with exogenous testosterone and other systemic steroids, isoniazid, lithium, and antiseizure medications.
- Management: Stop the offending drug, if possible.
- Treat cystic acne with tetracycline, doxycycline, or minocycline. If severe and unresponsive to these antibiotics, consider isotretinoin. Because of its toxicity and teratogenicity, isotretinoin use is restricted in the United States; see VA Criteria for Use at <http://www.pbm.va.gov/criteria/HighlyTeratogenicRetinoidsAndHigh-DoseVitaminACFU.pdf>

Onychomycosis

- Refers to invasion of nails by dermatophytes (tinea unguium; with 3 subtypes), yeast, or molds.
- Dermatophytes cause more toenail infections, yeast cause more fingernail infections, and molds cause <10% of toenail infections.
- Prevalence in the general population is approximately 8%.
- Increased prevalence among patients with HIV infection, with more severe disease if CD4 count is <400 cells/ μ L.
- Thought to be the cause of 50-60% of abnormal-looking nails.
- Differential diagnosis includes psoriasis, eczematous conditions, senile ischemia, trauma, and lichen planus.
- Poor response to treatment: Before starting treatment, inform patients about high rates of treatment failure (25-50%) and recurrence (20-50%).

Type	Findings/ Distribution	Diagnostic Clues	Management
Distal subungual onychomycosis (see photo at end of chapter) Infection with <i>Trichophyton rubrum</i> in vast majority of cases	Affects great toe first; can affect all toes Begins with discoloration of distal corner of nail, spreads across nail, then extends toward cuticle	Culture: most sensitive and specific KOH preparation: clip or file nail-plate and collect scales from most proximal area	Indications for treatment: cellulitis, pain, patient desire for treatment Oral therapies* (in order of decreasing efficacy), pulse dosing: <ul style="list-style-type: none"> • Terbinafine 250 mg QD for 1 week each month • Itraconazole 200 mg QD for 1 week each month • Fluconazole 150 mg once weekly

	Distal nail plate can break off, becoming heaped and irregular	<p>Look for hyphae and arthrospores</p> <p>Low sensitivity and specificity, but up to 100% sensitive if >2 preparations examined</p> <p>If negative, consider biopsy for histopathology</p>	<p>Treat 2 months (fingernails), 3-4 months (toenails)</p> <p>Fluconazole 400 mg once weekly for 6 months has shown efficacy in immunocompromised patients; fluconazole has fewer drug interactions than itraconazole</p> <p>Cure rates range from 76% with terbinafine to 48% with fluconazole</p> <p>Topical therapies generally ineffective; ciclopirox topical nail lacquer can be used with patients who cannot safely take oral therapy; trials show 7% cure rate</p> <p>Surgery: removal of nail in isolated nail infection or dermatophytoma</p> <p>See Potential ARV Interactions , below, and Common Medications , p.307.</p>
Proximal subungual onychomycosis	Discoloration begins at cuticle and extends distally	Same as above	Same as above
Trichophyton rubrum most common			
Marker of HIV infection, immunocompromised state			
White superficial onychomycosis	Starts as dull white spots, then spreads centrifugally	White areas are soft and can be scraped with a curette for culture or KOH slide	Same as above
Trichophyton mentagrophytes most common			

<p>Candida onychomycosis <i>Candida albicans</i></p> <p>More common in patients with HIV infection</p>	<p>Common cause of fingernail infection</p> <p>Often in previously damaged nails</p> <p>Rarely in toenails</p> <p>Nail thickening and discoloration</p> <p>Can lead to onycholysis</p>	<p>Fingernail scraping should be sent for culture of yeast</p>	<p>Oral therapies (in order of decreasing efficacy), pulse dosing:</p> <ul style="list-style-type: none"> • Itraconazole 200 mg QD for 1 week each month • Terbinafine 250 mg QD for 1 week each month <p>Treat 2 months (fingernails), 3 months (toenails)</p>
<p>Mold (eg, <i>Aspergillus</i>, <i>Scopulariopsis</i>)</p>	<p>Rare cause of toenail infection</p>	<p>Consider when dermatophyte infection is ruled out</p>	<p>Oral therapies (in order of decreasing efficacy), pulse dosing:</p> <ul style="list-style-type: none"> • Itraconazole 200 mg QD for 1 week each month • Terbinafine 250 mg QD for 1 week each month <p>Treat 2 months (fingernails), 3 months (toenails)</p>

* See **Potential ARV Interactions**, below, and **Common Medications**, p. 307.

Antifungal safety monitoring:

Terbinafine, itraconazole, and fluconazole can cause hepatotoxicity.

- Obtain pretreatment liver function values.
- Monitor the development of hepatic symptoms.
- Monitor liver function in patients with underlying liver disease.



POTENTIAL ARV INTERACTIONS

Pharmacokinetic interactions between many ARVs (PIs, NNRTIs, and maraviroc) and antifungal medications may significantly affect serum levels of the ARV or the antifungal medication. Some of these require dosage adjustment or careful monitoring, and some combinations are contraindicated. See **Common Medications**, p. 307 for further information.

Psoriasis

(see photo at end of chapter)

Etiology	Findings/ Distribution	Diagnostic Clues	Management
<p>Activation of lymphocytes causes shortened epidermal life cycle (10 times shorter than normal), leading to epidermal hyperproliferation</p>	<p>Silvery scales on red plaques</p> <p>More common on extensor surfaces</p> <p>In HIV infection, can have unusual distribution, such as inverse psoriasis on palms and on soles of feet</p>	<p>More severe and more difficult to treat in patients with low CD4 cell counts</p> <p>Patients with CD4 counts of <200 cells/μL not on ART can have lesions on >50% of body</p> <p>May see unusual presentations of inverse and diffuse psoriasis</p> <p>Biopsy shows epidermal hyperplasia, parakeratosis, neutrophils, diminished granulosum layer</p>	<p>Clobetasol 0.05% ointment BID</p> <p>OR</p> <p>Calcipotriene topical 0.005% ointment BID</p> <p>Ultraviolet light</p> <p>Acitretin 10-25 mg daily; avoid during pregnancy; can cause dyslipidemia</p> <p>Interactions: acitretin + tetracycline carries risk of pseudotumor cerebri; avoid combination</p> <p>In cases of extensive psoriasis, consider initiating ART (or maximizing efficacy of ART)</p>

Topical steroid relative potency (1 = least potent; 10 = most potent)

1	4	7	10
<p>Hydrocortisone 1% cream/lotion/ointment</p>	<p>Triamcinolone (TAC) 0.1% cream/ointment</p> <p>Alclometasone 0.05% cream/ointment</p> <p>Desonide 0.05% cream/lotion/ointment</p>	<p>Fluocinonide (Lidex) 0.05% cream/gel/lotion/ointment</p>	<p>Clobetasol 0.05% cream/gel/ointment/solution</p>

HPV-Associated Warts

(see photo at end of chapter)

Etiology	Findings/ Distribution	Diagnostic Clues	Management
<p>Human papillomavirus; most common subtypes 6, 11; also associated with dysplastic subtypes 16, 18, 31, 33, 35</p> <p>Worse and more difficult to treat in patients with low CD4 nadirs</p>	<p>Condyloma acuminata: soft, skin-colored fleshy warts</p> <p>Perianal lesions can be rough and cauliflower-like</p> <p>In and around genitalia and anus, around mouth, palmar surface of hands, on feet</p>	<p>Can recur despite effective ART</p>	<p>Can recede on their own in 3 months with or without ART</p> <p>Start with liquid nitrogen (10-second bursts with 30-second thaw), podophyllin (for genital warts), or paring (for large lesions) every 3 weeks for 12 sessions</p> <p>Patients can be instructed to use duct tape and other exfoliative techniques at home between office treatment sessions (eg, for lesions on the extremities, apply duct tape nightly and pull off during the day; use pumice stone daily to sand down lesions)</p> <p>For genital warts, may add imiquimod if initial treatment is not effective</p> <p>Consider laser treatment, surgical excision (and send for pathology)</p> <p>Repeat treatments are usually required</p> <p>Can recur after any of the treatment modalities; none is 100% effective</p> <p>For anal lesions, see Anal Dysplasia, p. 83.</p>

Glossary of Dermatologic Descriptors

Primary Lesions

Macule: circumscribed area of skin, up to 1 cm in diameter, with a change from normal skin color, which is neither raised above nor depressed below the surrounding skin. Many use the term for lesions much larger than 1 cm. Term does not include purpura.

Patch: a flat, circumscribed, discoloration of skin or mucous membrane >1 cm in diameter.

Papule: discrete solid area of skin that is elevated by palpation above the surrounding skin and <1 cm in diameter. Variations include acuminate, keratotic, flat-topped, follicular, umbilicated, pedunculated, and necrotic.

Plaque: similar to a papule but >1 cm in diameter. Often formed by the confluence or coalescence of papules. Secondary features may include, among others, atrophy, lichenification, and hyperkeratosis.

Nodule: discrete, solid, palpable, round or oval (ellipsoidal) lesion of the skin measuring ≤ 1 cm in diameter (or long axis). Applies to processes involving any or all levels of the skin, and is a general term for any mass, benign or malignant.

Tumor: a term used by some for a “nodule” >1 cm in diameter. Applies to processes involving any or all levels of the skin, and is a general term for any mass, benign or malignant.

Vesicle: a circumscribed fluid-filled lesion <1 cm in diameter that usually is elevated above the surrounding skin. May be described as solitary, grouped, umbilicated, dyshidrotic, spongiotic, multilocular, or unilocular.

Bulla: a circumscribed fluid-filled lesion >1 cm in diameter that usually is elevated above the surrounding skin. May attain diameters of several cm and are described as tense or flaccid.

Pustule: discrete elevated vesicle or bulla of skin, usually small, containing purulent exudate composed of inflammatory leukocytes (pus), with or without cellular debris. May be superficial, deep-seated, follicular, grouped, etc, and may arise secondarily from a vesicle.

Wheal: an evanescent, round or irregular, often flat-topped elevation of skin with a pale red color, arising from edema in the superficial dermis. May vary from 2-3 mm to 10 or more cm in diameter, with round or arcuate configurations. Should be distinguished from angioedema, a massive edema involving the entire dermis and subcutaneous tissues.

Secondary Lesions

Scar: a hard plaque of dense fibrotic tissue covered by a thin epidermis. A mark of injury from any sort of process (physical or pathologic).

Atrophy: usually refers to thinning of the epidermis leaving an easily wrinkled or shiny surface. Atrophy also may apply to thinning of dermal or subcutaneous tissue, with or without changes in the epidermis.

Ulcer: loss of skin tissue or substance from the surface downward, leaving an uncovered or denuded wound that is slow to heal.

Erosion: a superficial denudation of the skin, usually implying the loss of the epidermis.

Fissure: a vertical splitting or separation of the skin.

Crust: dried surface fluid, often serous (inspissated serum), with or without tissue debris; includes the term “scab.”

Excoriation: a scratch mark, often with denudation of the skin to form a small ulcer. Exposure of the corium by mechanical removal of the epidermis.

Scale: a thin flake of epithelium (mostly composed of corneocytes) that is separated from the underlying intact skin proper.

Lichenification: a thickening of the skin surface *and* an increase of skin markings, usually seen with chronic coalescence of papular lesions, especially atopic eczema.

Vegetating: a lushly growing, proliferating process, usually with elevated or exophytic features.

Linear/Figurate: technically **not** secondary features, but included here for convenience. These are **configurations** that skin lesions may assume, and the descriptors aid in their diagnostic identification. Figurate includes geometrical shapes (eg, annular, arciform, cyclic).



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Dermatological Images

Molluscum Contagiosum

<http://dermatlas.med.jhmi.edu/derm/IndexDisplay.cfm?ImageID=-280318089>

Seborrheic Dermatitis

<http://dermatlas.med.jhmi.edu/derm/IndexDisplay.cfm?ImageID=-586555642>

Eosinophilic Folliculitis

<http://dermatlas.med.jhmi.edu/derm/IndexDisplay.cfm?ImageID=1059415431>

Pityrosporum Folliculitis

<http://dermatlas.med.jhmi.edu/derm/IndexDisplay.cfm?ImageID=1689503733>

Onychomycosis, Distal

<http://dermatlas.med.jhmi.edu/derm/IndexDisplay.cfm?ImageID=-1998842971>

Psoriasis

<http://dermatlas.med.jhmi.edu/derm/IndexDisplay.cfm?ImageID=77950693>

HPV-Associated Warts

<http://dermatlas.med.jhmi.edu/derm/IndexDisplay.cfm?ImageID=197153797>

KEY POINTS

- Diabetes is an independent risk factor for CAD and significantly increases the risk of stroke, peripheral vascular disease, retinopathy, chronic kidney disease, and dementia.
- Preventive health care is critical for patients with diabetes to reduce the risks of CV and cerebrovascular disease, limb loss, vision loss, and renal damage.
- The risk of diabetes for HIV-infected patients consists primarily of traditional factors, with some added risk from the use of PIs and NRTIs, which may exacerbate underlying diabetes risk.
- Primary prevention:
 - Screen for diabetes and impaired fasting glucose with a fasting glucose test before starting ARVs, and 3 months after starting or changing ARVs. If initial screening results are normal, check fasting glucose annually. If impaired fasting glucose is present, check every 3-6 months.
 - Encourage weight loss for patients who are overweight, and exercise for all.
- Secondary prevention:
 - For treatment of Type 2 diabetes, start with monotherapy (metformin is preferred for obese patients); sequentially add other classes of oral agents. If the HbA1c goal has not been reached with use of ≥ 2 oral agents, add insulin.
 - Reduce CV risks by controlling blood pressure and lipid levels, counseling on smoking cessation, and initiating antiplatelet therapy.
- Tertiary prevention:
 - Screen annually for:
 - Renal disease
 - Retinopathy (dilated eye examination)
 - Lower extremity complications

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.



BACKGROUND

- Diabetes is an independent risk factor for the development of CAD and is considered a CAD risk equivalent for the purposes of lipid management and antiplatelet therapy (see **Dyslipidemia**, p. 143).
- Diabetes significantly increases the risk of stroke, peripheral vascular disease, retinopathy, chronic kidney disease, and HIV dementia.
- Risk of diabetes for HIV-infected patients consists primarily of traditional factors (see **Evaluation**, below).
- PIs and some NRTIs confer added risk of Type 2 diabetes, and these medications may exacerbate underlying diabetes risk.
- New-onset diabetes is estimated to occur in 1-6% of HIV-infected patients on PIs. In one study, 7% of patients on PIs were diagnosed with diabetes using the oral glucose tolerance test (OGTT).
- The same study showed that an additional 16% of patients had impaired glucose tolerance (IGT).
- The pathogenesis of insulin resistance among patients on PIs is not fully understood. It is hypothesized that inhibition of the GLUT-4 insulin-stimulated glucose-transport system by some PIs plays a role.
- NRTIs that affect fat distribution can cause an increase in lipolysis, which can lead to a higher risk of insulin resistance.
- Increased insulin resistance is seen among patients who have developed lipohypertrophy, with a dorsocervical fat pad (“buffalo hump”) or increased upper chest fat or intraabdominal fat.
- Obesity is a major risk factor for Type 2 diabetes in HIV-infected persons and in the general population.

Veterans with HIV*

- Diabetes, Type 2: 15%
- Diabetes, Type 1: 3%
- Ischemic heart disease: 11%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to these conditions

Definitions

State	Definition/Diagnosis
Insulin resistance	<ul style="list-style-type: none"> • Failure of target tissues to respond appropriately to insulin • This leads to decreased muscle uptake of glucose and sometimes to increased hepatic gluconeogenesis. Insulin production is increased to overcome the insulin resistance and maintain glucose homeostasis. Over time, even high levels of endogenous insulin may not control serum glucose levels, resulting in IGT, followed by diabetes.

Impaired fasting glucose	<ul style="list-style-type: none"> Fasting blood glucose (FBG) (>8-hour fast) = 100-125 mg/dL
IGT	<ul style="list-style-type: none"> Serum glucose \geq140-199 mg/dL on 2-hour OGTT (serum glucose 2 hours after intake of 75 g oral glucose)
Diabetes mellitus	<ul style="list-style-type: none"> FBG \geq126 mg/dL, or Random glucose \geq200 mg/dL + symptoms, or 2-hour OGTT \geq200 mg/dL Results must be confirmed by retesting (any method) on a different day



EVALUATION

History

Risk factors include:	Medications that increase diabetes risk include:
<ul style="list-style-type: none"> Family history of diabetes Increasing age Obesity Fat redistribution Hepatitis C Medications (see list at right) 	<ul style="list-style-type: none"> PIs: Most (except unboosted ATV) have been implicated, particularly: <ul style="list-style-type: none"> IDV RTV LPV/r NRTIs: d4T, ddI Pentamidine Niacin Human growth hormone Corticosteroids Antipsychotics: including olanzapine, quetiapine, ziprasidone



SCREENING

- Fasting glucose (and fasting lipid panel) before starting ARVs
- Fasting glucose
 - 3 months after starting or changing ARVs
 - Every 3-6 months for patients with IGT, to screen for diabetes and need for treatment
 - Annually, if initial glucose measures are within normal limits

- Consider 2-hour OGTT for patients with impaired fasting glucose or significant risk factors (eg, family history, obesity, fat redistribution)

Initial Evaluation of Newly Diagnosed Diabetic Patients

Physical examination	<ul style="list-style-type: none"> • Blood pressure • Weight, height, and BMI (BMI is available through the Vitals section of the CPRS Cover Sheet; see Dyslipidemia, p. 146, for BMI formula) • Retinal eye examination (refer to Ophthalmology for dilated examination) • Foot risk assessment: <ul style="list-style-type: none"> • Visual inspection of feet for breaks in skin, erythema, trauma, pallor on elevation, dependent rubor, changes in size/shape of foot, nail deformities, extensive callus, tinea pedis, edema • Neurologic examination: <ul style="list-style-type: none"> — Monofilament test for decreased sensation — Vibratory sense at great toe IP joint, pinprick sensation over hallux, ankle reflexes (for peripheral neuropathy) • Peripheral pulses, presence of foot hair • Limb-threatening conditions: acute ischemia, foot ulceration, puncture wound, ingrown toenail, signs of systemic infection
Laboratory evaluation	<ul style="list-style-type: none"> • Glycosylated hemoglobin (HbA1c): reflects glycemia over previous 3-month period • Fasting lipid panel • Electrolytes, BUN, creatinine (assess for renal function and metabolic acidosis) • Urine albumin/creatinine ratio (microalbuminuria: 30-299 mcg/mg; macroalbuminuria: ≥ 300 mcg/mg; see Renal Disease, p. 211) • LFTs • TSH

R_x MANAGEMENT

Basic Concepts

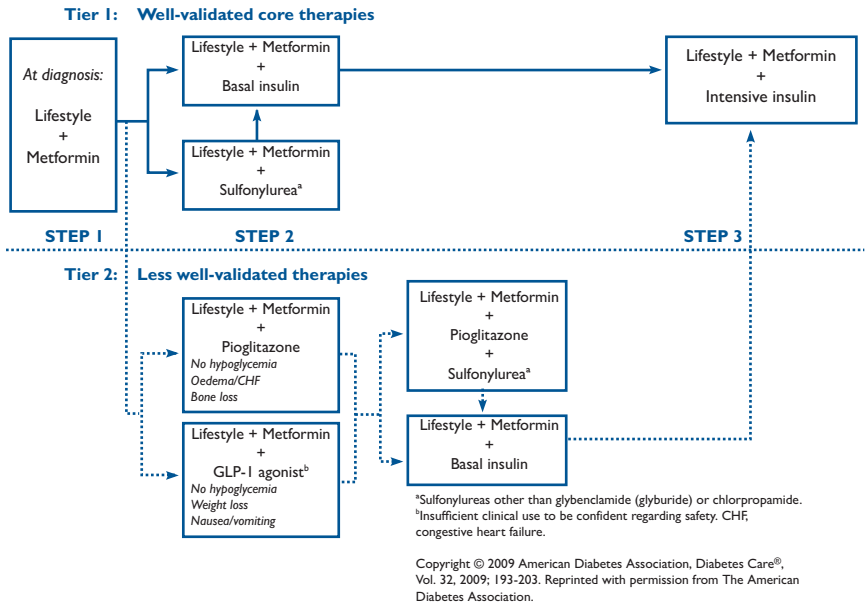
- Standards of treatment and management of diabetes for patients with HIV generally are the same as those for diabetic patients without HIV; see below.
- Emphasize behavior modification in **all** patients with IGT and Type 2 diabetes; see below. This includes:
 - Avoiding obesity
 - Weight loss for those who are overweight

- Diet
- Exercise
- Minimizing alcohol intake
- Refer all patients for basic diabetes education.
- Treatment goals:
 - HbA1c <7%, while avoiding hypoglycemia.
 - Less-stringent goals may be appropriate for patients with advanced microvascular disease, comorbidities, or short life expectancy.
 - **Note:** Recent studies in HIV-uninfected patients with Type 2 diabetes have failed to prove that patients with tighter glucose control (HbA1c <6.5%) have better CV outcomes than patients with somewhat higher HbA1c levels, and in one study, more-intensive glycemic control was associated with more CV events.
 - Reduce other CV risks by controlling blood pressure and lipid levels, counseling on smoking cessation, and initiating antiplatelet therapy.
 - Glycemic control may reduce microvascular disease but may not reduce risk of macrovascular events, including MI. Controlling other CV risk factors in diabetic patients is critical.
 - Reduce risks of limb loss, vision loss, and renal injury.
- For Type 2 diabetes, start with monotherapy (metformin is preferred for obese patients). Sequentially add other classes of oral agents if needed. If the HbA1c goal has not been reached on ≥2 oral agents, add insulin. Oral sulfonylurea should be stopped if the patient is taking insulin more than once a day.
- Note that PI-related diabetes tends to be nonketotic and usually responds to oral agents.
- Self-monitoring of blood glucose (SMBG) is critical for maintaining glycemic control; glucometers and test strips can be ordered through the Prosthetics Service at the local VA Medical Center.

Switching ART Regimens

- For patients who are taking ARV agents that may be causing or exacerbating hyperglycemia, consider discontinuing the problematic ARVs if safe and effective alternatives are available.
 - For example, substitute ATV or an NNRTI in place of a PI, or an unboosted PI (eg, ATV or FPV) for an RTV-boosted PI.
 - Replace d4T with another agent.
- Before making ARV substitutions, carefully consider the possible effect on HIV virologic control and the potential adverse effects of new ARVs.
- In some cases, antidiabetic agents may still be necessary after ARV substitution.

Figure 1. Algorithm for the Metabolic Management of Type 2 Diabetes



- Reinforce lifestyle interventions at every visit.
- Check HbA1c every 3 months until the goal is reached and then at least every 6 months. The interventions should be changed if HbA1c is above goal.
- Thiazolidinediones are nonformulary within the VHA; see PBM Criteria for Use at <http://www.pbm.va.gov/criteria/TZD%20criteria.pdf>.

Management of Diabetes Mellitus

Intervention	Dosage	Comments
Behavior modification	Reinforce at every visit	<ul style="list-style-type: none"> • Institute for all patients • Weight loss for overweight or obese patients, avoiding overweight for others • Limit alcohol use (no more than 2 standard drinks/day for men, 1 standard drink/day for women; see Alcohol Misuse, p. 3) • Balanced American Diabetes Association diet (see http://www.diabetes.org/home.jsp for further information) • Daily exercise; at least 2.5 hours per week • For further resources, see <i>MOVE!</i> (http://www.move.va.gov), the VA NCP weight management program (http://www.diabetes.org), and the VA Obesity Clinical Practice Guidelines (http://vawww.oqp.med.va.gov/CPGintra/cpg/cpg.htm)

Diet	<ul style="list-style-type: none"> • 50-60% carbohydrates (preferably complex) • 10-20% protein • <30% fats (<7% saturated fats) • <300 mg/day of cholesterol • Limit trans fats 	<ul style="list-style-type: none"> • Institute for all patients • Refer for dietary counseling and diabetes education as needed • For further resources, see <i>MOVE!</i> (http://www.move.va.gov), the VA NCP weight management program (http://www.diabetes.org), and the VA Obesity Clinical Practice Guidelines (http://vawww.oqp.med.va.gov/CPGintra/cpg/cpg.htm)
Education	<ul style="list-style-type: none"> • As needed 	<ul style="list-style-type: none"> • Refer all patients for diabetes education

Medications

Oral agents

Biguanide: metformin	<ul style="list-style-type: none"> • Start with 500 mg BID or 850 mg daily • Increase as needed to 850 mg TID or 1,000 mg BID (maximum of 2,550 mg/day divided into 2-3 doses) 	<ul style="list-style-type: none"> • Preferred first-line treatment for most patients, especially those with BMI >25 • Insulin sensitizer • May promote weight loss, which is useful for overweight patients • Potential adverse effects: nausea, diarrhea, gas, abdominal pain (take with food to reduce GI effects), lactic acidosis • Contraindicated in renal insufficiency (men: Cr level >1.5 mg/dL; women: Cr level >1.4 mg/dL), CHF • For patients on NRTIs, especially d4T and ddl, there may be compounded risk of lactic acidosis • May improve lipoaccumulation (mixed results in studies) but may worsen lipodatrophy
Sulfonylureas: glyburide, glipizide	<ul style="list-style-type: none"> • Glyburide: start with 1.25-2.5 mg QAM or BID (maximum of 20 mg/day, may be divided into 2 doses) <p style="text-align: center;">OR</p> • Glipizide: start with 2.5-5 mg QAM; maximum of 40 mg/day (divided into 2 doses) 	<ul style="list-style-type: none"> • Increase insulin secretion • Dose cautiously in patients with renal insufficiency: glyburide is 50% renally cleared and has T_{1/2} of 10 hours; glipizide is 80% renally cleared and has T_{1/2} of 2-5 hours; start at low dosage, increase slowly; decrease dosage or discontinue if renal function worsens

	<p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Glipizide XL 5-10 mg QAM • Take 30 minutes before a meal 	<ul style="list-style-type: none"> • Glipizide does not have an active metabolite; use preferentially in chronic renal failure • Potential adverse effects: hypoglycemia, weight gain (approx. 4-5 lb in the first year), rash, elevation of serum transaminase levels
<p>Thiazolidinedione: pioglitazone rosiglitazone</p>	<ul style="list-style-type: none"> • Start with 15 mg QD • Increase as needed, up to 45 mg QD 	<ul style="list-style-type: none"> • Only for combination therapy in selected patients; see PBM Criteria for Use at http://www.pbm.va.gov/criteria/TZD%20criteria.pdf • Not recommended for monotherapy unless: <ul style="list-style-type: none"> • Patient is intolerant of or has contraindications to both sulfonylureas and metformin; and • Target HbA1c is likely to be attained • Absolute contraindications: <ul style="list-style-type: none"> • Type I diabetes or prediabetes • CHF: NYHA Class III or IV • Active liver disease or ALT >2.5 times upper limit of normal • Jaundice or CHF on another thiazolidinedione • Currently not on VHA formulary; pioglitazone is the preferred agent for nonformulary use • Monitor fluid/volume status • Potential adverse effects: weight gain (~10 lb in first year of treatment), edema, CHF; reduction in bone mineral density in women; possible increased risk of MI; caution in patients with high risk of CV events (particularly with rosiglitazone) • Rosiglitazone: studies conflict, but possible increased risk of MI and CV death

		<ul style="list-style-type: none"> • May improve nonalcoholic hepatic steatosis • May improve lipoatrophy (mixed results in studies) 	
Sitagliptin	<ul style="list-style-type: none"> • 100 mg QD <ul style="list-style-type: none"> • Reduce to 50 mg QD for patients with CrCl 30-50 mL/min • Reduce to 25 mg QD for patients with CrCl <30 mL/min and ESRD 	<ul style="list-style-type: none"> • Nonformulary in VHA • Only for patients who meet specific criteria; see PBM Criteria for Use at http://www.pbm.va.gov/criteria/Sitagliptin.doc • Potential serious adverse effects include anaphylaxis, angioedema, and Stevens-Johnson syndrome 	
Exenatide	<ul style="list-style-type: none"> • 5 mcg SQ BID 	<ul style="list-style-type: none"> • Nonformulary; restricted to diabetes specialists in VHA 	
Insulin	See below for formulations and dosing; potential adverse effects: weight gain, hypoglycemia		
	Onset	Peak (hours)	Duration (hours)
Rapid acting			
Insulin lispro	10-15 min	1-2	3-5
Insulin aspart	10-15 min	1-2	3-5
Short-acting: regular	0.5-1 h	2-4	4-8
Intermediate acting			
NPH	1-3 h	4-10	10-18
Lente	2-4 h	4-12	12-20
Long acting			
Insulin detemir	2-3 h	None	Up to 24
Insulin glargine	2-3 h	None	24+
Premixed insulins			
70/30 (70% N + 30% R)	0.5-1 h	2-10	10-18
75% NPL + 25% lispro	10-15 min	1-3	10-16
70% NPA + 30% aspart	10-15 min	1-3	10-16

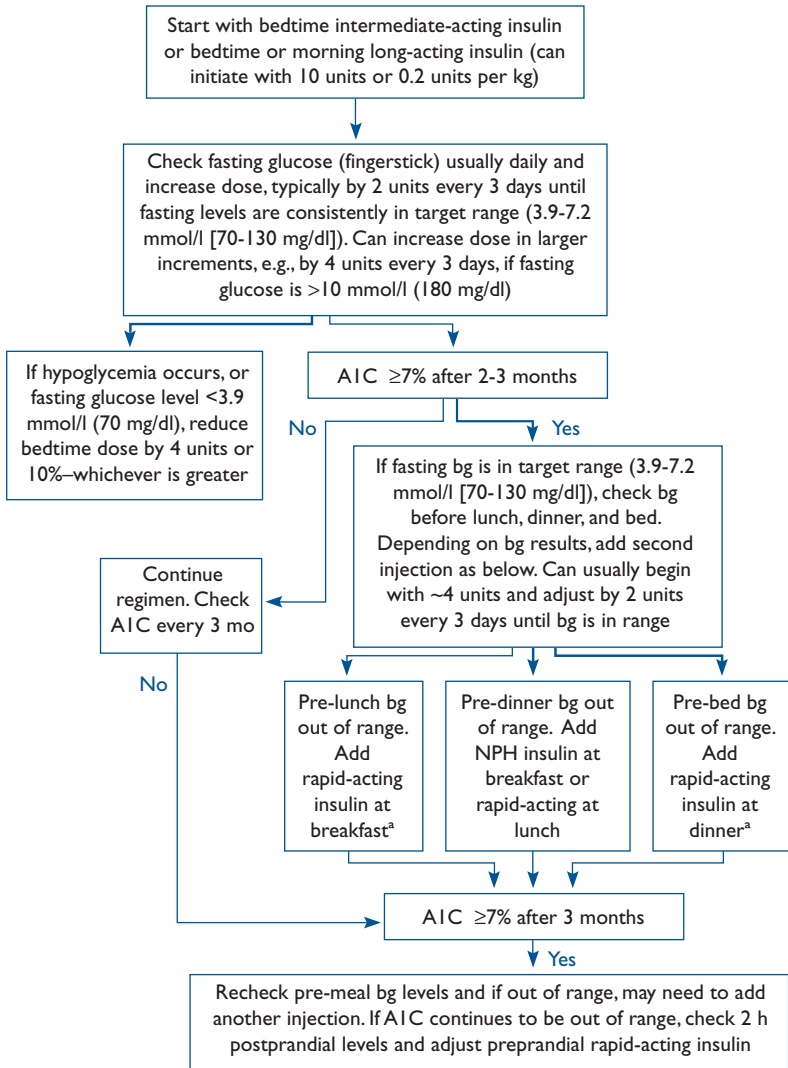
Abbreviations: N = NPH; NPA = neutral protamine aspart; NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro; R = regular

Note: Glargine cannot be diluted or mixed with other insulins.

Insulin regimen selection

- Optimal insulin dosing mimics physiologic insulin release and consists of a basal component along with a prandial component, which is used to metabolize ingested carbohydrates.
- Individualization of insulin therapy is critical for ensuring optimal glycemic control.
- SMBG is critical to successful glycemic control with insulin.
- Patients should be educated regarding symptoms of hypoglycemia (eg, sweating, anxiety, disorientation, tachycardia) and instructed to ingest hard candy, juice, or another rapidly absorbed glucose source if symptoms occur.
- **Insulin dosing for Type 1 diabetes**
 - First choice: glargine + premeal regular insulin (rapid-acting analogues [lispro and aspart] are preferred because of improved glycemic control and decreased risk of hypoglycemia; administer 10-15 minutes before or immediately after meals)
 - Second choice: NPH or detemir 2 times per day + premeal regular insulin (lispro or aspart preferred)
 - Third choice: NPH 2 times per day or at night + regular insulin (lispro or aspart) TID; the patient must not miss meals
 - Starting basal dosage is 0.6 units/kg per day, given as 1 dose of glargine or divided as 2 doses of NPH or detemir; adjust dosage based on SMBG
 - Starting prandial dosage is 5-10 units given 10-15 minutes before or immediately after meals; adjust dosage based on SMBG
- **Insulin dosing for Type 2 diabetes** (see Figure 2)

Figure 2. Initiation and Adjustment of Insulin Regimes



Insulin regimens should be designed taking lifestyle and meal schedule into account. The algorithm can only provide basic guidelines for initiation and adjustment of insulin.

^aPremixed insulins not recommended during adjustment of doses; however, they can be used conveniently, usually before breakfast and/or dinner, if proportion of rapid- and intermediate-acting insulins is similar to the fixed proportions available. bg, blood glucose

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Other Therapies

Important for reduction of macrovascular disease, including CV events

Intervention	Dosage	Comments
Aspirin	81 mg daily	<ul style="list-style-type: none"> Consider for patients aged >40 years, with other CV risks, or history of CV disease
Smoking cessation	N/A	<ul style="list-style-type: none"> Assess readiness at each visit Refer to cessation programs when patient is ready Offer adjuncts as needed (eg, nicotine patches, bupropion) See Smoking Cessation, p. 53
ACE inhibitor or ARB	Varies by agent	<ul style="list-style-type: none"> For treatment of microalbuminuria and hypertension in diabetic patients
Hydrochlorothiazide	25 mg daily	<ul style="list-style-type: none"> For treatment of hypertension

Monitoring and Other Prevention Strategies

Method	Goal	Comments
HbA1c	<ul style="list-style-type: none"> <7%; less-stringent control may be appropriate for patients with advanced microvascular disease, comorbidities, or short life expectancy 	<ul style="list-style-type: none"> Every 3 months if not at goal or after change of medication or dosage Every 6 months if at goal
SMBG	<ul style="list-style-type: none"> Postprandial goal: <180 mg/dL (for type 2 diabetes) Fasting goal: 90-130 mg/dL 	<ul style="list-style-type: none"> Patients on insulin: measure 3 times daily before meals until glucose is controlled; then measure once daily alternating prebreakfast, lunch, supper, and bedtime Midnight SMBG may be helpful to detect hypoglycemia if FBG is persistently elevated (from the dawn phenomenon [Somogyi effect]) Patients not on insulin: if unstable or in poor glycemic control, measure fasting glucose several times per week, or on specified timeline; if controlled, measure 2 times/week Patients should be educated regarding symptoms of hypoglycemia (eg, sweating, anxiety,

		<p>disorientation, tachycardia) and instructed to ingest hard candy, juice, or other rapidly absorbed glucose source if symptoms occur</p> <ul style="list-style-type: none"> Note: SMBG has no benefit if not used to guide therapy
Blood pressure	<ul style="list-style-type: none"> SBP: <130 mmHg DBP: <80 mmHg 	<ul style="list-style-type: none"> At each office visit. Treat if elevated. (see Hypertension, p. 171)
Fasting lipids	<ul style="list-style-type: none"> LDL: <100 mg/dL HDL: >40 mg/dL TG: <150 mg/dL 	<ul style="list-style-type: none"> Every 3-6 months if adjusting medications Annually if stable and at goal Use statins or other lipid-lowering agents as indicated Be aware of possible interactions between PIs and statins (see Dyslipidemia, p. 143; and Lipid-Lowering Medications, p. 315) With most PIs, rosuvastatin or pravastatin is preferred; alternatively, low dosage of atorvastatin May need to increase dosage when using statins with NNRTIs
LFTs	<ul style="list-style-type: none"> ALT <2.5 times upper limit of normal 	<ul style="list-style-type: none"> Monitor every 6 months in patients on sulfonylureas or statins
Urine albumin/Cr ratio	<ul style="list-style-type: none"> Slow progression of renal injury Albumin/Cr ratio <30 mg/g 	<ul style="list-style-type: none"> Treat albuminuria with ACE inhibitor or ARB (see Renal Disease, p. 211)
Foot examination	<ul style="list-style-type: none"> Prevention of ulcers, infections Detection of neuropathy Early intervention 	<ul style="list-style-type: none"> Perform foot risk assessment annually (see Initial Evaluation, above) Educate patient about preventive foot care Refer to Podiatry as needed for lesions and protective footwear Refer to Vascular Surgery for evaluation of arterial insufficiency
Retinal eye examination	<ul style="list-style-type: none"> Vision maintenance; early diagnosis of retinopathy 	<ul style="list-style-type: none"> Annually, by an ophthalmologist Laser therapy available for diabetic retinopathy

Influenza vaccine	• Decreased risk of infection	• Annually
Pneumococcus vaccine	• Decreased risk of infection	• Every 5 years
Counseling on diet, weight loss, and exercise	• Improved glycemic control	• On diagnosis and at every visit



WHEN TO REFER

- Refer all patients with diabetes for education.
- All patients with Type 1 diabetes:
 - Should be referred to a diabetes clinic with multidisciplinary resources (eg, diabetologist, diabetes nurse, educator/manager, and registered dietitian) for institution and adjustment of insulin therapy.
 - If expeditious referral is not possible, the primary care provider should institute “survival” insulin therapy: see **Insulin dosing for Type 1 diabetes**, p. 136.
- Refer to Podiatry for foot lesions, ingrown toenails, foot deformities, or protective footwear.
- Refer to Vascular Surgery for evaluation of arterial insufficiency.
- Refer to Endocrinology for recurrent hypoglycemia or refractory hyperglycemia.
- Refer to an emergency department for patients suspected of diabetic ketoacidosis or nonketotic hyperglycemia based on orthostatic hypotension, tachycardia, disorientation, or ketotic breath.



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Dyslipidemia

KEY POINTS

- Dyslipidemia is a well-described risk factor for CV disease, and occurs in a high proportion of patients with HIV infection.
- Both HIV infection itself and ARV medications may cause lipid abnormalities.
- Other risk factors for CV disease are common in HIV-infected populations:
 - Other metabolic abnormalities (eg, insulin resistance and diabetes, which may be caused or exacerbated by ARV medications)
 - Hypertension
 - Smoking
 - Inactivity
- Patients should be treated for dyslipidemia based on their lipid levels and other risk factors for CV disease.
- LDL cholesterol is the primary target for lipid-lowering therapy.
- Some lipid-lowering medications are contraindicated for use with ARV medications, and others require dosage adjustment.



BACKGROUND

- Dyslipidemia is an important risk factor for CV disease, and occurs in a high proportion of people with HIV infection. As advances in ART extend the life spans of people with HIV infection, it is likely that morbidity and mortality from CV disease will increase. It is important to identify patients' CV risk factors and to reduce those that are modifiable.
- CV risk is associated with:
 - Elevated LDL and TC

Veterans with HIV*

Dyslipidemia: 38%
Ischemic heart disease: 11%
Hypertension: 45%
Diabetes, Type 2: 15%
Tobacco use: 38%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to these conditions

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- Low HDL
- Elevated TG

Of these, elevated LDL is most closely linked to CV risk, and usually is the primary target of therapeutic interventions.

- Dyslipidemia is associated both with HIV infection itself and with ARV medications. It is not yet clear whether HIV infection or ARV medications increase the risk of CV disease, independent of their effects on lipids.
- Patients with untreated HIV infection commonly show:
 - ↓TC
 - ↓LDL cholesterol
 - ↓HDL cholesterol
 - ↓TG
- Patients treated with ARV medications commonly show:
 - ↑TC, LDL, and TG levels
 - Low HDL
- Dyslipidemia among patients taking ARV medications probably is related to multiple factors, including:
 - Individual patient characteristics
 - HIV infection itself
 - ARV medications
- Certain agents in each of the 3 major classes of ARVs may cause lipid abnormalities.
 - PIs: may markedly ↑TC, LDL, and TG levels (particularly RTV and RTV-boosted PIs; unboosted ATV does not typically affect lipids)
 - NNRTIs: effects are more variable, particularly with EFV; NVP is less likely to cause abnormalities; NNRTIs may ↑TC, LDL, and TG
 - NRTIs: d4T may ↑TC and TG
 - Fusion inhibitors, CCR5 antagonists, integrase inhibitors: not associated with dyslipidemia
- For patients with CHD or CHD risk equivalents (see below), if possible, select ARV regimen to minimize the risk of dyslipidemia.



SCREENING

- Check fasting lipids before starting ART.
- Check fasting lipids ≤3-6 months after starting or changing ARVs.
 - If normal: screen at least once per year
 - If abnormal: monitor closely until LDL goal is achieved



Note: The following recommendations are based on **National Cholesterol Education Program (NCEP) guidelines** for the evaluation and management of dyslipidemia. These are widely used, but have not been validated in HIV-infected patients.

History

The need for lipid management is based on lipid levels and on risk factors for coronary artery disease events. In the history, focus on factors that suggest CHD, CHD equivalents, or CV risk.

- **CHD risk equivalent:** considered equal in risk to known CHD
- **CHD risk factor:** a condition associated with greater risk of serious cardiac events

CHD	CHD Risk Equivalents	CHD Risk Factors
<ul style="list-style-type: none"> • History of MI • Unstable angina • Stable angina • CHD procedures • Evidence of clinically significant myocardial ischemia 	<ul style="list-style-type: none"> • Diabetes mellitus • Peripheral vascular disease • Carotid artery disease • Abdominal aortic aneurysm • Transient ischemic attacks • 2 or more CHD risk factors with a 10-year risk of CHD >20% (see the 10-year cardiac event risk calculator online at http://hin.nhlbi.nih.gov/atp/iii/calculator.asp) 	<ul style="list-style-type: none"> • Male sex • Cigarette smoking • Hypertension (systolic blood pressure ≥ 140 mmHg or taking antihypertensive medication) • HDL <40 mg/dL (if HDL is ≥ 60 mg/dL, subtract 1 risk factor) • Patient age ≥ 45 (men) or ≥ 55 (women) • Family history of premature CHD in first-degree relatives aged <55 (men) or <65 (women)

In addition, consider the factors below:

History	<ul style="list-style-type: none">• Factors that contribute to dyslipidemia:<ul style="list-style-type: none">• Obesity, chronic liver disease, alcohol consumption, high-fat or high-carbohydrate diet, genetic disorders of lipid metabolism, chronic kidney disease, and prothrombotic or proinflammatory states• Factors that contribute to hypertriglyceridemia:<ul style="list-style-type: none">• Genetic disorders, obesity, diabetes, alcohol consumption, hypothyroidism, nephritic syndrome, chronic kidney disease• Causes of secondary dyslipidemia, including diabetes, hypothyroidism, nephrotic syndrome, liver diseases• Family history of obesity, diabetes, and lipid abnormalities• Medications<ul style="list-style-type: none">• ARVs, especially those known to increase cholesterol or TG levels (eg, RTV and RTV-boosted PIs, EFV, d4T)• Other medications that may cause lipid abnormalities (eg, corticosteroids, anabolic steroids, progestins, beta-blockers, thiazide diuretics, quetiapine)
Physical examination	<ul style="list-style-type: none">• Blood pressure• Weight, height, and waist circumference (for patients of European descent, abnormal is >40 inches [men] or >35 inches [women])• Obtain BMI: normally available in the Vitals section of the CPRS Cover Sheet; otherwise $BMI = \text{weight (kg)}/\text{height (m}^2\text{)}$; calculator available online: http://www.nhlbisupport.com/bmi/.<ul style="list-style-type: none">• Underweight: BMI <18.5• Normal weight: 18.5-24.9• Overweight: 25-29.9• Obese: ≥ 30• Cardiovascular examination: murmurs, gallops• Stigmata of hyperlipidemia and hypertriglyceridemia: xanthelasma and tendon xanthomas, which are associated with extremely elevated LDL levels; eruptive xanthomas and hepatomegaly, which may be present in the setting of extremely elevated TG levels (chylomicronemia)
Laboratory evaluation	<ul style="list-style-type: none">• Fasting (8- to 12-hour fast) lipid panel: measured TC, LDL, HDL, and TG levels; calculated non-HDL, and TC/HDL ratio• Fasting glucose

Assessment Tools

Determine whether intervention is needed according to the patient's lipid values and CHD risks, following these 3 steps. **Note that for most patients, LDL is the main indicator of need for lipid-lowering therapy.**

1. Determine CHD risks (above).
2. Determine risk category, LDL goal, and LDL threshold for treatment using **Table 1**.
 - The NCEP also recommends estimating the patient's 10-year risk of MI using the assessment tool derived from the Framingham Heart Study (<http://hin.nhlbi.nih.gov/atp/iii/calculator.asp>). Note that this tool does not estimate *lifetime* risk of MI, which for many patients is substantially higher than their 10-year risk. Intervention to treat lipid abnormalities may be warranted even in patients with a low 10-year risk, to prevent CV events later in life.
3. Assess TG risk level using **Table 2**; determine whether TG-lowering treatment is needed.

Table 1. LDL Cholesterol Goals and Thresholds for Treatment*

Risk Category	LDL Goal*	LDL Threshold to Initiate Therapeutic Lifestyle Changes	Consider Drug Therapy
Lower risk: No CHD or CHD equivalents and 0-1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (at 160-189 mg/dL, drug therapy optional)
Moderate risk: No CHD or CHD equivalents; ≥2 risk factors and 10-year estimated risk <10%	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Moderately high risk: No CHD or CHD equivalents; ≥2 risk factors and 10-year estimated risk 10-20%	<130 mg/dL (optional goal: <100 mg/dL)	≥130 mg/dL	≥130 mg/dL
High risk: CHD or CHD equivalent	<100 mg/dL (optional goal: <70 mg/dL)	≥100 mg/dL	≥100 mg/dL

* Non-HDL cholesterol target levels are 30 mg/dL higher than corresponding LDL cholesterol levels. Adapted from NCEP, et al. See **References**.

Other issues:

- Consider drug therapy to decrease LDL (or non-HDL) if TC is >240 mg/dL or HDL cholesterol is <35 mg/dL.
- If TG is >400 mg/dL, the LDL cholesterol calculation is unreliable. Use non-HDL cholesterol as a surrogate target of therapy (non-HDL = TC – HDL); the non-HDL goal is 30 mg/dL higher than the LDL goal.
- If TG is 200-500 mg/dL, LDL is the primary target of initial therapy (see **Table I** for LDL intervention levels); if TG is ≥500 mg/dL, TG may be the initial target of therapy (see below).

Hypertriglyceridemia is associated with CAD risk, but it is unclear whether it is an independent risk factor; hence indications for treatment are less certain than those for cholesterol abnormalities.

Table 2. Classification of Triglyceride Levels

Risk Category	Triglyceride Measurement	Initiate Therapy
Normal	<150 mg/dL	
Borderline High	150-199 mg/dL	
High	200-499 mg/dL	<ul style="list-style-type: none">• TLC• Consider drug therapy for those with CHD, CHD equivalents, high risk of CHD
Very High	≥500 mg/dL	<ul style="list-style-type: none">• Low-fat diet (<15% of caloric intake); pharmacologic therapy probably will be required• Consider drug therapy• If severe (>1,000 mg/dL), treat to decrease risk of pancreatitis

Adapted from NCEP, et al. See **References** below.

Rx MANAGEMENT

The primary goal of lipid-lowering therapy for most patients is to lower LDL to target levels. The potential benefits of lipid-lowering therapy for HIV-infected patients should be balanced against drug toxicities, as well as the risk of CV mortality relative to HIV-associated mortality.

- If the TG level is very high, it may have to be reduced before LDL is treated directly (see below).
- Low HDL is not usually a primary target of therapy; data are conflicting as to whether raising HDL confers CV benefits.

A multimodal approach to treatment is important:

- Lifestyle modification
- Lipid-modifying medication
- Changes in ARV medication (or other exacerbating medication), if possible
- Management of associated conditions (eg, diabetes)

See **Table 1** for LDL levels at which either TLC or drug therapy should be initiated, and for the target goals for LDL cholesterol.

Lifestyle Modification

Lifestyle modification is fundamental to the management of dyslipidemia and should be initiated in all patients with dyslipidemia. Behavioral changes may be difficult for patients, but can yield significant results in improving lipid values and reducing CHD risk.

Encourage patients to:

- Reduce dietary cholesterol and saturated fat (all patients)
- If overweight, lose weight
- Maintain or increase aerobic exercise (all patients)
- Reduce alcohol consumption (especially for those with high TGs)
- Stop smoking, and reduce other CHD risk factors

Medication

See **Table 3** and **Characteristics of Lipid-Lowering Medications**, below, for information about lipid-lowering medications. Therapies should be intensified or augmented until lipid targets are met.

Table 3. Suggested Drug Treatments for Lipid Abnormalities

Lipid Abnormality	First Choice	Second Choice	Comments
Isolated high LDL, non-HDL cholesterol	Statin	Niacin (time-release formulation)	<ul style="list-style-type: none">• Be aware of possible statin-ARV interactions (see below and Lipid-Lowering Medications, p. 315); use pravastatin, fluvastatin, rosuvastatin, or atorvastatin for most patients taking PIs• Patients taking PIs may have increased risk of myopathy• Start with low statin dosages

		<p>Fibrate (reserve for patients intolerant of other agents who have high LDL, low HDL)</p> <p>Ezetimibe (third choice)*</p>	<ul style="list-style-type: none"> • If incomplete response to statin, consider: <ul style="list-style-type: none"> • Increasing statin dosage • Switching to more potent statin (rosuvastatin or atorvastatin) • Adding niacin (time-release formulation) • Adding ezetimibe • Bile acid sequestrants in general should be avoided unless there are no other options; may interfere with absorption of ARVs and other medications • Ezetimibe should be used as monotherapy only for patients unable to tolerate statins who do not respond to other agents • Avoid combining statin and fibrate: increased risk of myopathy • Triple therapy with statins, niacin, and ezetimibe is not recommended
Isolated high TG	N-3 fatty acid Niacin (time-release formulation) Fibrate		<ul style="list-style-type: none"> • Fibrates are most effective in lowering TG • If response is inadequate, add second agent • Atorvastatin may lower TG (as well as LDL)
High LDL + high TG	Statin + N-3 fatty acid or niacin (time-release formulation)	Fibrate	<ul style="list-style-type: none"> • Dual therapy likely to be most effective • Could start with single agent (eg, niacin) and add second agent if response is inadequate • Avoid combination of statin and fibrate: increased risk of myopathy
Isolated low HDL	Niacin (time-release formulation)	Fibrate	<ul style="list-style-type: none"> • Initiate CV exercise

* See PBM Criteria for Use at <http://www.pbm.va.gov/criteria/Ezetimibe>.

Characteristics of Lipid-Lowering Medications

Statins (HMG-CoA reductase inhibitors): Decrease TC, LDL, and non-HDL cholesterol levels; atorvastatin also decreases TG levels. There is substantial evidence that statins reduce CV events. First-line treatment for most patients with hypercholesterolemia or combined hypercholesterolemia + hypertriglyceridemia (see **Table 3**).

Many have significant drug interactions with PIs and NNRTIs; some combinations are contraindicated (see **Lipid-Lowering Medications**, p. 315). Possible adverse effects include, GI disturbance, myopathy, rhabdomyolysis, liver toxicity (check LFTs 1 month after initiating, then every 3 months). Contraindicated in women who are pregnant or nursing; use caution in patients with active or chronic liver disease.

Recommended starting dosages of statins for patients taking PIs:

Pravastatin: 20 mg PO QD

Fluvastatin: 20 mg PO QD

Atorvastatin: 10 mg PO QD

Rosuvastatin: 5-10 mg PO QD

When given concomitantly, statins and fibrates increase the risk of rhabdomyolysis; in general, this combination should be avoided.

Fibrates: Decrease TG and increase HDL; modestly decrease LDL. Gemfibrozil has been shown to reduce risk of CV events (in HIV-uninfected individuals); fenofibrate has not. In one study, clofibrate was associated with increased risk of noncardiac mortality. An option for initial treatment of isolated hypertriglyceridemia and an alternative treatment for combined hypertriglyceridemia and hypercholesterolemia.

Not metabolized by the cytochrome P450 hepatic enzyme system; no significant drug interactions with ARVs. Contraindicated in severe renal or hepatic disease. Fibrates generally should not be used with statins because of increased risk of myositis. Other possible adverse effects: GI disturbance, gallstones, dizziness. Recommended dosages:

Fenofibrate: 50-200 mg PO QD

Gemfibrozil: 600 mg PO BID, 30 minutes before meals

N-3 (omega-3) polyunsaturated fatty acids: Decrease TG levels. May be effective as initial or adjunctive therapy. Limited data suggest CV benefit. Usual dosage 2-6 grams daily. Possible adverse effects: fishy taste, GI disturbance.

Niacin: Increases HDL, decreases both TC and TG. May be effective as adjunctive therapy, but may worsen insulin resistance. Other possible adverse effects include elevated serum transaminase levels, flushing (to decrease flushing, premedicate with aspirin; titrate dosage slowly, use time-release formulations [eg, Niaspan]). Contraindicated in chronic liver disease and severe gout; relatively contraindicated in diabetes, peptic ulcer disease, and hyperuricemia.

Bile acid sequestrants: Generally should be avoided unless no other options; may interfere with the absorption of other drugs (including ARVs), and may increase TG levels.

Ezetimibe: Has not been studied thoroughly in HIV-infected individuals, but appears to be effective in lowering TC and LDL. However, because of lack of data showing that ezetimibe decreases CV events, it should not be used as monotherapy except in well-defined circumstances (see PBM Criteria for Use at <http://www.pbm.va.gov/criteria/Ezetimibe>). Usually used in combination with statins if LDL is not controlled adequately with a statin alone. Contraindicated in patients with liver disease.

Switching ARVs

- For patients with CHD or CHD equivalents, try to select ARV medications associated with the lowest risk of dyslipidemia.
- For patients with dyslipidemia caused by ARV agents, consider discontinuing lipogenic ARVs if safe and effective alternatives exist.
 - For example, substitute ATV or NVP in place of a lipogenic PI or substitute an unboosted PI (eg, ATV or FPV) for a RTV-boosted PI.
 - Replace d4T with TDF, or perhaps ABC*.
- Before making ARV substitutions, consider the possible effect on HIV virologic control and the potential adverse effects of new ARVs.
- In some cases, antihyperlipidemic agents may still be necessary after ARV substitution.

* Recent data from the D:A:D observational study associated ABC with increased risk of MI. There were insufficient data to analyze the effect of TDF. See **References**.



POTENTIAL ARV INTERACTIONS

Interactions with ARVs: Most PIs inhibit the metabolism of most statins and can significantly increase serum statin levels, thus increasing the risk of toxicity, including rhabdomyolysis. Some combinations are contraindicated. Of the statin drugs, pravastatin is the least affected by most PIs (DRV is an exception). Atorvastatin, if used, must be initiated cautiously and at a low dose. EFV can induce the metabolism of some statins, causing therapeutically significant decreases in their concentrations. See **Lipid-Lowering Medications**, p. 315, for further information.



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Gastroesophageal Reflux Disease (GERD)

KEY POINTS

- Typical symptoms of GERD are heartburn and regurgitation.
- Less common GERD symptoms (eg, cough) may mimic other conditions.
- Evaluation of GERD in patients with HIV depends on the stage of infection.
- In patients with a CD4 count of >350 cells/ μ L with typical GERD symptoms, a trial of empiric acid suppression therapy may be undertaken in lieu of other diagnostic testing.
- In patients with more advanced HIV infection, evaluation for OIs affecting the esophagus should be considered, along with empiric GERD therapy.
- Patients with GERD symptoms lasting >5 years should be evaluated by endoscopy for Barrett esophagus because of the increased risk of esophageal carcinoma.
- Patients with alarm symptoms (eg, unexplained dysphagia or weight loss, hematemesis) should be evaluated by endoscopy for malignancy or other GERD complications.



BACKGROUND

- GERD is defined by the American College of Gastroenterology as “symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus.” However, there is no universally accepted definition of the condition, and no gold standard for its diagnosis.
- Uncomplicated GERD is characterized by typical symptoms of heartburn, regurgitation, or both.

Veterans with HIV*

Esophageal disease: 19%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to this condition

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- Complicated GERD includes Barrett esophagus (see below), esophageal strictures, hemorrhage or perforation, and extraesophageal complications such as aspiration, asthma, chronic coughing, chest pain, and laryngopharyngitis.
- Etiology involves lower esophageal sphincter (LES) dysfunction with reflux of acidic gastric contents into the esophagus, often resulting in damage to esophageal mucosa. Decreased esophageal motility and abdominal distention also may play a role.
- Symptoms of heartburn are common in Western countries: 25% of the general population is reported to have heartburn at least once a month, 12% has heartburn at least weekly. GERD can have a very negative impact on quality of life.
- There is no reported association of GERD with HIV infection. For HIV-infected patients, however, the differential diagnosis of GERD symptoms includes several HIV-related conditions (see **Partial differential diagnosis**, p. 161).
- Diagnosis usually depends on the presence of symptoms **and/or** the confirmation of esophagitis with esophagogastroduodenoscopy (EGD) or other testing.
- Esophagitis (esophageal erosions or other mucosal damage) is seen on EGD or histology in <50% of patients. The majority of patients with GERD symptoms have no evidence of esophagitis on EGD (ie, nonerosive reflux disease, or NERD).
- The severity and course of symptoms of esophagitis and NERD are similar.
- The condition is often chronic, with remissions and relapses, but usually not progressive. Possible complications include:
 - Esophageal stricture
 - Esophageal ulcers
 - Barrett esophagus
 - Adenocarcinoma
 - Bleeding
 - Perforation
 - Aspiration
- The symptoms and esophageal mucosal injuries caused by GERD usually respond to acid-suppressive treatment, though some complications (eg, Barrett esophagus) may not improve with treatment.



EVALUATION

- There is no gold standard for diagnosis of GERD.
- Uncomplicated GERD may be diagnosed by clinical symptoms alone.

- EGD should be considered at presentation for patients with symptoms of complicated GERD (extraesophageal or alarm symptoms; see below) and those at risk of Barrett esophagus (see below).
- The differential diagnosis of symptoms referable to the esophagus in patients with HIV depends on the stage of infection.
 - In patients with CD4 counts of <350 cells/mL, the differential diagnosis should include esophageal OIs, such as candidiasis and CMV infection.
 - In patients with higher CD4 counts, evaluation should focus on GERD, and on Barrett esophagus and alarm symptoms that suggest malignancy or other conditions (see below); however, the possibility of OIs should be considered as well.
- Patients with symptoms lasting for >5 years should be evaluated for Barrett esophagus because of the associated increase in risk of esophageal adenocarcinoma.

Check for alarm symptoms:

- Dysphagia
- Odynophagia
- Unexplained weight loss
- GI bleeding (hematemesis, melena, bloody stool)
- Anemia
- Chest pain
- Choking/dysphagia
- Failure to improve with therapy

In HIV-infected patients with relatively high CD4 counts, these suggest malignancy, ulceration, or stricture. If present, refer for immediate evaluation via EGD. Consider starting trial of acid suppression therapy while awaiting further evaluation.

Barrett Esophagus

- Metaplasia, with replacement of esophageal squamous epithelium by abnormal columnar epithelium
- Associated with severe GERD, but may occur in asymptomatic patients
- Increases risk of esophageal adenocarcinoma 50-fold compared with GERD alone
- Unclear whether acid suppression prevents progression of Barrett esophagus or development of adenocarcinoma
- Patients with a history of GERD symptoms for >5 years, especially those ≥50 years of age, should be evaluated for Barrett esophagus by EGD
- Reflux symptoms should be controlled before EGD to maximize sensitivity and specificity of EGD

- The surveillance interval for Barrett esophagus is determined by the grade of dysplasia at initial EGD
 - For low-grade dysplasia, EGD should be repeated within 6 months to exclude higher-grade dysplasia
 - For high-grade dysplasia, EGD should be repeated within 3 months

Risk factors	<ul style="list-style-type: none"> • Obesity: 1.5- to 2-fold risk of GERD, increasing with higher BMI • Pregnancy • Fatty foods • Hiatal hernia • Stress • Medications: beta-blockers, calcium channel blockers, anticholinergics (LES relaxation), NSAIDs, aspirin (mucosal injury) • Lifestyle factors: Many of these cause relaxation of the LES, but there is little evidence that GERD results. Associations, if true, appear to be weak, though some patients may be sensitive to these factors. <ul style="list-style-type: none"> • Diet: carbonated sodas, caffeinated beverages, chocolate, saturated fats, peppermint, acidic foods, low fiber • Alcohol use • Smoking
History	<p>History is usually the basis of GERD diagnosis; however:</p> <ul style="list-style-type: none"> • Patients may have atypical symptoms or be asymptomatic. • Severity of symptoms does not predict severity (or presence) of mucosal damage; conversely, severity of esophagitis does not predict severity of symptoms. • There may be great variability in symptoms and findings upon diagnostic testing, and the two may not correlate. • Absence of symptoms does not rule out GERD. <p>Symptoms:</p> <ul style="list-style-type: none"> • Heartburn: retrosternal burning pain (because of potential for misunderstanding, it may be helpful to avoid the term “heartburn” and instead ask patients about “a burning feeling rising from the stomach or lower chest up toward the neck”) • Regurgitation: reflux of gastric contents (acid, with or without food); very specific for GERD • Dysphagia • Odynophagia • Symptoms of “extraesophageal” GERD: <ul style="list-style-type: none"> • Cough • Asthma

- Chest pain
- Hoarseness/voice changes

(Note: GERD is a common cause of chronic cough, wheezing, and chest pain.)

Associated factors:

- Ask about risk factors, above.
- Duration of symptoms; patients with a long history of GERD symptoms should be evaluated for Barrett esophagus (see above).
- Symptoms after meals (symptoms after a large or fatty meal: highly specific for GERD)
- Symptoms with recumbency (particularly after a meal)
- Nocturnal symptoms
- Treatments tried and symptom response (improvement with acid-lowering medications supports the diagnosis)

Physical examination

- Performed mostly to evaluate for other causes (infections, asthma, cardiac disease, cancer)
- Vital signs; O₂ saturation
- Inspection of oropharynx (ulcerations, candidiasis, lesions, masses), neck (nodes, masses), and lungs (wheezes, crackles)
 - Absence of oropharyngeal candidiasis does not exclude esophageal candidiasis.
- Abdomen: masses, tenderness
- Evaluation for malignancy and infection if history and examination suggest these diagnoses

Diagnostic tests

- Diagnosis of GERD usually is made on the basis of clinical evaluation; in patients with symptoms consistent with GERD, history usually is sufficient to move to a trial of empiric acid-lowering therapy (4-8 weeks) without further evaluation.
- Exceptions require immediate and appropriate evaluation:
 - Chest pain (rule out cardiac origin)
 - Other alarm symptoms (see above)
 - Other atypical symptoms or findings; high suspicion of an alternative diagnosis
- Hematocrit and fecal occult blood testing may be indicated if anemia caused by an upper GI source is suspected.
- *Helicobacter pylori* testing is of little value in evaluation of GERD.

• Empiric proton pump inhibitor (PPI) therapy

- Response to acid-lowering therapy (typically PPI therapy) supports a diagnosis of GERD, though studies of correlation show varying results, and symptom improvement may not correlate with findings on EGD or pH monitoring. Sensitivity 78% and specificity 54% for GERD; use of high dosages of PPI may improve sensitivity.

- **EGD**

- If there is no clinical improvement after 4-8 weeks, consider EGD or other testing as below.
- (Note that a small number of patients have GERD symptoms that are not related to gastric acid.)
- Useful for diagnosing esophagitis and complications (eg, strictures, Barrett esophagus), but is normal in >50% of patients with symptoms: high specificity (>90%) but low sensitivity (50%) (ie, normal endoscopy does not exclude GERD). Severity of mucosal injury does not necessarily correlate with symptoms.
- The role of EGD in the initial evaluation of patients with uncomplicated GERD is somewhat controversial. The VHA Pharmacy Benefits Management Strategic Healthcare Group and the American College of Gastroenterology propose that a trial of therapy is preferable to EGD for most patients.
- Perform EGD as part of initial evaluation for complicated GERD (eg, if alarm symptoms or other concerning symptoms are present), or if alternative diagnoses are likely (eg, candidiasis or CMV esophagitis, esophageal cancer, gastritis, and peptic ulcer disease), or if patient is at risk of Barrett esophagus (see above).
 - Consider trial of acid-lowering therapy while awaiting EGD; may result in partial (or full) remission of GERD; will improve sensitivity for detection of Barrett esophagus.
- Perform EGD for patients whose symptoms persist despite therapy; consider for patients with long duration of symptoms (eg, >5 years).
- The surveillance interval for Barrett esophagus is determined by the grade of dysplasia at initial EGD (see **Barrett Esophagus**, p. 157).

- **Ambulatory pH monitoring**

- Presence of acid in the esophagus does not correlate well with symptoms.
- Does not detect nonacid reflux.
- Limited availability, uncomfortable for patients.
- Consider for patients with persistent symptoms if the EGD is negative for mucosal damage and for those with unusual, extra-esophageal, or refractory symptoms.
- Can monitor control of reflux in patients on acid-reducing medications (eg, for patients who are considering surgery).

- **Barium esophagram**

- Detects severe esophagitis and strictures reliably, but is not sensitive or specific for milder or nonerosive disease.
- Not sensitive for detection of Barrett esophagus.

Partial differential diagnosis

- Infectious esophagitis (symptoms usually include odynophagia, dysphagia)
 - Candidiasis
 - CMV
 - Herpes simplex virus
- Dyspepsia
- Peptic ulcer disease
- Gastritis
- “Pill esophagitis”
- Stricture
- Hiatal hernia
- Esophageal dysmotility
- Cancer (esophageal, gastric)
- Gastroparesis
- Coronary artery disease

Rx MANAGEMENT

Acute/Initial Treatment

Goals of therapy:

- Symptom relief
- Healing of esophageal erosions (if present)
- Prevention of complications (data demonstrate reduction in esophageal strictures, but do not clearly show that treatment prevents or slows development of Barrett esophagus or adenocarcinoma)

As discussed in the **Evaluation** section, empiric acid-suppressing treatment may be initiated on the basis of GERD symptoms. The rate of symptom response to adequate therapy is high (>80%), so patients whose symptoms do not improve should be evaluated for other causes.

Medications

Acid-suppressive agents

- Mainstay of GERD treatment.
- Primary acid-suppressive treatments are PPIs and H2 receptor antagonists (H2RAs).
- For symptom control and healing of esophagitis, the order of efficacy is: high-dose PPI > standard-dose PPI > half-dose PPI > high-dose H2RA > standard-dose H2RA.

- Patients with erosive esophagitis, extraesophageal symptoms, or a history of failure to respond to H2RAs should be started on standard-dose PPI rather than an H2RA.
- For patients with NERD, the optimal initial treatment strategy has not been defined. Some authorities prefer to start with PPIs at maximal doses and step down to less-intensive therapy after symptom remission; others prefer to start with less-intensive therapy and step up if symptom relief or esophageal healing is incomplete.
- PPIs and H2RAs may affect serum levels of some ARVs; these drug-drug interactions may influence which type of medication is selected for initial treatment of GERD (see **Potential ARV Interactions** below).
- Most GERD patients (>60%) gain symptom relief, and approximately 80% have healing of esophagitis at 8-12 weeks.

Antacids

- No role as primary therapy (typically, patients have self-treated with antacids without symptom relief).
- May be helpful for some patients as supplement to PPI therapy, to be used as needed for breakthrough symptoms.

Prokinetic agents

- Metoclopramide is the only prokinetic agent available in the United States.
- Increases LES resting tone, esophageal peristalsis, and gastric emptying.
- Less effective than PPIs; similar to but perhaps less effective than H2RAs.
- Associated with CNS adverse effects (eg, irreversible tardive dyskinesia).
- Should be used only as adjunct to acid suppression, not monotherapy.

Dietary and Lifestyle Modification

- Generally aimed at avoiding decreases in LES function, or increases in abdominal pressure or position, which promote reflux of acid above the LES.
- Adjunct to acid suppression in selected patients; not suitable for sole therapy.
- Limited data on efficacy from randomized controlled trials for most measures.
- Specific modifications should be based on individual circumstances and identified triggers.

Initial Interventions for GERD

PPIs

- Available PPIs have comparable efficacy at equivalent dosages.
- Greater efficacy and more rapid symptom control than H2RAs.

- Optimal starting dosage is unclear; some authorities prefer to start with high dosages and step down to less-intensive therapy after symptom remission, others prefer to start at lower dosages and increase treatment intensity if needed.
- Should be taken a half hour before breakfast (or dinner).
- Usually well tolerated. Potential adverse effects include GI symptoms (abdominal pain, diarrhea, nausea), headache, rash, and liver toxicity.
- No dosage adjustment needed for renal impairment.
- May require lower dosage in hepatic impairment; dosage not defined.
- Decrease absorption of drugs with pH-dependent bioavailability, particularly ATV. (See **Potential ARV Interactions** below.)

Generic Drug Name	Dosage Range	Comments
Esomeprazole	20-40 mg QD	If difficulty swallowing, can open capsule and sprinkle contents on applesauce
Lansoprazole	15-30 mg QD or 30 mg BID	If difficulty swallowing, can open capsule and sprinkle contents on applesauce
Omeprazole	20-40 mg QD	If difficulty swallowing, can open capsule and sprinkle contents on applesauce; immediate-release form contraindicated with hypocalcemia or alkalosis
Pantoprazole	40 mg QD or 40 mg BID	No dosage adjustment needed for hepatic impairment; may cause false-positive THC result on urine toxicology screen
Rabeprazole	20 mg QD or 20 mg BID	Delayed-release tablet

H2RAs

- Less effective than PPIs for acid suppression, relief of symptoms, and healing of esophagitis; approximately 40% of patients gain symptom relief. Treatment with H2RAs may be adequate for some patients.
- Potential adverse effects vary somewhat according to the specific H2RA. They include cytopenias, rash, GI intolerance, and arrhythmias.
- Dosage adjustment is required for patients with renal insufficiency.
- Cimetidine interacts significantly with many other drugs.
- See **Potential ARV Interactions** below.

Cimetidine	800 mg BID or 800 mg TID	Multiple drug interactions (see Potential ARV Interactions below)
Famotidine	20 mg BID or 40 mg BID	May decrease ATV absorption

Nizatidine	150 mg BID or 300 mg BID	May decrease ATV absorption
Ranitidine	150 mg BID or 150 mg QID	May decrease ATV absorption; may decrease FPV, LPV, RTV levels

Antacids

- Typically contain aluminum hydroxide, magnesium hydroxide, calcium carbonate, sodium bicarbonate, or combinations of these compounds.
- Liquid formulation is preferable to tablets because of more rapid action.
- Usual dosage is 15-30 mL QID (after meals and at bedtime).
- If tablets are used, they should be thoroughly chewed and followed by full glass of water.
- Antacids combined with alginic acid (eg, Gaviscon) may be superior to antacids alone.
- Adverse events:
 - Antacids containing magnesium: diarrhea
 - Antacids containing aluminum or calcium: constipation
 - Hypophosphatemia with chronic use
 - Magnesium and/or aluminum retention in chronic renal failure
- Multiple drug interactions caused by binding to form insoluble complexes, including PIs and integrase inhibitors. (See **Potential ARV Interactions** below.)

Prokinetic Agents

Metoclopramide	10-15 mg QID (after meals and at bedtime)	Associated with irreversible tardive dyskinesia, other CNS effects; may consider metoclopramide as adjunctive therapy (add-on to PPI)
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Dietary and Lifestyle Modification

Dietary	<ul style="list-style-type: none"> • In most patients, avoiding the following is useful: <ul style="list-style-type: none"> • Carbonated beverages • Voluminous meals • In selected patients, avoiding the following triggers may be useful: <ul style="list-style-type: none"> • Fatty meals • Sweets, including chocolate • Spicy foods/raw onions • Caffeinated beverages • Citrus products/juices
Lifestyle	<ul style="list-style-type: none"> • In most patients, the following are useful: <ul style="list-style-type: none"> • Weight loss • Smoking cessation

- Lying on the left side when sleeping
- Avoiding excessive physical activity (running)
- In selected patients, the following may be useful:
 - Avoiding alcohol
 - Elevating head of bed (for nocturnal symptoms)

Evaluate Treatment Response (after 4-8 weeks):

Possible responses to treatment	Options for treatment and evaluation
Adequate control of symptoms	<ul style="list-style-type: none"> • Preferred: Step-down (decrease in intensity) of therapy (eg, from high-dose PPI to standard-dose PPI, or from PPI to H2RA), with goal of eventually discontinuing therapy; monitor symptoms • Discontinue therapy and monitor symptoms • Continue current therapy
Partial control of symptoms	<ul style="list-style-type: none"> • Increase intensity of therapy (eg, to high-dose PPI) • Extend the course of treatment (reevaluate after additional 4-8 weeks) • Refer to GI for further evaluation
Lack of response	<ul style="list-style-type: none"> • Increase intensity of therapy • Consider alternative diagnosis • Refer to GI for evaluation

More than 60% of patients respond to adequate therapy. Most authorities recommend that all patients who do not respond to a trial of PPI therapy be referred for further evaluation. In patients with low CD4 counts, consider candidiasis or CMV esophagitis, and other HIV-associated conditions.

Relapse of GERD Symptoms

- Restart the medication at the dosage that was effective in controlling the patient's symptoms.
- If relapse occurs on H2RA, step up therapy to PPI.
- Consider referral for further diagnostic testing.

Chronic GERD Symptoms

- Goals: Suppress symptoms, prevent relapses.
 - Limited data on optimal strategy for long-term acid suppression

- Chronic maintenance: consider for frequent or rapid relapses, severe disease
- Episodic treatment as needed for relapses: consider for patients with mild GERD
- It is rational to use the lowest possible dosage of PPI or H2RA that controls symptoms, but recurrences are common with decreased intensity or discontinuation of medications; some data suggest that efficacy of H2RAs may decline over time.
- Chronic PPI therapy appears to be safe, but data from controlled trials are not available and risks are not fully known.
 - May decrease absorption of vitamin B12; use with caution for patients with risk factors for B12 deficiency.

Surgery and Endoscopic Treatments

Most surgical and endoscopic therapies (eg, fundoplication) alter LES function, and have variable success. Criteria for selecting patients are not completely defined, but usually include those with large-volume reflux, good responses to medical therapy, or intolerance to medical treatment. Following surgery, a high proportion of patients continue to require acid-lowering medications for control of symptoms. Refer to GI for evaluation.



WHEN TO REFER

Gastroenterology	<ul style="list-style-type: none"> • Severe symptoms • Atypical symptoms • Screening for Barrett esophagus • Alarm symptoms suggesting malignancy, ulceration, or stricture • Failure to improve, incomplete response, or relapse on empiric acid-suppression therapy • Consider for chronic symptoms requiring continuous therapy • Evaluation for OIs by EGD
Surgery	<ul style="list-style-type: none"> • Evaluation for fundoplication for: <ul style="list-style-type: none"> • Large-volume reflux • Long-term control of symptoms • Intolerance to medical therapy



POTENTIAL ARV INTERACTIONS

Acid-lowering medications have interactions with various ARVs. Consult dosing information, as certain combinations require specific dosing strategies, and some are contraindicated.

PPIs: interactions with ARVs are incompletely studied

- All PPIs:
 - ↓ATV levels (ATV requires an acidic GI environment for absorption); see specific dosing recommendations below
 - ↓ IDV (predicted)
- Omeprazole (in addition to All PPIs, above):
 - ↓ NFV, ETV
 - ↓ SQV

H2RAs:

- All H2RAs:
 - ↓ATV levels (ATV requires an acidic GI environment for absorption); see specific dosing recommendations below
- Cimetidine (in addition to All H2RAs, above):
 - ↓ NVP levels; dosage adjustment not established
 - May ↑ FPV levels; consider alternative agents
 - May ↓ DRV levels
- Ranitidine
 - May ↓ FPV and LPV/r levels; dosage adjustments not established

Antacids

- Maalox, Mylanta, Tums, milk of magnesia, others
 - May ↓ levels of ATV, FPV,TPV; separate dosing by 2 hours
- Calcium (eg, Tums, Mylanta)
 - May bind integrase inhibitors and interfere with their activity (until further information is available, separate dosing by at least 2 hours)

Dosage Recommendations: ATV with PPIs or H2RAs

	ARV-Naive Patients	ARV-Experienced Patients
PPI	<ul style="list-style-type: none"> • ATV/r 300/100 mg QD; PPI dosage not to exceed the equivalent of omeprazole 20 mg QD, with the PPI to be taken approximately 12 hours before ATV/r. • Unboosted ATV is not recommended. 	<ul style="list-style-type: none"> • PPIs are not recommended.
H2RA	<ul style="list-style-type: none"> • ATV/r 300/100 mg QD; H2RA dosage not to exceed the equivalent of famotidine 40 mg BID; give ATV/r with the H2RA and/or ≥ 10 hours after the H2RA. • Unboosted ATV is not recommended; if used with H2RA, H2RA should not exceed the equivalent of famotidine 20 mg per dose or daily total of 40 mg; give ≥ 2 hours after and/or ≥ 10 hours before ATV/r. 	<ul style="list-style-type: none"> • ATV/r 300/100 mg QD; H2RA dosage not to exceed the equivalent of famotidine 20 mg BID; give ATV/r with the H2RA and/or ≥ 10 hours after the H2RA. • If TDF is used in the regimen, give ATV/r 400/100 mg QD. Administer H2RA as described above. • Unboosted ATV is not recommended.

Source: Reyataz package label



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Hypertension

KEY POINTS

- Hypertension is an independent, reversible risk factor for cardiovascular, cerebrovascular, and renal disease that is underdiagnosed and undertreated.
- HIV-infected patients have a high prevalence of hypertension and other cardiovascular risk factors.
- In most cases, the treatment of hypertension should start with lifestyle modification and a thiazide diuretic. Other antihypertensive drugs may be useful, depending on the patient's additional comorbidities.

Note: This chapter does not address hypertensive emergency or urgency in detail.



BACKGROUND

Rationale for Detecting and Treating High Blood Pressure

- Elevated blood pressure (BP) is an independent risk factor for myocardial infarction (MI), stroke, heart failure, and kidney disease.
- The relationship between BP and these disease events is continuous; the risk of cardiovascular disease doubles for every 20 mmHg increase in systolic BP or 10 mmHg increase in diastolic BP. This effect applies across the spectrum of BP, from normal to severely elevated.
- In clinical trials, treatment of hypertension is associated with substantial reductions in the incidence of MI, stroke, and heart failure.
- “Prehypertension” (as defined in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC 7], see **Table I** below) confers an increased risk of developing hypertension and often warrants therapeutic intervention. Because the short-term pharmaceutical treatment of prehypertension has not been shown to forestall the development of hypertension, some experts have questioned the benefit of labeling patients with this diagnosis.

Veterans with HIV*

Hypertension: 45%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to this condition

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- Although hypertension can be controlled for most patients by a combination of lifestyle changes and pharmaceutical therapy, hypertension remains poorly controlled for many patients.

Special Considerations regarding Hypertension and ART

Although a relationship between ART and other components of the metabolic syndrome, such as hyperlipidemia and elevated blood glucose, has been established, it is not clear whether HIV or specific ARVs are independent risk factors for hypertension.

Some early studies suggested a link between PI-based ART and elevated BP. More recent and larger studies, including the D:A:D study, found that this relationship was accounted for by other factors, such as age, race, and, in particular, increases in BMI that occurred after initiation of ARVs. Another study suggests a link between the duration of ART and BP. Prolonged ART, defined as 2-5 years in duration, was independently associated with development of hypertension in the MACS study, whereas ART of <2 years in duration was not.

Treatment Goals (see Table 1)

- Current VA recommendations are to lower BP to a target of **<140/90** (**<140/80 for patients with diabetes**) to reduce the risk of cardiovascular events and other end-organ damage.
- JNC 7 and the American Heart Association (AHA) recommend a target BP of **<130/80** for patients with:
 - Diabetes
 - Chronic kidney disease (CKD)
- AHA also recommends a target BP of:
 - **<130/80** for patients with:
 - Coronary artery disease (CAD) or its equivalents
 - CAD equivalents: carotid or peripheral arterial disease, abdominal aortic aneurysm
 - 10-year Framingham Risk Score $\geq 10\%$
 - **<120/80** for patients with left-side heart failure



EVALUATION



SCREENING

- Although an optimal screening interval has not been defined, the current VA/DoD guidelines recommend annual BP screening. JNC 7 recommends screening for hypertension every 2 years for patients with BP <130/85, and more frequently for patients with BP >130/85.
- Checking BP at all clinic visits should be encouraged.

How to Measure Blood Pressure in the Office

- The patient should be seated in a chair for 5 minutes, feet on the floor, with arm at heart level.
- The patient should not have smoked, had caffeine, or exercised within 30 minutes before BP measurement.
- Cuff bladder should encircle $\geq 80\%$ of arm.
- The average of at least 2 measurements per office visit should be recorded.
- The diagnosis of prehypertension or hypertension (see **Table 1**) is based on the presence of an elevated BP taken on at least 2 office visits over a 2-month period. For Stage 2 hypertension, evaluation or referral should be performed within 1 month of the initial measurement.

Table 1. Definition and Treatment of High Blood Pressure

Blood Pressure (mmHg)	Classification	Treatment (associated tables in bold)
<120/80	Normal	No treatment indicated. Encourage lifestyle measures as shown in Table 3 .
Systolic: 120-139 or Diastolic: 80-89	Prehypertension	Lifestyle modification (Table 3) and Treat comorbidity,* if present and appropriate. If diabetic, treat to target BP of <140/80. ^{#§}
Systolic: 140-159 or Diastolic: 90-99	Stage I hypertension	Goal: BP <140/90 (140/80 if diabetic)^{#§} Lifestyle modification (Table 3) and Start medication <ul style="list-style-type: none"> • If no comorbidity,* use thiazide (preferred) or angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), beta-blocker (BB), calcium channel blocker (CCB), or fixed-dose combination (FDC) of agents. • If comorbidity,* choose from table of disease-specific antihypertensives (Table 4).

<p>Systolic: >159 or Diastolic: >99</p>	<p>Stage 2 hypertension</p>	<p>Goal: BP <140/90 (140/80 if diabetic)^{#§} Lifestyle modification (Table 3) and Start 2 medications</p> <ul style="list-style-type: none"> • If no comorbidity,* use thiazide plus ACEI, ARB, BB, or CCB, dosed separately or as an FDC. • If comorbidity,* choose from table of disease-specific antihypertensives (Table 4). <p>Consider gradual BP reduction starting with 1 agent for patients at risk of postural hypotension (eg, elderly).</p>
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* Comorbidities include diabetes, CAD, peripheral vascular disease, cerebrovascular disease, heart failure, or renal disease defined as a reduced GFR (CrCl <60 mL/min/1.75 m²) or albuminuria (>300 mg/dL).

[#]The JNC 7 Report recommends a target BP of <130/80 for diabetic patients. AHA 2007 guidelines recommend a target BP of <130/80 for patients with diabetes, CKD, known CAD, or CAD equivalents (carotid or peripheral arterial disease, abdominal aortic aneurysm), or 10-year Framingham Risk Score ≥10%.

[§]VA/DoD guidelines recommend a target BP of <140/90 for patients with renal disease; some authorities recommend a target BP of <130/80.

Adapted from VA/DoD Guidelines, JNC 7 Report, and AHA Guidelines. See **References**, VA/DoD, Chobanian, Rosendorff.

Office Evaluation of the Hypertensive Patient

Specific findings of end-organ damage or cardiovascular comorbidities should guide the choice or intensity of therapy and prompt possible additional workup. The basic evaluation of the hypertensive patient, adapted from the JNC 7, is shown in **Table 2**. Although <5% of patients have secondary hypertension, clinicians should be alert to possible underlying causes such as Cushing syndrome or sleep apnea. Workup of secondary hypertension is addressed in VA/DoD guidelines at <http://vawww.oqp.med.va.gov/CPGintra/cpg/cpg.htm>.

Table 2. Evaluation of Hypertensive Patients for End-Organ Damage and Treatable Comorbidities

Component	Evaluation	Possible Findings
History	<ul style="list-style-type: none"> • Review of systems • Past medical history • Health-related behavior • Family history 	<ul style="list-style-type: none"> • Dyspnea, chest pain, edema, polyuria/polydipsia • CAD, CHF, diabetes, renal disease • Tobacco use, physical activity • Early CAD, diabetes

Physical examination	<ul style="list-style-type: none"> • Vital signs • Ophthalmologic examination • Peripheral circulation • Cardiac examination • Respiratory examination 	<ul style="list-style-type: none"> • Elevated BMI • Arteriovenous nicking, papilledema (hypertensive retinopathy) • Diabetic retinopathy • Bruits: carotid, abdominal, or femoral (peripheral vascular disease) • Decreased peripheral pulses • LVH, S3, S4, distended neck veins (hypertrophy, failure) • Crackles/wheezes
Studies	<ul style="list-style-type: none"> • Electrolytes, BUN, Cr, glucose, Ca²⁺ • Fasting lipids • Urinalysis • ECG • Spot urine protein/Cr ratio 	<ul style="list-style-type: none"> • Decreased renal function, diabetes, hyperaldosteronism • Hyperlipidemia • Proteinuria, glycosuria, hematuria • LVH, CAD

Rx MANAGEMENT

Initial Management

Lifestyle modification

- **All hypertensive patients should be encouraged to attempt lifestyle modification** (see **Table 3**).
- Whenever possible, tobacco use should be addressed (see **Smoking Cessation**, p. 53).

Table 3. Lifestyle Modifications Shown to Reduce Blood Pressure

Area to Modify	Goals	Anticipated SBP Reduction
Diet	<p>DASH (Dietary Approaches to Stop Hypertension) diet:</p> <ul style="list-style-type: none"> • HIGH in fruit/vegetables, lean protein, low-fat dairy products, nuts, fiber, K⁺, Mg⁺, Ca⁺, whole grains (risk of hyperkalemia in patients with renal disease) • LOW in lean red meat, sugars <p>For specific dietary recommendations, including serving sizes and ingredients, see the DHHS online DASH diet guide: http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf</p> <p>Low sodium diet: ≤2.4 g/day</p>	8-14 mmHg

Exercise	>30 minutes of aerobic exercise daily <ul style="list-style-type: none"> • Aerobic activity = brisk walking 	4-9 mmHg
Alcohol	≤2 alcoholic drinks/day (men) or ≤1 drink/day (women) <ul style="list-style-type: none"> • 1 drink = 0.4 oz (12 g) of ethanol: 12 oz beer, 5 oz wine, or 1.5 oz 80-proof (40%) liquor See Alcohol Misuse , p. 3	2-4 mmHg
Weight	Maintain BMI 18.5-24.9 <ul style="list-style-type: none"> • BMI = weight (kg)/height (m²) • U.S. DHHS BMI calculator: http://nhlbisupport.com/bmi/ 	5-20 mmHg per 10 kg weight loss

Resources

Diet: The HealthierUSVeterans program has useful dietary resources at http://vaww.prevention.va.gov/HealthierUSVeterans_Toolkit.asp. Nutritional information is available from the Veterans Canteen Service at <http://vaww.vscscanteen.aac.va.gov/NutritionalInfo.asp>.

Exercise and weight loss: The VHA MOVE program is a national weight management program for veterans; for further details, see <http://vaww.move.med.va.gov/>.

Alcohol misuse: See **Alcohol Misuse**, p. 3. Also, VA resources for reducing alcohol use are available at <http://vaww.hepatitis.va.gov/vahep?page=prtop03-wp-01-res>.

Adapted from JNC 7 Report. See **References**, Chobanian.

Medications

- **Many patients will require pharmacologic therapy.**
- **Considerations in choosing antihypertensive medication:**
 - Thiazide diuretics have been shown to prevent cardiovascular events related to hypertension and are recommended as first-line therapy for most patients. For patients with renal or cardiovascular comorbidity, other agents may offer additional benefit (see **Table 4** and **Table 5**, below).
 - BBs, ACEIs, ARBs, and long-acting CCBs also have been shown to reduce the cardiovascular complications of hypertension.
 - Many patients require 2 agents for sufficient control. Add a second agent if upward titration of the initial agent does not adequately control BP.
 - Patients with Stage 2 hypertension generally should be started on 2 drugs, including a thiazide diuretic.
 - Patients with renal or cardiovascular comorbidities may gain particular benefit from specific types of antihypertensive drugs (see **Table 4** and **Table 5**).
 - Many antihypertensive drugs that are commonly prescribed together are marketed as single-tablet FDCs. These can be useful if the patient tolerates the same dosage of each drug given separately.
 - Whenever possible, use medications that can be given once daily to promote adherence.

Table 4. Classes of Antihypertensives Favored in the Setting of Specific Comorbidities

Comorbidity	Diuretic	BB	ACEI	ARB	CCB	Aldosterone Antagonist
CHF	x	x	x	x		x
Post-MI		x	x			x
High risk of CAD	x	x	x		x	
Diabetes	x	x	x	x	x	
CKD			x	x		
Prevention of recurrent stroke	x		x			

Adapted from JNC 7 Report. See **References**, Chobanian.

Evaluation of Treatment Response

- Home BP monitoring can provide extremely useful information on BP control; BP cuffs for home use can be ordered through the local Prosthetics Service. Devices with a memory function are preferable to patient recall or diary-keeping.
- Patients should be seen within 1 month after initiating therapy to assess efficacy, adherence, and toxicity. (Patients requiring blood tests, those at high risk of end-organ damage, and those at risk of postural hypotension should be seen earlier.)
- If BP is controlled to the target range, adequacy of control should be reevaluated at least every 3-6 months.
- If BP is not controlled:
 - Explore adherence to regimen and educate patients about the importance of controlling hypertension.
 - Be alert to use of concomitant medications that may increase BP (eg, NSAIDs, decongestants, erythropoietin, cyclosporine) and to substance use (eg, alcohol, methamphetamine, cocaine).
 - Consider titration of initial drug regimen (usually doubling of dosage; see **Table 5**).
 - Add an agent from a second class. Agents shown to decrease morbidity and mortality are preferred (ACEI, ARB, BB, long-acting CCB).
 - If a thiazide diuretic was not the initial drug chosen, it should be used as part of combination therapy unless contraindicated or not tolerated.
 - Consider joint care management with a clinical pharmacist.



WHEN TO REFER

Hypertension Clinic, Cardiology, or Renal	<ul style="list-style-type: none"> • Failure to achieve target BP after addition of second drug class • Workup indicating secondary hypertension
Emergency Department	<ul style="list-style-type: none"> • Hypertensive emergency: BP >180/120 complicated by: <ul style="list-style-type: none"> • Hypertensive encephalopathy • Intracranial hemorrhage • Acute MI or unstable angina • Dissecting aortic aneurysm • Acute heart failure with pulmonary edema • Hypertensive urgency: BP >180/120 without target organ dysfunction. May see: <ul style="list-style-type: none"> • Headache • Epistaxis • Shortness of breath • Severe anxiety

Table 5. Antihypertensives: Drug Dosing and Interactions with ARVs

Notes

1. Dosages listed here are **for hypertension only**. Many of these agents (eg, ACEIs) have additional indications, such as for congestive heart failure, for which lower dosages may be appropriate.
2. “**Divided**” means “**1/X of the daily dosage, given X times per day.**” Therefore, “100 mg daily, divided BID” means 50 mg BID. It does not mean 100 mg BID.
3. Drugs listed are representative of their respective classes only; other drugs within each class are also used, and specific dosing information should be followed.

Generic Drug Name	Usual Starting Dosage/ Dosage Titration	Comments/Drug Interactions
Thiazide Diuretics		
<p>Pros: Cardioprotective in ALLHAT study; first-line therapy in JNC 7, VA/DoD guidelines. Thiazide diuretics and CCBs may be more effective than other antihypertensives for African American patients.</p> <p>Cons: Risk of hypokalemia. Monitor electrolytes periodically. Other potential adverse effects include rash, hyperglycemia, sexual dysfunction, and frequent urination. Should not be given to patients with a history of gout, as they may trigger attacks.</p>		

Chlorthalidone	Start at 12.5-25 mg QD; may increase up to 50 mg QD; dosages higher than 50 mg carry risk of hypokalemia without added benefit	
Hydrochlorothiazide (HCTZ)	Start at 12.5-25 mg QD; may increase up to 50 mg QD, though dosages higher than 25 mg carry risk of hypokalemia without added benefit	
Beta-Blockers (BBs)		
<p>Pros: Useful for patients with concomitant CAD, CHF, previous MI.</p> <p>Cons: When discontinuing, taper over course of 14 days to avoid rebound hypertension, angina, MI, or arrhythmia. May be less effective for patients without CAD, especially elderly patients. Use with caution in patients with reactive airway disease. Potential adverse effects include bradycardia, hypotension, fatigue, and sexual dysfunction.</p>		
Atenolol	Start at 25-50 mg QD or divided BID; maximum 100 mg per day	ATV may ↑ atenolol concentrations; no dosage adjustment appears to be necessary.
Metoprolol	Start at 50 mg BID; maximum 225 mg BID	CYP 2D6 substrate; PIs may ↑ metoprolol levels.
Metoprolol Extended Release	Start at 50-100 mg QD; maximum 400 mg QD	CYP 2D6 substrate; PIs may ↑ metoprolol levels.
Propranolol	Start at 20 mg BID; maximum 640 mg per day in divided doses	
Propranolol Extended Release	Start at 60 mg QD; maximum 640 mg QD	Extended-release formulation cannot be substituted for immediate-release form on a mg per mg basis; may require dosage change.
Mixed Alpha-/Beta-Blockers		
<p>Pros: Cardioprotective.</p> <p>Cons: Same as for BBs. Avoid in patients with decompensated heart failure who are dependent on sympathetic stimulation.</p>		
Carvedilol	Start at 6.25 mg BID; titrate slowly; usual dosage: 12.5-50 mg/day, divided BID	CYP 2D6 substrate; PIs may ↑ carvedilol levels.

Labetalol	Usual dosage: 200-800 mg/day, divided BID	IV form useful in hypertensive emergencies.
ACE Inhibitors		
Pros: Cardioprotective, renal protective.		
Cons: Avoid during pregnancy; use with caution in patients who are elderly, are fluid depleted, or have renal insufficiency. Risk of hyperkalemia. Check electrolytes 1 week after starting ACEI. Other potential adverse effects include angioedema, cough, renal insufficiency, and sexual dysfunction.		
Benazepril	Start at 10 mg QD; maximum 80 mg per day; usual dosage: 20-40 mg QD or divided BID; may need BID dosing for continuous BP control	Start at 5 mg QD if patient is elderly, has renal insufficiency, or is taking a diuretic.
Fosinopril	Start at 10 mg QD; maximum 80 mg per day, but no additional effect over 40 mg per day; usual dosage: 10-40 mg QD or divided BID; BID dosing may be needed for continuous BP control	Start at 5 mg QD if patient is elderly, has renal insufficiency, or is taking a diuretic.
Lisinopril	Start at 10 mg QD; maximum 80 mg QD but no additional effect over 40 mg per day; usual dosage: 20-40 mg QD	Start at 2.5-5 mg QD if patient is elderly, has renal insufficiency, or is taking a diuretic.
Ramipril	Start at 2.5 mg QD; maximum 20 mg QD; usual dosage: 2.5-20 mg QD or divided BID; may need BID dosing for continuous BP control	Start at 1.25 mg QD if patient is elderly, has renal insufficiency, or is taking a diuretic.
Angiotensin Receptor Blockers (ARBs)		
Pros: Cardioprotective, renal protective.		
Cons: Avoid during pregnancy; use with caution in patients who are elderly, are fluid depleted, or have renal insufficiency. Risk of hyperkalemia. Other potential adverse effects include angioedema and renal dysfunction.		
Candesartan	Usual starting dosage: 16 mg QD, may be divided BID; maximum 32 mg per day	Start at lower dosage in patients with moderate or worse hepatic impairment, volume depletion.
Irbesartan	Start at 150 mg QD; maximum 300 mg QD	Start at 75 mg QD for patients with volume depletion.

Losartan	Start at 50 mg QD; maximum 100 mg QD or divided BID	Start at 25 mg QD for patients with volume depletion or hepatic insufficiency.
Telmisartan	Usual starting dosage: 40 mg QD; maximum 80 mg QD	Start at 20 mg QD in elderly, patients with hepatic impairment or volume depletion; monitor closely.
Valsartan	Start at 80 mg QD; maximum 320 mg QD	

Calcium Channel Blockers (CCBs)

Pros: CCBs and thiazide diuretics may be more effective than other antihypertensives for African American patients.

Cons: Metabolism of CCBs is inhibited by PIs; if CCBs must be used with PIs, reduce initial dosage and titrate up while monitoring for side effects (eg, hypotension, conduction block, bradycardia, and peripheral edema). Metabolism of CCBs may be induced by the NNRTIs EFV and NVP, leading to blunted antihypertensive effect.

Avoid immediate-release forms. Avoid in patients with CHF.

Amlodipine	Start at 2.5 mg QD; maximum 10 mg daily	See Cons above.
Diltiazem Sustained Release	Start at 60 mg BID; maximum 360 mg per day in divided doses	
Diltiazem Extended Release	Start at 120 mg QD; maximum 540 mg QD	
Nifedipine Extended Release	Start at 30 mg QD; maximum 120 mg QD	
Verapamil Sustained Release	Start at 120 mg QD; maximum 480 mg per day, but divide BID if using >240 mg per day	Immediate-release formulation is not recommended for treatment of hypertension.
Verapamil Extended Release	Covera HS: Start at 180 mg QHS; maximum 480 mg QHS Verelan PM: start at 100 mg QHS; maximum 400 mg QHS	Immediate-release formulation is not recommended for treatment of hypertension.

Potassium-Sparing Diuretics and Aldosterone Antagonists

Pros: May be useful in patients with hypokalemia; often combined with a thiazide diuretic.

Cons: may cause hyperkalemia: monitor K⁺

Spironolactone	Usual dosage is 50 mg to 100 mg QD or divided BID	Monitor for hyperkalemia; check K ⁺ 1 week after starting spironolactone. Potential adverse effects include liver toxicity, gynecomastia, and sexual dysfunction.
Triamterene	Start at 100 mg BID; maximum daily dosage is 300 mg	Monitor for hyperkalemia; check K ⁺ 1 week after starting triamterene.

Direct Vasodilators and Anti-Adrenergic Agents

(Note: Alpha-blockers used for treatment of benign prostatic hypertrophy are not recommended as monotherapy for hypertension; however, these may cause hypotension especially in patients who are taking other antihypertensive medications.)

Clonidine	PO: Start at 0.1 mg BID; increase to usual maintenance dosage of 0.2-1.2 mg divided BID to TID; maximum 2.4 mg in divided doses Patch: Start at 0.1 mg/24-hour patch, increasing to desired effect; maximum dosage is 0.6 mg/24-hour patch	Possible adverse effects include bradycardia, sedation. Risk of rebound hypertension upon discontinuation: taper over course of 7 days.
Hydralazine	Start at 10 mg QID; increase by 10-25 mg/dose to effective dosage; may divide effective daily dosage BID; maximum 300 mg per day in divided doses	Possible adverse effects include lupus-like syndrome, requiring discontinuation. May cause reflex tachycardia; use with caution in patients with CAD.
Doxazosin	Start at 1 mg QHS; maximum 16 mg per day	Not a first-line agent. Possible adverse effects include risk of CHF, dizziness, postural hypotension, drowsiness, and syncope; all more likely if doxazosin is given with other vasodilators, including PDE-5 inhibitors. Risk of syncope with initial dosages; start at lowest dose QHS. If drug is interrupted, restart at 1 mg QHS dosing.

Prazosin	Start at 1 mg BID or TID; usual maintenance dosage 20 mg/day divided BID or TID; maximum 40 mg divided BID or TID	Not a first-line agent. Possible adverse effects include risk of CHF, dizziness, postural hypotension, drowsiness, and syncope; all more likely if prazosin is given with other vasodilators, including PDE-5 inhibitors. Risk of syncope with initial dosages; start at lowest dose QHS. If drug is interrupted, restart at 1 mg QHS.
Terazosin	Start at 1 mg QHS; usual daily dosage 1-5 mg QD or divided BID; maximum 20 mg per day	Not a first-line agent. Possible adverse effects include risk of CHF, dizziness, postural hypotension, drowsiness, and syncope; all more likely if terazosin is given with other vasodilators, including PDE-5 inhibitors. Risk of syncope with initial dosages; start at lowest dosage QHS. If drug is interrupted, restart at 1 mg QHS dosing.



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Liver Disease and Cirrhosis

KEY POINTS

- Chronic liver disease is common among HIV-infected patients, and is increasingly a cause of mortality and morbidity as effective ART allows persons with HIV to live longer.
- HIV infection may accelerate liver damage caused by HCV or HBV infection. HCV infection is particularly common among HIV-infected patients, especially those who acquired HIV through injection drug use (IDU).
- Long-term complications of HBV and HCV infection include cirrhosis, end-stage liver disease (ESLD), and hepatocellular carcinoma (HCC).
- It is essential that providers working with HIV patients be able to identify liver disease and determine whether cirrhosis has developed.
- Long-term management of cirrhosis is important to providing optimal prevention and treatment of complications.
- Some ARVs may cause liver toxicity (hepatotoxicity) but most can be used safely by patients with liver disease, with proper monitoring. Patients should not be undertreated for HIV because of concurrent liver disease.

Note: Current information on VHA policy, guidelines, and tools related to liver disease can be found online at <http://www.hepatitis.va.gov/>.



BACKGROUND

Any disease or injury that chronically affects the liver can cause fibrosis (scarring); this process ultimately may progress to cirrhosis.

Cirrhosis is characterized by diffuse interlacing bands of fibrous tissue dividing the hepatic parenchyma into micronodular or macronodular areas.

Veterans with HIV*

Cirrhosis: 2%
Decompensated liver disease: 1%
HCC: 0.3%
HCV: 28%
HBV: 11%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to these conditions

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

Epidemiology of HIV and Liver Diseases

- High morbidity and mortality: In the U.S. general population, cirrhosis accounts for 40,000 deaths per year and for the loss of more than 228,000 years of potential life.
- As HIV patients with access to ART survive longer, comorbidities such as chronic liver disease have become leading causes of illness and death. ESLD is now a leading cause of death in patients with HIV/HCV or HIV/HBV coinfection.
- HIV infection accelerates progression of liver disease associated with HCV or HBV.
- Other factors that cause more severe liver disease, including alcohol misuse, drug-associated hepatotoxicity, male gender, and fatty liver (steatosis), are also more common in the HIV-infected population.

Potential Causes of Liver Disease, Especially among HIV-Infected Patients

Common	Less Common
<ul style="list-style-type: none">• Alcoholic hepatitis• Alcoholic cirrhosis• Chronic hepatitis B• Chronic hepatitis C• Nonalcoholic fatty liver disease	<ul style="list-style-type: none">• Drug-induced liver injury• Autoimmune hepatitis• Primary biliary cirrhosis• Primary sclerosing cholangitis• Hemochromatosis• Wilson disease• Alpha-1 antitrypsin deficiency

- **Prevalence of viral hepatitis among HIV-infected individuals in the United States**
 - 30-40% coinfecting with HCV
 - 9-27% of heterosexuals
 - 1-12% of men who have sex with men
 - 72-95% of injection drug users
 - 28% of veterans
 - 6-14% coinfecting with HBV
 - 4-6% of heterosexuals
 - 9-17% of men who have sex with men
 - 7-10% of injection drug users
 - 11% of veterans
- Risk factors for liver diseases other than viral hepatitis are common in the HIV-infected population.

- Abnormalities in liver enzyme levels are common among HIV-infected persons, even in the absence of HCV or HBV infection.
 - Cross-sectional studies have shown a high prevalence of elevated AST (20%), ALT (15%), and alkaline phosphatase (43%).
- Alcohol consumption is common among people with HIV infection.
 - Rates of heavy drinking among people with HIV are almost twice those found in the general population. Approximately 8% of persons with HIV report heavy drinking in the past month.
 - Alcohol use disorders were diagnosed in 33% of HIV-infected veterans in VA care in 2007.
- Other comorbidities associated with liver disease:
 - Diabetes mellitus
 - Hyperlipidemia
 - Obesity
 - Hemophilia
 - Ulcerative colitis



EVALUATION

- At initial assessment, HIV-infected patients should be evaluated for clinical, biochemical, and virologic evidence of chronic liver disease.
- Frequency of reassessments depends on the presence and severity of existing disease, risk factors for liver disease (eg, IDU, alcohol misuse), and prescription of potentially hepatotoxic medications (eg, NVP).

Clinical Features of Liver Diseases

(see below for features of decompensated cirrhosis)

History	<p>More than 40% of patients with cirrhosis are asymptomatic.</p> <ul style="list-style-type: none"> • Fatigue • Weight loss • Inability to concentrate • Decreased libido • Pruritus (in cholestatic liver diseases) 		
Physical examination	<p>Perform a thorough physical examination with special attention to the abdomen, skin, and neurologic system. Note that patients may display no abnormalities. Abnormal findings include:</p> <table style="width: 100%; border: none;"> <tr> <td style="vertical-align: top;"> <ul style="list-style-type: none"> • Jaundice • Spider angiomata • Palmar erythema • Caput medusa </td> <td style="vertical-align: top;"> <ul style="list-style-type: none"> • Asterixis • Gynecomastia • Testicular atrophy • Temporal wasting </td> </tr> </table>	<ul style="list-style-type: none"> • Jaundice • Spider angiomata • Palmar erythema • Caput medusa 	<ul style="list-style-type: none"> • Asterixis • Gynecomastia • Testicular atrophy • Temporal wasting
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- Hepatomegaly (palpable liver)
- Splenomegaly
- Ascites
- Clubbing
- Hypertrophic osteoarthropathy
- Dupuytren contracture
- Fetor hepaticus

ARVs and Hepatotoxicity

Many ARVs may cause liver damage, particularly in patients with preexisting liver disease. These include:

- NVP*
- Most PIs, particularly DRV,TPV
- d4T, ddl

Note: ATV and IDV may cause isolated hyperbilirubinemia through inhibition of uridine diphosphate-glucuronosyltransferase (UGT) activity; this does not indicate liver disease.

* Increased risk if NVP is initiated in men with CD4 counts >400 cells/μL or in women with CD4 counts >250 cells/μL.

Biochemical Features of Liver Disease and Common Causes

Elevated aminotransferases (AST, ALT)	Elevated alkaline phosphatase (with or without bilirubin elevation)	Elevated bilirubin (without increase in alkaline phosphatase)
<ul style="list-style-type: none"> • Chronic HCV • Chronic HBV • Autoimmune hepatitis • Nonalcoholic steatohepatitis (NASH) • Drug effect/hepatotoxicity • Alcohol 	<ul style="list-style-type: none"> • Primary biliary cirrhosis • Sclerosing cholangitis • Drug-induced liver injury • Infiltrative liver disease • Sarcoidosis • Granulomatous hepatitis 	<ul style="list-style-type: none"> • Cirrhosis • Drug effect (eg,ATV and IDV commonly cause isolated elevation of unconjugated bilirubin)

(Note: A Web-based course on liver function test abnormalities is available at <http://www.hepatitis.va.gov/vahep?page=prtop02-ed-01>.)

Laboratory Findings and Specific Liver Diseases

Disease	Typical Findings (may not be present)
Alcoholic liver disease	<ul style="list-style-type: none"> • History of alcohol abuse • AST/ALT ratio often >2:1 • AST and ALT both <500 IU/mL (if no other injurious processes) • GGT may be ↑

Chronic hepatitis C	<ul style="list-style-type: none"> • Anti-HCV (HCV Ab) + • HCV RNA + • AST, ALT may be ↑ or normal
Chronic hepatitis B	<ul style="list-style-type: none"> • HBsAg + (in some cases may be –) • HBV DNA + (usually; may be undetectable in patients who take ARVs with activity against HBV) • HBeAg may be + or – • AST,ALT usually ↑; may be normal
Primary biliary cirrhosis	<ul style="list-style-type: none"> • Antimitochondrial antibodies +
Primary sclerosing cholangitis	<ul style="list-style-type: none"> • History of inflammatory bowel disease • ANA often + • ASMA often +
Autoimmune hepatitis	<ul style="list-style-type: none"> • ANA often + • ASMA often + • Anti-LKM-I often + • Hypergammaglobulinemia
Steatohepatitis/Nonalcoholic fatty liver disease (NAFLD)	<ul style="list-style-type: none"> • History of diabetes mellitus • History of metabolic syndrome (obesity, dyslipidemia, diabetes mellitus) • ↑ AST and/or ALT • Fatty infiltration of liver on imaging

Abbreviations: ANA = antinuclear antibodies; ASMA = antismooth muscle antibodies; GGT = gamma-glutamyltransferase; LKM = liver/kidney microsomes

Virologic Features of Liver Disease

HBV Diagnostic Tests and Interpretation

	Acute Hepatitis B	Recovery from Acute Hepatitis B	Chronic HBsAg+ Disease	Chronic HBeAg- Disease	Successful Vaccination	Recovery from Acute Hepatitis B with Loss of HBsAb
HBsAg	+ (may clear)	-	+	+	-	-
Anti-HBs	-	+	-	-	+	-
Anti-HBc IgM	+ (may be only marker during window period)	-	-	-	-	-
Anti-HBc	+	+	+	+	-	+ (also termed "isolated HBcAb+")
HBeAg	+	-	+	-	-	-
Anti-HBe	-	+ (in some cases)	-	+	-	+ (in some cases)
DNA (PCR if required)	+	-	+	+	-	- (in rare cases may be +)

HCV Diagnostic Tests and Interpretation

	Acute Hepatitis C	Spontaneously Resolved or Successfully Treated Hepatitis C	Chronic Hepatitis C	Low-Level Chronic Hepatitis C	False-Positive Hepatitis C
Anti-HCV	- or +	+	+	+	+
HCV RIBA	- or +	+	+	+	-
HCV RNA Quantitative	+	-	+	-	-
HCV RNA Qualitative	+	-	+	+	-
HCV Genotype	+	-	+	+ or -	-

Cirrhosis

Definitions:

Compensated cirrhosis: Cirrhosis is present but patient is without any specific clinical complication of cirrhosis.

Decompensated cirrhosis: Patient develops at least 1 complication of cirrhosis, such as ascites, jaundice, encephalopathy, or variceal hemorrhage.

Signs/Symptoms of Cirrhotic Decompensation	Causes
Upper GI bleeding	Variceal hemorrhage
Confusion	Encephalopathy
Abdominal distention	Ascites
Edema	Hypoalbuminemia
Leg and muscle cramps	Reduced circulating plasma volume
Jaundice	Hyperbilirubinemia (liver insufficiency)
Dyspnea	Pleural effusion (hydrothorax), hepatopulmonary syndrome

Diagnostic Tests for Cirrhosis

Liver biopsy (“gold standard”): histological diagnosis made by liver biopsy or at autopsy.

Alternatives to liver biopsy:

- Diagnosis can be made clinically, using available clinical and laboratory data but without obtaining a liver biopsy.
- Diagnosis may be made radiologically.

Potential Laboratory Findings in Patients with Cirrhosis

Indicators of liver insufficiency	Indicators of portal hypertension
↑ Bilirubin	↓ Platelets (earliest finding)
↑ Prothrombin time or INR	↓ Leukocytes and neutrophils
↓ Albumin	↑ Globulins

Role of abdominal imaging in liver disease

- Radiological imaging can sometimes detect findings of cirrhosis and may obviate the need for liver biopsy. Findings that suggest the presence of cirrhosis include:

- Small, contracted liver
 - Surface nodularity, increased echogenicity of liver
 - Splenomegaly
 - Ascites
 - Collateral veins (the most important finding indicative of cirrhosis)
 - (See **Management of Complications of Cirrhosis and Chronic Liver Disease**, p. 195)
- The major use of abdominal imaging is for detecting complications of cirrhosis (eg, ascites, HCC, and hepatic or portal vein thrombosis) in cirrhotic patients.
 - In patients with chronic liver disease but without cirrhosis, abdominal imaging can be completely normal or can show fatty liver; a nonspecific finding.
 - Useful radiology studies include abdominal ultrasound, abdominal CT scan, and abdominal MRI.

Staging and Classification of Cirrhosis

Child-Turcotte-Pugh Score

- Originally developed to estimate the risk of death after portacaval shunt surgery; this modified version was intended to assess the risk of nonshunt operations.
- The score is determined by assessing clinical (subjective) complications of cirrhosis and laboratory (objective) abnormalities indicative of liver dysfunction.

Child-Turcotte-Pugh Classification of Liver Disease

Parameter	Points Assigned		
	1	2	3
Ascites	Absent	Slight (or diuretic responsive)	Moderate/Tense (or refractory to diuretics)
Encephalopathy	None	Grade 1-2 (or precipitant induced)	Grade 3-4 (or chronic)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (mg/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (seconds over control) or INR	PT: 1-3 or INR: <1.7	PT: 4-6 or INR: 1.7-2.3	PT: >6 or INR: >2.3

Grade A = Total score 5-6

Grade B = Total score 7-9

Grade C = Total score 10-15

Model for End-Stage Liver Disease (MELD) Score

- The MELD score is a newer method for predicting 3-month survival. It is used for liver allocation (transplant) by the United Network for Organ Sharing (UNOS) and has been adopted for use in the nontransplant setting.
- It is used to determine how urgently a patient needs a liver transplant within the coming 3 months.
- It is the strongest predictor of mortality in HIV-infected patients with ESLD.
 - Used for patients ≥ 12 years of age
 - Expressed on a numerical scale, ranging from 6 to 40
 - Computed using 3 routine laboratory test results: bilirubin, INR, and CrCl:

$$\text{MELD} = 3.78[\text{Ln serum bilirubin (mg/dL)}] + 11.2[\text{Ln INR}] + 9.57[\text{Ln serum creatinine (mg/dL)}] + 6.43$$

A calculator for determining MELD scores is available on the Mayo Clinic website: <http://www.mayoclinic.org/meld/mayomodel6.html>

- HCC and other complications of cirrhosis are ascribed additional MELD points.

R_x MANAGEMENT

Goals: prevention of further liver damage, slowing progression of liver disease, management of cirrhotic complications

Prevention of further insults to the liver:

- HAV vaccination
- HBV vaccination
- Pneumococcus vaccination
- Influenza vaccination
- Avoid or minimize hepatotoxic drugs
- Maintain normal BMI (avoid obesity)
- For hepatically metabolized drugs, adjust dosages according to package insert instructions

Slow progression of liver disease:

- Abstinence from alcohol use for all, regardless of underlying disease process: counsel or refer for treatment, as appropriate (see **Alcohol Misuse**, p. 3)
- Avoidance of hepatotoxic or nephrotoxic medications (eg, NVP, ddl, NSAIDs, aminoglycosides)

- Treatment of HIV, if coinfecting with HBV or HCV: ARV therapy for HIV may slow progression of HBV and HCV
- Treatment of chronic HCV, if eligible: pegylated interferon-alfa in combination with ribavirin
- Treatment of chronic HBV, if eligible: currently FDA-approved medications for treatment of HBV include 3TC, TDF, telbivudine, entecavir, adefovir, and pegylated interferon-alfa. Another ARV, FTC, is also active against HBV, but is not approved for treatment of HBV.
 - It is very important to note that, when using HBV antiviral agents that are also active against HIV (eg, 3TC, FTC, TDF, or entecavir) in a patient coinfecting with HIV and HBV, these agents should **not** be used as monotherapy. In coinfecting patients, the HBV medications must be used as combination therapy within a multidrug, fully suppressive HIV regimen to avoid development of HIV resistance.
- Treatment of autoimmune hepatitis: can include prednisone or immunosuppressive agents

Management of Complications of Cirrhosis and Chronic Liver Disease: Detection, Prevention, Treatment

(**Note:** Patients with cirrhosis are best managed in collaboration with a GI specialist, particularly those with severe or recurrent complications. A summary of VA Hepatitis C Resource Center recommendations on management of cirrhosis can be found at <http://www.hepatitis.va.gov/doc/va01-pr/prtop08/prtop08-01-quicknotes.doc>.)

Ascites

Overview:

- The most common complication of cirrhosis
- 30% of patients with compensated cirrhosis develop ascites within 5 years
- 2-year survival rate of patients with ascites is 50%

Primary prophylaxis: none recommended, other than low-salt diet (1-2 g Na/day); may liberalize salt intake if salt restriction results in poor food intake

Treatment: Diuretics (eg, spironolactone alone or together with furosemide)

- Start with spironolactone 50-100 mg daily, then add furosemide 20-40 mg daily and sequentially increase as necessary and tolerated to maximum dosage of spironolactone 400 mg daily and furosemide 160 mg daily
- Avoid NSAIDs because of risk of hepatorenal syndrome
- Patients with massive ascites may require therapeutic large-volume paracenteses, often with albumin supplementation; should be treated in consultation with a GI/hepatology specialist
- Refractory ascites may require placement of a transjugular intrahepatic portosystemic shunt (TIPS)

Spontaneous Bacterial Peritonitis (SBP)

Overview:

- Bacterial infection of ascitic fluid that occurs in the absence of an intraabdominal source of infection
- Diagnosis: Polymorphonuclear leukocyte (PMN) count of >250 cells/ μL in the ascitic fluid, obtained via paracentesis
- Patients may be asymptomatic, may have very subtle clinical findings, or may have fever, abdominal pain, and altered mental status

Primary prophylaxis: Fluoroquinolone may be initiated in the hospitalized patient with severe liver disease and renal dysfunction

Treatment: Third-generation cephalosporin, ampicillin/sulbactam, or fluoroquinolone, given IV for initial occurrence; avoid aminoglycosides

Secondary prophylaxis: Fluoroquinolone or TMP-SMX

Variceal Hemorrhage/GI Bleeding

Overview:

- ~25% of patients with cirrhosis and varices experience hemorrhage from gastroesophageal varices in the first year after diagnosis
- The bleeding-related mortality is around 30%

Screening: Upper endoscopy (EGD) is recommended for every patient with cirrhosis

Primary prophylaxis: Nonselective beta-blockers or endoscopic variceal ligation are recommended for prophylaxis in patients with medium or large varices, to prevent the first episode of variceal hemorrhage

- Recommendation: Propranolol; start 10-20 mg PO BID, increase as tolerated (goal is to titrate to a heart rate of 50-60 bpm, if tolerable)
- Starting beta-blockers is not recommended unless varices have been documented

Treatment: When a variceal bleed occurs, immediate hospitalization and GI consultation are needed for treatment

Secondary prophylaxis: After a variceal bleed, the combination of nonselective beta-blockers and endoscopic variceal ligation are recommended to decrease the risk of another bleed

Hepatic Encephalopathy

Overview:

- Variable abnormalities of neurological and psychiatric function, including insomnia, hypersomnia, irritability, confusion, disorientation, hyperactive deep tendon reflexes, and asterixis
- Diagnosis: Based on clinical picture rather than laboratory or imaging results

Primary prophylaxis: None

Treatment: Mainly consists of identification and treatment of precipitating factors

- Lactulose: start at 30 cc PO every 1-2 hours until bowel evacuation, titrate to 2-3 soft bowel movements per day, but avoid diarrhea as it will lead to volume depletion and dehydration
- Rifaximin: 400 mg PO TID is an alternative for patients who cannot tolerate lactulose

Secondary prophylaxis: None; once precipitating factors are eliminated, lactulose can be discontinued; in patients with chronic encephalopathy, chronic treatment with lactulose is warranted

- Sedatives and tranquilizers should not be used
- Constipation should be avoided

Hepatocellular Carcinoma (HCC)

Overview:

- Incidence varies widely according to geographic location, as well as among various ethnic groups within the same country
- In the United States, the incidence of HCC is rising and has almost doubled during the past 2-3 decades, chiefly among patients with cirrhosis secondary to HCV; in the VHA, the number of HCC cases nearly doubled between 2004 and 2007
- A study of 384 patients with HCV and compensated cirrhosis found that 1.4% per year developed HCC
- 20-56% of patients who develop HCC have previously undiagnosed cirrhosis
- In chronic HBV, HCC can occur before the development of cirrhosis, but in other chronic liver diseases, HCC typically does not occur until there is cirrhosis

Risk factors:

- Age
- Duration of liver disease
- Male sex
- HBV (can occur in patients with inactive, carrier HBV [HBsAg+, normal ALT, undetectable or low-level HBV DNA] and in those with chronic HBV [HBsAg+, elevated ALT, high HBV DNA])
 - Chronic HCV with cirrhosis
 - Hereditary hemochromatosis with cirrhosis, alcoholic cirrhosis
- Cirrhosis of almost any other cause

Screening: See below

Treatment: Potential indication for liver transplant; other treatment options include tumor resection, radiofrequency tumor ablation, transarterial chemoembolization, or chemotherapy; refer to Hepatology or Oncology



Screening for Hepatocellular Carcinoma

(based on American Association for the Study of Liver Diseases [AASLD] 2005 guidelines for screening of HCC)

Patients who should be screened for HCC:

(Note that some patients with chronic HBV are at increased risk even in the absence of cirrhosis)

- HBsAg+ Asian males ≥ 40 years of age
- HBsAg+ Asian females ≥ 50 years of age
- HBsAg+ and cirrhosis of any gender/age
- HBsAg+ Africans ≥ 20 years of age
- HBsAg+ with a family history of HCC
- Cirrhosis resulting from alcohol use
- Cirrhosis resulting from HCV
- Cirrhosis resulting from hemochromatosis
- Cirrhosis resulting from primary biliary cirrhosis
- Patients on transplant waiting list
- Patients with cirrhosis resulting from NAFLD, autoimmune hepatitis, or alpha-1 antitrypsin deficiency: few data, no recommendations

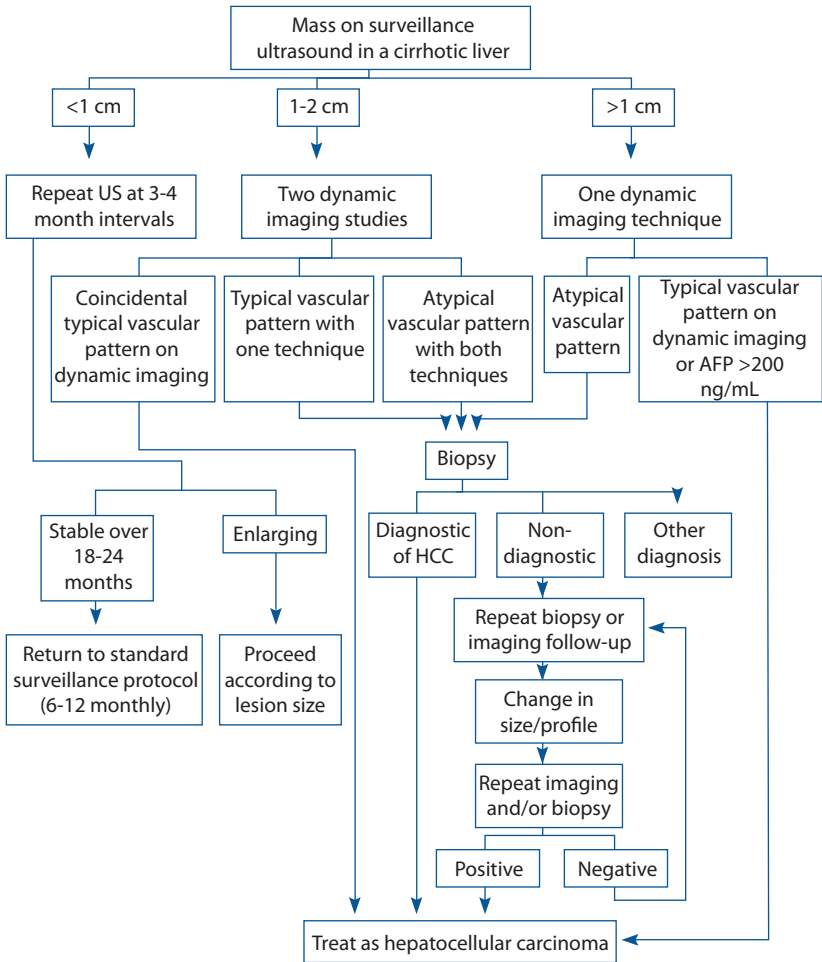
Recommended technique and time intervals for HCC screening

- Surveillance should be performed every 6-12 months using ultrasound. Because ultrasound is particularly operator dependent, some centers where ultrasound reliability is low may choose to use either CT or MRI for surveillance imaging.
- Alpha-fetoprotein (AFP) should not be used alone as a screening tool for HCC unless ultrasound is not available: it has poor sensitivity and specificity.
 - AFP measurement is recommended if a focal hepatic mass is detected with ultrasound or other abdominal imaging.
 - AFP level does not correlate well with other clinical features of HCC, such as size, stage, or prognosis.
 - Based on a systematic review, with a cutoff of 20 mcg/L, AFP has sensitivity of 41-65% and specificity of 80-94%.

How to work up a hepatic mass found on screening ultrasound

- For a mass <1 cm in diameter found on ultrasound in a cirrhotic liver: repeat ultrasound in 3-4 months to look for stability versus a change in size.
- For a mass ≥ 1 cm in diameter found on ultrasound in a cirrhotic liver: CT scan with dynamic vascular imaging.
- For evaluation, see **Figure 1** below.

Figure 1. AASLD algorithm for evaluation of liver mass found on screening ultrasound



Source: Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology*. 2005 Nov;42(5):1208-36. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Liver Transplantation

Note: Current information on VA transplantation policy and procedures can be found at the website for the VA National Transplant Program at www.va.gov/transplant. Resources for providers can be found at <http://www.hepatitis.va.gov/vahep?page=prtop08-03-rr>.

Background

- Chronic hepatitis C with progression to ESLD or HCC is the most common reason for liver transplantation, both within the VA system and in the United States general patient population.
- VA patients may be referred for liver transplantation within the VA system or at affiliated academic medical centers.
- Currently, approximately 100 liver transplants are performed annually within the VA system, with survival rates that meet or exceed UNOS averages.
- HIV-infected patients are eligible for consideration for liver transplantation at selected VA transplant centers.
- Referral for liver transplantation involves submission of a transplantation package to the VA Central Office; if approved, the package is forwarded to one of the national VA liver transplant centers for further evaluation.
- For HIV-infected transplant candidates, the application package must contain an infectious disease evaluation using a template specified by the VA National Transplant Program.
- In cases of fulminant hepatic failure or other critical situations, emergency applications may be made by contacting the VA National Transplant Program.

Transplant referral

- The local VA Medical Center Transplant Referral Coordinator should be consulted as soon as referral for liver transplantation is under consideration.
- Update Child-Turcotte-Pugh and MELD scores regularly. For purposes of ESLD follow-up, patients should be seen as follows based on MELD scores (note: other factors may indicate more frequent follow-up):
 - ≤ 10 : at least every 6-12 months
 - 11-18: at least every 3 months
 - 19-24: at least every month
 - ≥ 25 : at least every week
- Refer for transplant evaluation if:
 - Child-Turcotte-Pugh score is ≥ 7 or MELD score is ≥ 15
 - MELD score is 11-13 and patient has refractory ascites or hyponatremia
 - Meets HCC criteria for transplantation (≤ 3 masses, all ≤ 3 cm in diameter; WHO performance status < 3 ; Child-Turcotte-Pugh score ≤ 9)

- Patients must be abstinent from all substances, including tobacco. Active substance use of any kind, or <6 months' sobriety, is the most common reason for rejection or deferral of patients for listing for transplantation; see **Alcohol Misuse**, p. 3; **Substance Use**, p. 69; and **Smoking Cessation**, p. 53.
- Patients also must have documented adequate social support for care during the peritransplant and posttransplant periods.

Posttransplant care

- Patients who have received liver transplants (whether inside or outside the VA system) will return to the referring VA Medical Center for care.
- 1-year survival rates are typically >80%.
- The major clinical issues in the posttransplant period are management of and toxicities from immunosuppressive agents required to prevent transplant rejection, drug interactions, and infectious complications of immunosuppression.
- See <http://www.hepatitis.va.gov/vahep?page=prtop08-03-cs-01#S7X> for more information on posttransplant care.



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Osteoarthritis

KEY POINTS

- Osteoarthritis (OA) is a joint disorder caused by the progressive breakdown and eventual loss of cartilage of one or more joints.
- Typical symptoms include joint pain exacerbated by activity and relieved by rest, morning stiffness, or stiffness after periods of inactivity.
- Evaluation of OA includes plain X rays; distinction from other arthritides may include ESR and rheumatoid factor (RF) determinations and synovial fluid examination to rule out infection or crystal disease.
- The goals of treatment are pain reduction, improvement of joint mobility, and prevention of functional impairment.
- All patients should receive nonpharmacologic interventions, including weight loss counseling as indicated. Pharmacologic interventions should start with the lowest-risk intervention for the level of impairment (acetaminophen, NSAIDs, or injections) and proceed along the analgesic ladder and levels of intervention (opioids, arthroscopy, or other surgical procedures).



BACKGROUND

OA is the most common form of arthritis in the United States. Risk factors include age, obesity, and history of joint trauma. Recreational running does not increase the risk of developing OA.

Veterans with HIV*

Osteoarthritis: 14%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to this condition

Definitions and Classification

- OA (also called degenerative joint disease) is a disorder caused by the progressive breakdown and eventual loss of cartilage of ≥ 1 joints. OA usually affects weight-bearing joints.
- OA can be **idiopathic** or **secondary**:
 - Idiopathic OA does not have a specific inciting cause, and typically involves the hands, feet, knees, hips, or spine.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- Secondary OA is caused or enhanced by another condition such as trauma, calcium pyrophosphate dehydrate deposition disease (CPPD), or other bone or joint disorders such as osteonecrosis, rheumatoid arthritis, gout, septic arthritis, or Paget disease. This form of OA can present with atypical joint involvement.
- Treatment of OA depends on whether it is **noninflammatory** or **inflammatory**. Symptoms of inflammatory OA include swelling, morning stiffness lasting >30 minutes, and night pain.

Diagnostic criteria for OA depend on the joint affected:

- **Knee osteoarthritis** = knee pain + ≥ 3 of the following:
 1. Age >50
 2. Morning stiffness for <30 minutes
 3. Crepitus on active motion of the knee (see **Evaluation** below)
 4. Bony tenderness
 5. Bony enlargement
 6. No palpable warmth
 - Other characteristics that add to the accuracy of the diagnosis: ESR <40 mm/hour, RF <1:40, synovial fluid with clear fluid and white blood cell (WBC) count of <2,000 cells/ μ L, and X rays showing osteophytes
- **Hand osteoarthritis** = hand pain + ≥ 3 of the following:
 1. Bony enlargement of ≥ 2 of the following joints: 2nd or 3rd distal interphalangeal (DIP) joint or proximal interphalangeal (PIP) joint, 1st carpometacarpal (CMC, base of thumbs) of either hand
 2. Bony enlargement of ≥ 2 DIP joints
 3. Swelling of <3 metacarpophalangeal (MCP) joints
 4. Deformity of at least 1 of the joints listed in #1
- **Hip osteoarthritis** = hip pain and ≥ 2 of the following:
 1. ESR <20 mm/hour
 2. Femoral or acetabular osteophytes on radiography
 3. Joint space narrowing on radiography
 - Other characteristics that add to the accuracy of the diagnosis: internal rotation of <15°, pain on internal rotation, morning stiffness, flexion <115°



Risk factors	<ul style="list-style-type: none"> • Age >40 years • Obesity
History	<p>Ask about history of:</p> <ul style="list-style-type: none"> • Trauma • CPPD • Osteonecrosis • Rheumatoid arthritis • Gout • Septic arthritis • Paget disease • Reactive arthritis
Differential diagnosis (Partial. Note that these may be superimposed on OA.)	<ul style="list-style-type: none"> • CPPD: Typically affects knees, wrists, MCP joints, hips; check synovial fluid. • Gout: Typically affects great toes, ankles, knees, wrists; acute onset with intense swelling and pain; check synovial fluid. • Rheumatoid arthritis: MCP and PIP joint involvement typically prominent; stiffness is worse after resting the joint; check RF. • Infectious monoarticular disease: typically affects a single joint; check synovial fluid. Common organisms include <i>Staphylococcus aureus</i>, <i>Streptococcus</i> organisms, <i>Neisseria gonorrhoeae</i>, <i>Borrelia burgdorferi</i>. In immunocompromised patients, etiologies include gram-negative bacteria, mycobacteria, fungi, and mycoplasma. • Osteonecrosis or avascular necrosis (AVN): Typically involves the femoral or humeral heads; patients with HIV are at increased risk of AVN (4% of HIV-infected patients had AVN in one study). Patients typically present with pain, particularly with weight-bearing and motion. Groin pain is seen with femoral head involvement, shoulder pain with humeral head involvement. AVN has been associated with corticosteroids, testosterone, statins, weight training, alcohol consumption, tobacco smoking, and presence of anticardiolipin antibodies. Magnetic resonance imaging (MRI) is the most sensitive test for early diagnosis; plain X rays will show changes after months to 5 years from onset. • Bursitis: Frequently secondary to trauma; does not limit motion unless joint is involved. Most common sites include prepatellar, olecranon, trochanteric, and bursae. Consider bursal fluid aspiration to rule out infection.

Symptoms	<ul style="list-style-type: none"> • Joint pain exacerbated by activity and relieved by rest • Morning stiffness or stiffness after periods of inactivity • Advanced disease: pain may be present with progressively less activity, eventually during rest and at night • Episodic flares: increases in pain and inflammation that may result from crystal disease
Physical examination	<p>Examination with particular attention to joints:</p> <ul style="list-style-type: none"> • Tenderness on palpation, usually without warmth or significant erythema • Effusions occasionally present • Crepitus: disruption of normally smooth surfaces of joints [Place hand on a joint, ask the patient to move that joint. If crepitus is present, bumps and cracks will be felt.] • Osteophytes: palpable bony enlargements along the joint periphery <p>Typical joints affected:</p> <ul style="list-style-type: none"> • Hands: DIP and PIP with Heberden nodes (bony enlargements) • Feet: especially the great toe • Knees: osteophytes, effusions, crepitus, limited range of motion • Hips: pain and limited range of motion • Spine: C5, T8, L3; can lead to spondylosis (osteophytes from the vertebral body impinging on the spinal canal) • Shoulders: anterior shoulder pain at the glenohumeral joint
Imaging	<ul style="list-style-type: none"> • Obtain plain X rays for patients with suspected OA • Radiographic changes in OA are insensitive in early disease and correlate poorly with symptoms; however, the following changes are fairly specific and make further imaging unnecessary: <ul style="list-style-type: none"> • Joint space narrowing • Osteophytes • Subchondral sclerosis • Subchondral cysts • Consider MRI of the knee in patients with knee locking, popping, or instability suggestive of meniscal or ligamentous damage (can be treated surgically). • Consider MRI if trying to rule out AVN
Diagnostic testing	<ul style="list-style-type: none"> • Joint aspiration: When the patient has a joint with significant effusion or presence of warmth and erythema, obtain synovial fluid for examination (refer to Rheumatology or Orthopedic Surgery if needed). Request cell count, crystal analysis, Gram stain, and culture. In OA, the synovial fluid typically has mild pleocytosis, normal viscosity, and modestly elevated protein.

	<ul style="list-style-type: none"> If the patient has sterile inflammatory synovial fluid (WBC >2,000 cells/μL and polymorphonuclear leukocytes [PMNs] >75% but no crystals and a negative culture), consider checking ESR (or C-reactive protein [CRP]), RF, and anti-cyclic citrullinated peptide (CCP) antibodies. Positive results can suggest a diagnosis of rheumatic disorder.
Diagnostic criteria	See diagnostic criteria above for specific joints.

Rx MANAGEMENT

- The goals of treatment are pain reduction, improvement of joint mobility, and prevention of functional impairment.
- All patients with OA should receive nonpharmacologic interventions in addition to analgesics, as indicated. Depending on noninflammatory vs inflammatory OA, advance up the analgesic and intervention “ladder”:
 - acetaminophen or NSAIDs +/- adjuvants \rightarrow
 - weak opioids +/- adjuvants \rightarrow
 - strong opioids +/- adjuvants.
- Obesity is the most important modifiable contributor to OA; all overweight patients should be encouraged to lose weight.

Intervention	Comments
Nonpharmacologic	
	<ul style="list-style-type: none"> Weight-loss programs as indicated For acute flares, short periods of rest only (12-24 hours), followed by passive joint exercises Range of motion and strengthening exercises that target weak muscle groups Exercise programs involving exercises such as swimming, biking, walking, yoga, and tai chi Knee OA: simple elastic sleeve brace or wedged shoe insoles to help reduce joint impact Psychoeducation and cognitive-behavioral therapy (CBT) coping skills training
Pharmacologic (for dosages and additional information, see Pain Medications , p. 321)	
Capsaicin	<ul style="list-style-type: none"> Topical medication, for noninflammatory and inflammatory OA

Acetaminophen	<ul style="list-style-type: none"> • First-line analgesia in noninflammatory mild OA • Possible adverse effects: hepatotoxicity (especially if taken with alcohol), nephrotoxicity (with chronic overdose) • Safer but less effective than NSAIDs for chronic OA
NSAIDs (eg, ibuprofen, naproxen)	<ul style="list-style-type: none"> • For persistent noninflammatory and inflammatory OA • Avoid in patients with peptic ulcer disease or cirrhosis • To minimize risks, use the lowest effective dosage and try to use for short periods of time • Avoid indomethacin: associated with increased joint destruction
Intraarticular corticosteroid injection	<ul style="list-style-type: none"> • For moderate, persistent symptoms • Triamcinolone or methylprednisolone suspensions <ul style="list-style-type: none"> • Finger or toe joints: 10 mg • Wrists, elbows, ankles: 20 mg • Shoulder, knee, hip: 40 mg • Refer to rheumatologist or orthopedic surgeon if expertise is not available in clinic • Do not inject the joint if there is any suspicion of joint infection (clues include rapid onset of a large effusion, fever, leukocytosis) • Ensure aseptic technique • Possible adverse effects: tendon rupture (particularly with undiluted glucocorticoids in the shoulder), nerve atrophy if glucocorticoids enter the nerve sheath, skin changes, iatrogenic infection (rare) • Can repeat every 3 months for up to 2 years if effective • Hip injections are technically difficult and should be done under fluoroscopic guidance by a rheumatologist, orthopedist, or interventional radiologist
Colchicine Opiate analgesics Options include:	<ul style="list-style-type: none"> • Consider for patients with refractory inflammatory OA: many have calcium pyrophosphate crystals in the synovial fluid • Use in conjunction with NSAIDs • Avoid use for patients with renal or hepatic disease • Use opioids for patients who have pain refractory to the interventions listed above (nonpharmacologic, capsaicin, acetaminophen, ibuprofen, injections, colchicine) or who cannot receive those interventions • Start with weak opioids and assess safety, efficacy, and usage; titrate up and move to stronger opioids as needed

<p>Tramadol (not a typical opiate; exact mechanism of action is unknown; acts in part as a central opioid agonist)</p> <p>Weak opioids</p> <ul style="list-style-type: none"> • Codeine • Hydrocodone + acetaminophen • Oxycodone + acetaminophen <p>Strong opioids</p> <ul style="list-style-type: none"> • Morphine • Oxycodone • Hydromorphone • Fentanyl transdermal 	<ul style="list-style-type: none"> • Use opioids cautiously with elderly patients • Opioid therapy for chronic pain should follow a fixed-dose schedule, not PRN dosing • Risk of dependence, overdose: monitor closely • Chronic opioid therapy should incorporate an opioid use agreement that includes functional goals for outcome, not reduced pain intensity alone • Note that tramadol 37.5 mg + acetaminophen 325 mg has shown pain relief equivalent to codeine 30 mg + acetaminophen 325 mg but with fewer adverse effects (major adverse effect: headache)
Surgical	
Arthroscopic irrigation or debridement	<ul style="list-style-type: none"> • For moderate persistent symptoms • Referral to an orthopedic surgeon • Irrigation with sterile saline • Suction of debris and blood • Removal of floating cartilage • Debridement of excess tissue or bone • Repair of tears as needed and to extent possible
Arthroscopic synovectomy	<ul style="list-style-type: none"> • For inflammatory OA with profound impairment • Referral to an orthopedic surgeon • Arthroscopic removal of involved synovial tissue
Major surgical procedure	<ul style="list-style-type: none"> • For end-stage OA, profound impairment • Referral to an orthopedic surgeon • Includes total joint replacement



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Renal Disease

KEY POINTS

- At the time of HIV diagnosis, all patients should be screened for renal dysfunction with a urinalysis (UA) and a calculated estimate of renal function.
- Elevated risk of developing kidney disease: African American race, hypertension, diabetes, family history, CD4 count <200 cells/ μ L, unsuppressed viral load, hepatitis C virus (HCV) infection. Persons meeting any of these criteria should be screened annually.
- Chronic kidney disease (CKD) increases the risk of developing cardiovascular disease.
- Acute renal failure (ARF) usually is attributable to prerenal causes or medication toxicity leading to acute tubular necrosis (ATN) (see **Table 5**).
- Patients with CKD should be referred to a nephrologist for evaluation and possible renal biopsy.
- HIV-infected persons with CKD are less likely to receive ART, even when ART is indicated.
- HIV-associated nephropathy (HIVAN) is an indication to start ART.
- Dosage of most NRTIs should be adjusted for impaired renal function (see **Table 4**).



BACKGROUND

- There is a high prevalence (30%) of abnormal renal function among patients with HIV disease.
- CKD is increasingly a cause of morbidity among people with HIV infection.
- Risk factors for CKD include African American race, hypertension, diabetes, family history of CKD, CD4 count <200 cells/ μ L, unsuppressed viral load, and HCV infection.

Veterans with HIV*

Renal failure, acute: 7%

Renal failure, chronic: 6%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 with an ICD-9 code corresponding to these conditions

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- Risk factors for HIVAN include African American race, low CD4 cell count, and family history of CKD. Prevalence of HIVAN is 3.5% among HIV-infected African American patients.
- African Americans are disproportionately affected by kidney disease.
- HIV-infected persons with CKD are less likely to receive ART, even when ART is indicated.
- ART should be given to patients with renal disease, if indicated, though most NRTIs must be dosed according to renal function and some ARVs should be avoided (see **Table 4** and **Table 5**).



SCREENING

- All HIV-infected patients should be screened for kidney disease at the time of HIV diagnosis or entry into care.
- Patients with additional risk factors or exposure to nephrotoxic medications should be screened annually.
- Individuals without risk factors may be rescreened based on clinical signs and symptoms.
- Screening tests: calculated estimate of renal function, UA, and quantitative spot measurement of proteinuria.
- If screening shows creatinine clearance (CrCl) or estimated GFR (eGFR) <60 mL/min/1.73 m², or proteinuria $\geq 1+$ on urine dipstick analysis, calculate spot urine albumin-to-Cr ratio or spot urinary protein-to-Cr (described below), obtain renal ultrasound to look for anatomic abnormalities (including size), and refer to nephrologist for management and possible biopsy.

I. Estimate renal function:

- The first evidence of renal dysfunction may be an elevated serum Cr (SCr) level. Increases in SCr from baseline should prompt an evaluation.
- In many patients, SCr may not be an accurate measure of renal function:
 - May be deceptively low in the elderly and persons with low muscle mass
 - May be deceptively high in African Americans and persons with high muscle mass
- A calculated estimate of renal function is a better measure because it corrects for these variations.
- The simplified **Modification of Diet in Renal Disease (MDRD) Study equation** for eGFR is thought to yield a more accurate estimate of renal function than the Cockcroft-Gault equation, which measures CrCl, a proxy for GFR.
- CrCl typically is used to determine medication dosage adjustments in patients with renal insufficiency.

Simplified MDRD Equation for Estimating Renal Function

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 186 \times [\text{serum creatinine (mg/dL)}]^{-1.154} \times [\text{age (years)}]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if African American}]$$

Normal GFR: ≥ 90 mL/min/1.73 m²

CKD: GFR < 60 mL/min/1.73 m²

Online calculator available at:

http://www.nkdep.nih.gov/professionals/gfr_calculators/orig_con.htm

- 2. Perform urinalysis (dipstick or formal);** look especially for proteinuria and hematuria (see **Urology**, p. 227, for evaluation of isolated hematuria).

Table 1. Dipstick Interpretation in Setting of Abnormal eGFR

Protein	Blood	Consider
Negative	Negative	False negative Microalbuminuria (see below), multiple myeloma and other paraproteinemias, prerenal causes (see Table 3), postrenal causes (see Table 3), ischemic nephropathy
Positive	Negative	False positive Benign or orthostatic proteinuria, hypertension, nephrosclerosis, diabetes, tubulointerstitial diseases, polycystic kidney disease (PCKD), nephrotic syndrome, glomerulonephritis (GN)
Positive	Positive	UTI, pyelonephritis, rapidly progressive GN, other GN, HIV-associated vasculitis, pulmonary-kidney syndrome, hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, malignant hypertension, nephrotic syndrome, nephrolithiasis with obstruction, atypical diabetes, PCKD

3. Quantitate proteinuria:

- Evaluate patients with $\geq 1+$ protein on dipstick **or** GFR < 60 mL/min/1.73 m².
- Dipstick UA is insensitive for microalbuminuria (albuminuria below level detected by conventional dipsticks).
- Microalbuminuria may be the first indication of renal dysfunction; if detected, treatment to slow progression of renal disease should be started (see below).
- Timed (ie, 24-hour) collections have largely been replaced by:

1. The **random urinary albumin-to-Cr ratio:**

$$\text{Albumin}_{\text{Urine}} \text{ [mg/dL]} / \text{Cr}_{\text{Urine}} \text{ [mg/dL]}$$

Highly sensitive for microalbuminuria; normal is <0.03. Should be used at initial screening and for follow-up, if microalbuminuria is diagnosed.

2. The **random urinary protein-to-Cr ratio:**

$$\text{Protein}_{\text{Urine}} \text{ [mg/dL]} / \text{Cr}_{\text{Urine}} \text{ [mg/dL]}$$

Highly sensitive for proteinuria, but not for microalbuminuria; normal is <0.15.

Used to estimate 24-hour urine protein excretion (the ratio corresponds to grams of urinary protein excreted per 24 hours; eg, ratio of 0.15 corresponds to 0.15 g [150 mg] of proteinuria per 24 hours). Can be used to grade degree of proteinuria (see box below); can be monitored over time.

Note: these estimates may be inaccurate in muscular or cachectic patients.

Degree of Proteinuria Based on Spot Urinary Protein-to-Cr Ratio

Normal:	<150 mg/24 hours
Trace proteinuria:	150-500 mg/24 hours
Mild proteinuria:	500 mg to 1 g/24 hours
Moderate proteinuria:	1-3 g/24 hours
Nephrotic range proteinuria:	>3 g/24 hours

- Patients with significant proteinuria should be referred for further evaluation

Types of Proteinuria

Overflow proteinuria: Trace or negative dipstick protein but disproportionately larger amount on 24-hour test. Suggests light-chain disease, paraproteinemia, lymphoproliferative process, or hemolysis (if dipstick is also positive for blood).

Tubular protein: 500-2,000 mg/24 hours
Differentiate from glomerular causes by UPEP +/- IEP.

- UPEP: albumin > globulin suggests glomerular proteinuria; globulin > albumin suggests light chains or paraproteinemia

Common causes include analgesic nephropathy, focal glomerular sclerosis (recurrent UTI, reflux), collagen vascular diseases (Sjögren syndrome, lupus), hepatitis, HIVAN (see below), PCKD, heavy metal toxicity, interstitial nephritis (drugs or infectious), granulomatous diseases.

Glomerular protein, suggested by moderate to heavy proteinuria:

Suggests a more serious disorder. Rule out HIVAN, diabetes progression, hepatitis, vasculitis, malignancy, GN. Significant glomerular damage with proteinuria of >3 g: refer to nephrologist.

Massive proteinuria: >6 g/24 hours

Focus evaluation on HIVAN, hepatitis-associated nephropathy, severe focal glomerulosclerosis. Refer to nephrologist.

Chronic Kidney Disease



EVALUATION

- CKD is characterized by the presence for ≥ 3 months of either of the following:
 - Structural or functional kidney abnormalities, with or without decreased GFR, as diagnosed by abnormal pathology or abnormal markers. Markers can include blood or urine abnormalities (urinary protein, red blood cells, white blood cells, casts, fat) or abnormalities on imaging studies.
 - GFR < 60 mL/min/1.73 m², with or without other evidence of kidney damage (see simplified MDRD equation, above).
- Proteinuria and eGFR < 60 mL/min/1.73 m² are associated with increased cardiovascular disease and increased all-cause mortality.
- Treatment of early-stage CKD in HIV-noninfected persons slows progression of kidney disease.
- CKD has 5 stages, based on estimated renal function (see **Table 2**).

Table 2. National Kidney Foundation Stages of Chronic Kidney Disease (based on eGFR)

Stage	Definition	eGFR (mL/min/1.73 m ²)	Recommendations
1	Kidney damage with normal eGFR	≥ 90	Treat comorbid conditions; slow progression of CKD; reduce cardiovascular risk factors
2	Kidney damage with mildly decreased eGFR	60-89	Estimate progression of CKD
3	Kidney damage with moderately decreased eGFR	30-59	Evaluate and treat complications of CKD

4	Kidney damage with severely decreased eGFR	15-29	Prepare for renal replacement therapy (RRT; dialysis)
5	Kidney failure*	<15*	RRT, if uremia present*

* Dialysis usually is initiated when eGFR falls below 10 mL/min/1.73 m².

Evaluation of CKD

Risk factors	<ul style="list-style-type: none"> • Diabetes • Hypertension • Toxic insults (including medications) • Autoimmune disease • HCV infection • Inherited kidney disease (eg, PCKD) • HIVAN (see below) • Chronic urinary tract obstruction • Paraproteinemias • ARF
History	<ul style="list-style-type: none"> • Chronic medical problems: diabetes, hypertension, prior kidney disease, collagen vascular disease, hepatitis, kidney stones, prostate disease • Symptoms associated with kidney disease, such as: decreased attentiveness, nausea, vomiting, anorexia, weight change, dyspnea, orthopnea, leg swelling, fatigue, muscle cramps, restless legs, peripheral neuropathy, pruritus, urinary urgency or frequency, nocturia, dysuria, oliguria • Medications and over-the-counter products: NSAIDs, ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics, analgesics, antibiotics, antiviral agents, lithium
Physical examination	<ul style="list-style-type: none"> • Height, weight • Vital signs including orthostatic blood pressure • Volume assessment (rales, jugular venous distention, peripheral edema) • Cardiac exam (S3, S4, heave, murmur, rub) • Vascular exam (pulses, bruits) • Abdominal findings (mass, bruit, palpable bladder, flank tenderness) • Digital rectal exam (prostate) in men • Neurological exam, including mental status • Integument (rash, stigmata of embolic disease or ischemia) • Joints (arthritis)

Diagnostic testing

- eGFR, urinalysis, spot urine albumin-to-Cr ratio or protein-to-Cr ratio, as above
- Renal ultrasound
- Basic workup for non-HIV-related causes:
 - Hepatitis B and C serologies
 - Cryoglobulins
 - SPEP/UPEP
 - Fasting blood glucose
 - Complement levels
 - Antinuclear antibodies and antineutrophil cytoplasmic antibodies(Note: significant false-positive rates in HIV-infected persons)



WHEN TO REFER

- Refer promptly to nephrologist for possible biopsy and for directing appropriate therapy, particularly if HIVAN is suspected
- HIVAN can progress rapidly from proteinuria to end-stage renal disease (ESRD), and requires biopsy for unequivocal diagnosis (see **HIV-Associated Nephropathy**, below)
- Biopsy also can distinguish HIVAN from other HIV-related causes of CKD, such as immune complex disease and thrombotic angiopathy, as well as non-HIV-related causes of CKD

Rx MANAGEMENT

Goals:

- **Slow progression of CKD**
- **Address metabolic and hematologic abnormalities**
- Determine whether patient has signs/symptoms of ARF (see below).
- Maintain blood pressure at $\leq 130/80$ mmHg.
- Initiate ACEIs or ARBs for patients with hypertension or proteinuria (see **Hypertension**, p. 171, for dosing information).
 - Closely monitor patients on ACEIs and ARBs for hyperkalemia.
- ART:
 - Initiate or maximize efficacy of ART if diagnosis of HIVAN is established (see below).
 - Avoid ARVs with significant renal toxicity (see below).

- Adjust dosing of ARVs (see below) and other drugs (eg, TMP-SMX, H2 receptor antagonists) for renal function, as needed.
- Avoid NSAIDs and other nephrotoxic medications.
- Screen for and/or maximize treatment for diabetes and dyslipidemia (see **Diabetes**, p. 127, and **Dyslipidemia**, p. 143).
- Screen for and treat hematologic abnormalities (eg, anemia).
- Advise on protein- and salt-restricted diet; refer to renal dietitian to avoid malnutrition.
- Refer for substance abuse counseling, when appropriate, to decrease risk of nephropathy associated with use of heroin or other illicit substances.
- Monitor renal function; consult Nephrology regarding other care.
- **Refer patients with moderate to advanced CKD for RRT (ie, dialysis) or kidney transplantation.**
 - Early referral and counseling for RRT improve outcomes.
 - HIV-infected and HIV-uninfected ESRD patients have similar outcomes.
 - Refer before Cr rises to 4 or eGFR falls below 25 mL/min.
 - Refer at least 6 months before anticipated need for RRT (plot inverse of Cr vs time to define likely rate of progression).
 - Referral for transplantation may be made to the VA National Transplant Program (<http://www.va.gov/transplant>).

HIV-Associated Nephropathy



EVALUATION

- Occurs almost exclusively in persons of African descent. Other risk factors include low CD4 cell count, high HIV RNA.
- Much less common since the advent of combination ART.
- Among African American men, between 1995 and 1999, incidence of HIVAN decreased whereas prevalence and survival increased, which is consistent with a beneficial effect of ART on preventing and treating HIVAN.
- Most often presents as nephrotic syndrome, with proteinuria and decreased GFR. May progress rapidly to ESRD, often over the course of several weeks to months (especially in patients not on ART).
- Peripheral edema may be present.
- Imaging typically shows large echogenic kidneys.
- Biopsy shows collapsing focal segmental glomerulosclerosis with tubular and interstitial damage.

Goal:

- **Slow progression of HIVAN**
- All patients with HIVAN should be started on ART regardless of CD4 count.
- Refer immediately to a nephrologist for evaluation (including biopsy) and possible treatment.
- For patients with hypertension or proteinuria, treat with ACEIs or possibly ARBs to reduce blood pressure to <125/75 mmHg, and to eliminate or decrease proteinuria as much as possible.
- Closely monitor patients on ACEIs and ARBs for hyperkalemia.
- Consider adding corticosteroids if renal function fails to improve on ART (consult with nephrologist). Recommended prednisone dosage is 1 mg/kg/day, to a maximum dosage of 80 mg/day. Treatment duration is 2 months, with a 2-4 month taper.
- Refer patients with progressive disease for dialysis or transplantation.

Acute Renal Failure



EVALUATION

- Definition of ARF:
 - Decrease in eGFR of $\geq 25\%$ over the course of days to weeks.
- In a prospective cohort of HIV-infected outpatients, incidence of ARF was 5.9 cases per 100 person-years. The most common causes of ARF were a pre-renal state and acute tubular necrosis (ATN).

Risk factors	<ul style="list-style-type: none"> • Male sex • HCV coinfection • HIV viral load of >10,000 copies/mL • CD4 count of <200 cells/μL • Presence of an opportunistic infection • History of an AIDS diagnosis • Current or prior ART
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- May be asymptomatic, or may present with volume overload (dyspnea, orthopnea), hypertension, metabolic abnormalities, decreased urine output, anorexia, nausea, vomiting, or encephalopathy.

Table 3. Possible Causes of ARF

Prerenal Causes
<ul style="list-style-type: none">• Hypovolemia: hemorrhage, dehydration attributable to diarrhea, vomiting, or inadequate fluid intake• Hypoperfusion: ischemia (septic shock, heart failure, cardiogenic shock); reduced oncotic pressure (hypoalbuminemia, anemia)
Intrinsic Renal Causes
<ul style="list-style-type: none">• Glomerulonephritis (any type)• ATN resulting from prolonged prerenal injury• ATN resulting from toxins, including nephrotoxic medications: IV radiographic contrast dye, pentamidine, amphotericin B, foscarnet, cidofovir, high-dose acyclovir, aminoglycosides, TDF• ATN resulting from rhabdomyolysis (crush injury, statins [including in association with PIs], fibrate derivatives, cocaine)• Acute interstitial nephritis (AIN) resulting from medications: TMP-SMX and other sulfa-containing compounds, beta-lactam antibiotics, rifampin, IDV, NSAIDs, salicylates, many other medications• AIN resulting from infection: streptococcus, cytomegalovirus (rare)
Postrenal Causes
<ul style="list-style-type: none">• External obstruction: retroperitoneal masses; ureteral compression, urethral compression or blockage (eg, severe benign prostatic hypertrophy)• Internal obstruction: crystal deposition, nephrolithiasis, clot

R_x MANAGEMENT

- Assess volume status and metabolic abnormalities.
- Provide supportive care (dialysis if necessary) and treat the underlying processes causing ARF.
- Dialysis is indicated for uremic pericarditis, encephalopathy, volume overload with pulmonary edema, hyperkalemia, or metabolic acidosis.

Selecting ARVs for Patients with Kidney Disease

- ART generally should not be avoided because of kidney disease.
- ART is indicated in patients with HIVAN.
- Accumulating evidence suggests ART decreases the risk of kidney disease in HIV-infected patients.
- NRTIs, except for ABC, are excreted renally; dosage should be based on steady-state CrCl or eGFR (see **Table 4**).
- TDF has been associated with rare cases of ARF and Fanconi syndrome.

- TDF also has been associated with slow decreases in eGFR, typically in patients with preexisting renal insufficiency (see **Table 5**).
- Agents from other classes (NNRTI, PI, fusion inhibitor, integrase inhibitor, chemokine coreceptor antagonist) do not undergo significant renal excretion and do not require dosage adjustment in patients with renal insufficiency.
- Serum levels of ATV, for unclear reasons, are substantially decreased in patients on hemodialysis; thus ATV should not be given to HIV treatment-experienced patients undergoing hemodialysis.
- IDV and (rarely) ATV have been associated with nephrolithiasis (see **Table 5**).
- Note that other medications commonly given to HIV-infected patients may also cause renal dysfunction (see **Table 5**).

Table 4. NRTI Dosing for Patients with Decreased Renal Function (based on CrCl)

Drug	Standard Dosage	Adjusted Dosage/Notes		
ABC	300 mg PO BID	Dosage adjustment for renal insufficiency does not appear necessary		
ddl	250-400 mg PO QD, depending on weight	CrCl (mL/min)	Weight ≥60 kg	Weight <60 kg
		≥60	400 mg QD	250 mg QD
		30-59	200 mg QD	125 mg QD
		10-29	125 mg QD	125 mg QD
		<10	125 mg QD	formulation not suitable
		Hemodialysis	125 mg QD	formulation not suitable
FTC	200 mg PO QD	CrCl (mL/min)		
		≥50	200 mg QD	
		30-49	200 mg Q48H	
		15-29	200 mg Q72H	
		<15	200 mg Q96H	
		Hemodialysis	200 mg Q96H, give after dialysis	
3TC	150 mg PO BID or 300 mg PO QD	CrCl (mL/min)		
		≥50	150 mg BID or 300 mg QD	
		30-49	150 mg QD	
		15-29	150 mg first dose, then 100 mg QD	
		5-14	150 mg first dose, then 50 mg QD	
		<5	50 mg first dose, then 25 mg QD	

d4T	20 mg to 40 mg PO BID, depending on weight	CrCl (mL/min)	Weight ≥60 kg	Weight <60 kg
		>50	40 mg BID	30 mg BID
		26-50	20 mg BID	15 mg BID
		10-25	20 mg QD	15 mg QD
		Hemodialysis	20 mg QD	15 mg QD
TDF	300 mg PO QD	Experience in patients with CrCl <60 mL/min is limited. Preliminary data suggest:		
		CrCl (mL/min)		
		≥50	300 mg QD	
		30-49	300 mg Q48H	
		10-29	300 mg twice weekly	
		Hemodialysis	300 mg weekly	
ZDV	300 mg PO BID	CrCl (mL/min)		
		<15	100 mg Q6-8H	
		Hemodialysis	100 mg TID	

Adapted from McNicholl IR, Rodriguez RA. Dosing of Antiretroviral Drugs in Adults with Renal Insufficiency and Hemodialysis. San Francisco: University of California San Francisco, Center for HIV Information; 2008. Available at: <http://hivinsite.ucsf.edu/InSite?page=md-rr-18>. Accessed November 1, 2008.

ARV and Other Medications Associated with Renal Dysfunction

A number of medications commonly prescribed for treatment of HIV infection or opportunistic illnesses may cause acute or chronic renal disease (see **Table 5**). Some of these should be avoided in patients with renal insufficiency.

Table 5. Renal Adverse Effects of Medications Commonly Taken by HIV-Infected Persons

Drug	Disorder/ Pathology	Findings	Comments/Suggestions
TDF	TDF-associated renal insufficiency	↑ Cr, usually small; slight (4% vs other NRTIs) decrease in eGFR over time	<ul style="list-style-type: none"> • Of unclear clinical significance, but warrants monitoring of renal function. • May be associated with duration of HIV infection, concomitant RTV-boosted PIs (which boost TDF levels), preexisting renal dysfunction, or diabetes. • Check serum and urine electrolytes, eGFR, UA before starting therapy and every 6 months on therapy,

	Proximal tubular injury (ATN)	Fanconi syndrome (metabolic acidosis, ↑ Cr; ↓ serum K ⁺ and phosphate, ↑ urine bicarbonate, phosphate, and glucose)	<p>especially in patients with eGFR ≤90 mL/min/1.73 m², renally secreted drugs, RTV-boosted PIs, diabetes, or hypertension.</p> <ul style="list-style-type: none"> • Adjust TDF dosage based on steady-state CrCl. • Rare, usually resolves with discontinuation of TDF, but can lead to permanent damage, ESRD. • May be more likely in patients with preexisting renal disease. • Check serum and urine electrolytes, eGFR, UA before starting therapy and every 6 months on therapy, especially in patients with eGFR ≤90 mL/min/1.73 m², renally secreted drugs, RTV-boosted PIs (which boost TDF levels), diabetes, or hypertension.
ATV	Nephrolithiasis	Symptoms of renal colic, dysuria, urgency; mild ↑ Cr; ATV-containing stones	<ul style="list-style-type: none"> • Case reports. • Treat with hydration; if symptoms do not resolve, or if symptoms recur, may need to discontinue drug.
IDV	AIN	↑ Cr, pyuria	<ul style="list-style-type: none"> • Usually resolves with drug discontinuation; may require steroids.
	Crystalluria	Asymptomatic, or symptoms of renal colic, dysuria, urgency; crystals on UA; mild ↑ Cr	<ul style="list-style-type: none"> • Treat with hydration. • If manifestations do not resolve, may need to discontinue drug. • Not necessary to discontinue for asymptomatic crystalluria.
	Nephrolithiasis	Renal colic, dysuria, urgency; mild ↑ Cr; crystals on UA; stones or filling defects on radiography	<ul style="list-style-type: none"> • Risk reduced by drinking 1.5-2 liters of liquids per day. • Treat with hydration; if symptoms do not resolve, or if symptoms recur, may need to discontinue drug.
Acyclovir	Crystalluria	May precipitate ARF	<ul style="list-style-type: none"> • Treat with hydration; avoid rapid intravenous bolus; adjust dosage for renal function.

Amphotericin B	Increased tubular permeability and/or renal vasoconstriction	↑ Cr, ↓ serum K ⁺ and Mg ⁺⁺ , ↓ urine bicarbonate; distal renal tubular acidosis; non-anion-gap metabolic acidosis	<ul style="list-style-type: none"> • More severe renal failure likely with concurrent nephrotoxins (aminoglycosides, foscarnet), diuretic use, hypovolemia, chronic renal failure. • Hydration with normal saline is somewhat protective. • Switch to lipid formulation of amphotericin B for rise in Cr of >2.5 mg/dL while on conventional amphotericin B; continue to monitor electrolytes.
Cidofovir	Proximal tubular injury	(See TDF, above)	<ul style="list-style-type: none"> • Incidence reduced with hydration (normal saline) and probenecid, which blocks absorption of drug by tubular epithelial cells. • Check Cr and urine protein within 48 hours before each dose and reduce dosage for decreased CrCl or eGFR. • Discontinue drug for either Cr ≥0.5 mg/dL above baseline or proteinuria ≥3+ on dipstick analysis.
Foscarnet	ATN Crystal deposition	↑ Cr, ↓ serum Ca ⁺⁺ , Mg ⁺⁺ , phosphorus; <i>sometimes</i> ↑ serum Ca ⁺⁺ and phosphorus	<ul style="list-style-type: none"> • Cr generally increases after 1-2 weeks of foscarnet therapy. • Renal toxicity is reduced with infusion of 0.5-1 liter of normal saline with or before foscarnet. • Toxicity is more likely with concomitant nephrotoxins.
Pentamidine (IV, rarely aerosolized)	Tubular toxicity (ATN)	↑ Cr; ↑ serum K ⁺ ; ↓ serum Mg ⁺⁺ and Ca ⁺⁺	<ul style="list-style-type: none"> • Discontinuation of pentamidine reverses toxicity, although that process can take several weeks.
TMP-SMX	Hyperkalemia caused by blockage of Na ⁺ channel in collecting tubule	↑ Serum K ⁺	<ul style="list-style-type: none"> • Usually seen with high-dose therapy (eg, PCP treatment), but sometimes seen with lower dosages. • Hyperkalemia more common with preexisting renal insufficiency.

	Impaired tubular secretion of Cr	↑ Cr	<ul style="list-style-type: none"> • Hyperkalemia often appears after 1 week of therapy. • Consider monitoring serum K⁺, especially with high-dose therapy.
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Urology:

Benign Prostatic Hypertrophy, Erectile Dysfunction, Epididymitis, Nephrolithiasis

KEY POINTS

Benign Prostatic Hypertrophy (BPH)

- Approximately 19% of men aged >38 have symptoms related to BPH; the proportion increases with age.
- Treat mild to moderate BPH with alpha-adrenergic antagonist monotherapy. Treat moderate to severe BPH with combination alpha-adrenergic antagonist and 5-alpha-reductase inhibitor therapy.

Erectile Dysfunction (ED)

- HIV-infected men are more likely than age-matched HIV-uninfected men to have ED. Some studies have found the prevalence of ED among HIV-infected men to be as high as 70%.
- First-line therapy: Phosphodiesterase 5 (PDE5) inhibitors. Note: serum levels of PDE5 inhibitors are increased significantly in the presence of CYP 3A4 inhibitors such as PIs. PDE5 inhibitors are contraindicated for use with patients receiving nitrates.

Epididymitis

- Among sexually active men aged <35, acute epididymitis is most frequently caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *Escherichia coli*, and other enteric organisms are common causes among men who practice insertive anal intercourse.
- Among HIV-infected men, especially those with advanced immunosuppression, fungi and mycobacteria can cause acute epididymitis and should be considered in the differential diagnosis when symptoms do not respond to first-line treatment.

Nephrolithiasis

- Formation of renal stones is influenced by diet, metabolism, comorbid conditions, and drugs.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- Some PIs can cause renal stones: IDV can precipitate within the urinary tract to form stones. ATV and NFV also have been reported to form stones.
- Diagnosis relies on imaging, although IDV-containing stones may be radiolucent on both plain X rays and CT.
- The majority of patients can be managed with hydration and analgesics. The underlying cause should be defined in order to determine therapy to prevent recurrences.

Benign Prostatic Hypertrophy



BACKGROUND

BPH is a nonmalignant overgrowth of prostate tissue (stromal components > epithelial cells), usually originating in the central/transitional zone of the prostate.

- BPH may cause symptoms of urinary obstruction, which vary widely in degree of severity.
- Symptoms typically appear slowly and progress gradually over the course of several years.
- Overall prevalence of BPH symptoms in men aged >38 is 19%; the prevalence increases with age.
- Approximately 40% of men will have pathologic evidence of BPH by age 60, increasing to 90% by age 90.
- Men with symptomatic BPH who are not treated have a 2.5% per-year risk of developing acute urinary retention.

Veterans with HIV*

BPH: 8%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to this condition



EVALUATION

- There are no consensus diagnostic criteria for BPH. Generally, diagnosis is made clinically on the basis of lower urinary tract symptoms (LUTS). The American Urological Association (AUA) has created the International Prostate Symptoms Score (IPSS) to evaluate LUTS. See **AUA IPSS chart**, below.

History

- Symptoms:
 - Increased frequency of urination
 - Nocturia
 - Hesitancy

	<ul style="list-style-type: none"> • Urgency • Weak urinary stream • Family history of BPH or prostate cancer • Medications that can impair bladder function, especially: <ul style="list-style-type: none"> • Anticholinergics and antihistamines • Medications that can increase outflow resistance: <ul style="list-style-type: none"> • Sympathomimetics • Type 2 diabetes, which increases risk of BPH • Sexual dysfunction, which occurs in about 62% of men with LUTS • Gross hematuria, which may signify calculi or bladder tumor • History of urethral trauma, urethritis, or urethral instrumentation, which can lead to a urethral stricture • Use the AUA IPSS chart, below, to score symptoms
Differential diagnosis (partial)	<ul style="list-style-type: none"> • Urinary tract infection (UTI), prostatitis • Neurogenic bladder • Prostate cancer • Bladder calculi • Bladder cancer • Urethral stricture • Bladder neck contracture • Medication adverse effects
Physical examination, laboratory tests, imaging	<ul style="list-style-type: none"> • Digital rectal examination to assess prostate size and detect nodules • Urinalysis: white blood cells (WBCs) (suggest infection), and red blood cells (suggest calculi or tumor) • To screen for prostate cancer: digital rectal examination and serum prostate-specific antigen (PSA) (Note: elevated PSA is not specific for cancer; may indicate prostate inflammation or large prostate resulting from BPH) • Optional: postvoid residual urine volume (>50 mL is abnormal, measured by straight catheter or bladder scanner); maximal urinary flow rate (<15 mL/sec is abnormal, measured in Urology Clinic) • If signs of significant obstruction, check serum creatinine; if creatinine level is high, obtain ultrasound of the bladder, ureters, and kidneys to check for hydronephrosis • Suspected bladder calculi or tumor: refer to Urology Clinic for urethroscopy

IPSS: AUA Symptom Index + Quality-of-Life Question

The International Prostate Symptom Score uses the 7 questions of the AUA Symptom Index (presented below) plus a disease-specific quality-of-life question (bother score).

The AUA Symptom Index for BHP and the Disease-Specific Quality-of-Life Question

Patient name: _____ DOB: _____ ID: _____ Date of assessment: _____
 Initial Assessment () Monitor during: _____ Therapy () after: _____ Therapy/surgery () _____
 AUA BPH Symptom Score

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
	None	1 time	2 times	3 times	4 times	5 or more times
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5
Total Symptom Score:						

IPSS Score:

0-7	Mild symptoms
8-19	Moderate symptoms
20-35	Severe symptoms

The Disease-Specific Quality-of-Life Question (bother score):

“If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?”

Delighted (0); Pleased (1); Mostly satisfied (2); Mixed (3); Mostly disappointed (4); Unhappy (5); Terrible (6)

Treatment Decisions:

IPSS ≤ 7 , or no bothersome symptoms: watchful waiting

IPSS ≥ 8 : discuss treatment options; consider referral to Urology for further testing

Reprinted from the *Journal of Urology* (1992), 148(5), Barry, M. J., Fowler Jr, F. J., O’Leary, M. P., Bruskwewitz, R. C., Holtgrewe, H. L., Mebust, W. K. and Cockett, A. T. (The Measurement Committee of the American Urological Association), ‘The American Urological Association Symptom Index for Benign Prostatic Hyperplasia’, pp. 1549-1557. (c) American Urological Association, 1992. Reproduced with permission.

Rx MANAGEMENT

- Behavior modifications:
 - Avoid drinking fluids before bedtime and before going out.
 - Avoid or reduce diuretics, including caffeine and alcohol.
 - Void twice in order to empty the bladder more completely.
- Avoid use of antihistamine, anticholinergic, and sympathomimetic agents.
- Medical treatment (for patients who have symptoms that are significant enough to create desire for therapy).
 - **Mild to moderate BPH** by AUA IPSS score: alpha-adrenergic antagonist monotherapy
 - **Terazosin:** 1 mg QHS; if tolerated, titrate upward every 5-7 days to effect (eg, increase to 2 mg, then 5 mg, 10 mg, 20 mg [maximum]). Usual dose is 10 mg; patient should experience clinical effect within 4-6 weeks.
 - **Doxazosin:** 1 mg QHS; if tolerated, titrate upward every 5-7 days to effect (eg, increase to 2 mg, then 4 mg, 8 mg, 16 mg [maximum]). Usual dose is 8 mg; patient should experience clinical effect within 4-6 weeks.

- Common adverse effects: orthostatic hypotension and dizziness, asthenia, and nasal congestion
 - Terazosin and doxazosin lower blood pressure more significantly than the other agents and therefore should be taken at bedtime; caution for additive hypotension if used concurrently with antihypertensives or sildenafil or vardenafil (for more details, see <http://www.pbm.va.gov/CriteriaForUse.aspx>).
- Uroselective alpha-adrenergic antagonists:
 - Not currently listed on the VHA National Formulary, but may be considered for patients who have significant orthostatic or postural hypotension on a nonselective alpha-adrenergic antagonist (see PBM Criteria for Use for these agents at <http://www.pbm.va.gov/CriteriaForUse.aspx>); tamsulosin is the preferred nonformulary uroselective agent:
 - **Tamsulosin:** 0.4 mg QD, can increase to 0.8 mg QD after 2-4 weeks
 - **Alfuzosin:** 10 mg QD
- Patients with hypertension should not, in general, be treated with an alpha-adrenergic antagonist as monotherapy for hypertension (see **Hypertension**, p. 171, as well as table of blood pressure changes expected with these agents at <http://www.pbm.va.gov/CriteriaForUse.aspx>).



POTENTIAL ARV AND OTHER DRUG INTERACTIONS

- **Alfuzosin:** Avoid use with patients who are taking P450 inhibitors.
 - PIs such as RTV, SQV, IDV, and NFV ↑ serum alfuzosin concentrations.
 - EFV also has been shown to ↑ alfuzosin concentrations.
 - Other P450 inhibitors including azole antifungals (eg, ketoconazole, voriconazole, posaconazole, and itraconazole) can ↑ alfuzosin concentrations to toxic levels. Concurrent use of alfuzosin and azoles can increase the risk of QTc prolongation.
- **Moderate to severe BPH** by AUA score, or BPH not controlled by an alpha-adrenergic antagonist alone: Combination therapy with 5-alpha-reductase inhibitor and maximum tolerated dosage of an alpha-adrenergic antagonist may be of benefit.
 - Combination therapy can reduce the size of the prostate gland over a 6- to 12-month period. Used alone, 5-alpha-reductase inhibitors have not shown efficacy for BPH treatment. Consider for patients who are on a maintenance dosage of an alpha-adrenergic antagonist (eg, terazosin 10 mg QD), or on the highest tolerated dosage if a maintenance dosage was not achieved; who have a large prostate (>40 mL, the size of a golf ball), and who show clinical progression of BPH symptoms as suggested by:
 - An increase in the AUA score ≥ 4 points from baseline, or

- A history of acute urinary retention, or
- Persistently bothersome symptoms despite adequate alpha-adrenergic antagonist therapy, as above
- Consider for patients who have not tried alpha-adrenergic antagonist therapy but who have an AUA score >12 and are at high risk of urinary retention or require an intervention.
- See PBM Criteria for Use at <http://www.pbm.va.gov/CriteriaForUse.aspx>.
- 5-alpha-reductase inhibitors
 - **Finasteride:** 5 mg QD. (Note: Finasteride has been associated with development of higher-grade prostate cancer in patients diagnosed with prostate cancer while on this agent.)
 - **Dutasteride:** 0.5 mg QD (may be more potent than finasteride).
 - Possible adverse effects: decreased libido, ejaculatory dysfunction, ED.
 - **Note:** These medications can cause PSA levels to decrease by 50%. This should be taken into account if PSA levels are being followed to track other diseases.



WHEN TO REFER

Refer to Urology for evaluation or possible surgical interventions for patients who develop:

- Hydronephrosis
- Urinary retention
- Bladder stones
- Renal dysfunction
- Recurrent infection
- Severe symptoms that do not respond well to medical therapy
- Elevated serum PSA or microscopic or gross hematuria

Erectile Dysfunction



BACKGROUND

- ED is the inability to achieve or maintain penile erection sufficient for satisfactory sexual performance (National Institutes of Health Consensus Panel definition).
- HIV-infected men have a higher prevalence of ED than age-matched HIV-uninfected men.

Veterans with HIV*

Erectile dysfunction: 18% (filled prescriptions for ED drugs)

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to this condition

- In some outpatient studies of HIV-infected men, the prevalence of ED is as high as 70%.
- Sexual dysfunction also occurs in women, but is less well studied.
- Sexual dysfunction often is multifactorial in etiology; causes can include:
 - Medication effects (see below)
 - Psychological: depression, stress
 - Endocrine: androgen deficiency, thyroid disease, diabetes mellitus
 - Neurologic: stroke, spinal cord or back injury, prostate surgery, pelvic trauma, multiple sclerosis, or dementia
 - Vascular: cardiovascular disease, hypertension
 - Metabolic and diet-related: obesity, dyslipidemia
 - Substance use: alcohol, tobacco; methamphetamine, cocaine, and heroin can initially increase libido but over time can cause inability to sustain an erection
- Among HIV-infected men, ED has been associated with:
 - Age >40
 - Depression, anxiety, posttraumatic stress disorder
 - Use of antidepressants (although the effect of these medications is difficult to separate from the effect of underlying depression)
 - Use of psychotropic medications (although the effect is difficult to separate from that of underlying psychiatric disease)
 - Duration of ART (higher prevalence of ED with longer duration of ART, regardless of regimen)
 - Presence of peripheral neuropathy
 - Hypogonadism
 - Up to 20% of HIV-infected men have low testosterone levels (see **Androgen Deficiency**, p. 89)
 - Heterosexual orientation
 - Nonuse of alcohol

Medications Commonly Associated with ED

- Antidepressants (particularly SSRI, serotonin-norepinephrine reuptake inhibitor [SNRI] classes)
 - Bupropion, mirtazapine, and nefazodone confer lower risk of ED
- Spironolactone
- Thiazide diuretics
- Beta-blockers (not clearly associated; mixed data)
- Clonidine
- Methyl dopa
- Ketoconazole
- Cimetidine



- The abridged International Index of Erectile Function (IIEF-5) is a validated question set used to diagnose the presence and severity of ED.
- The sensitivity of the IIEF-5 is 98% and the specificity is 88%, using a cutoff score of 21.

The IIEF-5 Questionnaire

Over the past 6 months:					
1. How do you rate your confidence that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/ never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/ always 5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/ never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/ always 5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/ never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/ always 5

IIEF-5 scoring:

The IIEF-5 score is the sum of the ordinal responses to the 5 items.

- 22-25 No erectile dysfunction
- 17-21 Mild erectile dysfunction
- 12-16 Mild to moderate erectile dysfunction
- 8-11 Moderate erectile dysfunction
- 5-7 Severe erectile dysfunction

Reprinted by permission from Macmillan Publishers Ltd: Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res.* 1999 Dec; 11(6):319-26. © 1999

History	<ul style="list-style-type: none">• Rapidity of onset: sudden onset points to psychogenic causes• Presence or absence of spontaneous erections: absence suggests vascular or neurogenic causes• Screen for depression, anxiety, and posttraumatic stress disorder (including rape, sexual assault, and military sexual trauma)• Screen for interpersonal conflict with sex partner(s)
Physical examination	<ul style="list-style-type: none">• Penis: corporal plaques associated with Peyronie disease (buildup of scar tissue in erectile tissues can cause pain or bending with erections)• Testes: size, symmetry, consistency, masses• Epididymis and vas deferens: swelling or varicoceles• If patient is aged >50, consider digital rectal examination and PSA for prostate cancer screening• Cardiovascular system (heart, femoral, and peripheral pulses): vascular health• Secondary sexual characteristics, gynecomastia: endocrine health• Neurologic screen: sensorimotor examination of S2-S4. Rapid screen:<ul style="list-style-type: none">• Anal wink test: anal sphincter contracts when perianal skin is stroked• Bulbocavernosus reflex test: anal sphincter contracts when the glans penis is squeezed• Anal sphincter tone: digital rectal examination; ask patient to contract the sphincter during the examination
Laboratory evaluations and other studies	<ul style="list-style-type: none">• Testosterone: to evaluate for hypogonadism (see Androgen Deficiency, p. 89)• Fasting glucose, HbA1c: screen for diabetes• Fasting lipid panel: screen for hyperlipidemia and underlying vascular disease• TSH to evaluate for hypothyroidism

- Consider referral to Urology for nocturnal penile tumescence (NPT) testing, which is a home test of number of nocturnal erections and level of penile rigidity a man experiences during sleep; a normal NPT measurement suggests psychogenic ED

Rx MANAGEMENT

- **It is critical that management of ED be accompanied by discussions regarding sexual health and practice of safer sex** (see **Prevention for Positives**, p. 39).
- **Obese patients:** Weight loss and increased physical activity are associated with improvement in erectile function in one third of patients.
- Psychotherapy with or without psychoactive medications is indicated for men with depression or anxiety (avoid antidepressant medications that may cause ED, if possible; see **Medications Commonly Associated with ED**, above).
- **Men with hypogonadism: androgen replacement (testosterone); see Androgen Deficiency**, p. 89.

Note: Testosterone preparations are classified as Schedule III controlled substances.

- **Intramuscular testosterone (eg, cypionate):** 200 mg IM every 2 weeks
- **Transdermal patch:** 5 mg QD
- **Gel:** 1% gel, 5-10 mg QD
- **Buccal:** 30 mg BID
- Possible adverse effects (particularly with IM testosterone) include mood swings, gynecomastia, testicular atrophy, acne, erythrocytosis, dyslipidemia, and elevation of serum transaminase levels. Also, pain and irritation at injection or application sites, local pruritus and erythema with patches (which can be relieved by topical steroids); bitter taste with the buccal delivery method.
- Contraindications: prostate cancer.
- Monitoring (particularly important with IM testosterone): testosterone levels 1-2 months after initiation. (**Note:** For patients on IM testosterone, check testosterone level at nadir, just before scheduled injection.); PSA every 6-12 months; hemoglobin and liver function tests every 3-6 months.
- **PDE5 inhibitors**
 - A summary of information on PDE5 inhibitors from the VA PBM can be found at <http://www.pbm.va.gov/DrugClassReviews.aspx>.
 - PDE5 inhibitors interact with PIs and often require dosage adjustment; see below.

- All are equally effective.
- Vardenafil is currently the PDE5 inhibitor on the VHA National Formulary. For information on obtaining another PDE5 inhibitor for a patient in whom vardenafil has been ineffective, see <http://www.pbm.va.gov/CriteriaForUse.aspx>.
- Tadalafil has a longer duration of action than sildenafil or vardenafil, up to 36 hours.
- If tolerated, titrate to effect.



POTENTIAL ARV INTERACTIONS

Serum levels of all PDE5 inhibitors are significantly increased in the presence of CYP 3A4 inhibitors such as PIs. See **Recommended Dosing** below.

Recommended Dosing of PDE5 Inhibitors

PDE5 Inhibitor	Dosing Instructions	Patients on PIs and Other Strong CYP 3A4 Inhibitors	Patients Not on Interacting Drugs
Vardenafil (Levitra)	Take on empty stomach 1 hour before sexual activity	Start: 2.5 mg per day Maximum: 2.5 mg per 72 hrs (ATV, DRV, RTV, TPV); 2.5 mg per 24 hours (other PIs)	Start: 2.5-10 mg per day (≤5 mg if age >65) Maximum: 20 mg every 24 hours
Sildenafil (Viagra)	Take on empty stomach 0.5-4 hours before sexual activity	Start: 25 mg per day Maximum: 25 mg every 48 hours	Start: 25-50 mg per day (25 mg if age >65) Maximum: 100 mg every 24 hours
Tadalafil (Cialis)	Take with or without food, before sexual activity	Start: 5-10 mg per day Maximum: 10 mg every 72 hours	Start: 5-10 mg per day Maximum: 20 mg every 24 hours

- Use low dosages or avoid for patients with significant liver disease.
- Possible adverse effects: (common) headache, flushing, dizziness, nasal congestion; (<2% but serious) hypotension, cardiac arrest, cerebrovascular hemorrhage, ischemic optic neuropathy, vision loss, priapism.
- All PDE5 inhibitors are contraindicated for use by patients who take nitrate drugs.
- Exercise caution if using PDE5 inhibitors concurrently with alpha-adrenergic antagonists (eg, terazosin) because of risk of hypotension, although tamsulosin 0.4 mg QD seems to be safe with tadalafil use (for more details, see <http://www.pbm.va.gov/CriteriaForUse.aspx>).
- Patients on a stable alpha-adrenergic antagonist regimen should start the PDE5 inhibitor at the lowest possible dosage.

- **Other agents:** Consider for patients in whom PDE5 inhibitors are contraindicated (eg, patients on nitrate drugs), not tolerated, or not effective.
 - **Yohimbine hydrochloride**, an α_2 -adrenergic antagonist. Starting dosage is 5.4 mg (may be increased to 10.8 mg) PO TID. Side effects include nausea, dizziness, and nervousness. No data on ARV interactions are available.

The following require referral to a urologist and instruction on proper use:

- **Penile self-injectable drugs** (eg, intracavernous alprostadil, papaverine, phentolamine)
 - Override sympathetic inhibition and encourage relaxation of the penile smooth muscle.
 - Require injection with an insulin syringe through the shaft of the penis into a corporeal body a few minutes before sexual activity.
- **Intraurethral alprostadil**
 - Alprostadil is instilled into the urethra, followed by penile massage for 1 minute to distribute the medication into the corpora cavernosae.
- **Vacuum devices**
 - Mechanical devices increase arterial inflow, and occlusive rings decrease venous outflow from the corpora cavernosae.
- **Refractory ED:** For patients who are refractory to or unable to use PDE5 inhibitors, injectables, intraurethrales, or vacuum devices, options include:
 - Referral for surgical implantation of penile prosthesis, including malleable rods and inflatable prostheses

Epididymitis



BACKGROUND

- **Acute epididymitis** is a syndrome consisting of pain, swelling, and inflammation of the epididymis lasting <6 weeks.
- **Chronic epididymitis** lasts ≥ 3 months and consists of pain in the scrotum, testicle, or epididymis, localized on physical examination.
- Testicular pain and swelling (orchitis) also may be present.
- It is often accompanied by dysuria, urinary frequency, and urgency.
- Among sexually active men aged <35, acute epididymitis is most frequently caused by infection, particularly by *C trachomatis* and *N gonorrhoeae*. *E coli* and other enteric organisms are common causes among men who practice insertive anal sex.

- Among HIV-infected men, especially those with advanced immunosuppression, fungi and mycobacteria cause acute epididymitis more frequently than they do among HIV-uninfected men. These should be considered in the differential diagnosis when symptoms do not respond to first-line treatment.
- Other causes include lower urinary tract obstruction (eg, BPH, occlusive sexual enhancement aids), surgical instrumentation.



EVALUATION

Symptoms	<ul style="list-style-type: none"> • Unilateral testicular pain, with or without swelling
Differential diagnosis	<ul style="list-style-type: none"> • Urethritis without epididymitis • UTI • Testicular abscess • Testicular tumor • Infarction • Testicular torsion <p>Note: Testicular torsion is a surgical emergency, because testicular viability is at risk:</p> <p>It is important to differentiate torsion and epididymitis. Torsion involves sudden and severe onset of pain, generally without evidence of inflammation or infection. Obtain urgent testicular ultrasound, urologic consultation, or both if torsion is suspected.</p>
Physical examination	<ul style="list-style-type: none"> • Examine testes and epididymis: exquisite tenderness and palpable swelling of the epididymis (usually begins at the tail and spreads to the rest of the epididymis and testicle), hydrocele, mass. • Spermatic cord: usually tender and swollen.
Laboratory evaluation and imaging	<ul style="list-style-type: none"> • If urethritis: Gram stain of urethral secretions; ≥ 5 WBC per oil immersion field indicates infection. Presence of gram-negative diplococci is diagnostic for gonococcal infection. • First-void urine: ≥ 10 WBC per high-powered field on microscopy indicates infection. Send urine for nucleic acid amplification tests (NAAT) for <i>C trachomatis</i> and <i>N gonorrhoeae</i>. Send urine culture if infection with other organisms (eg, <i>E coli</i>) is suspected. • Testicular/scrotal ultrasound: Radiologic evaluation is not routinely necessary, but is important if other testicular conditions such as torsion, mass, and abscess are suspected. Doppler ultrasonography is 70% sensitive and 88% specific in diagnosing acute epididymitis.

- Consider hospitalization for patients who are febrile and for those with severe pain that suggests other diagnoses (eg, torsion, testicular infarction, and abscess) that require more complicated evaluation.
- **Acute epididymitis:**
 - Begin empiric antibiotic treatment based on suspected cause.
 - *C trachomatis* or *N gonorrhoeae* confirmed or suspected:
 - Ceftriaxone 125 mg or 250 mg IM, or cefixime 400 mg PO for single dose
 - Plus
 - Doxycycline 100 mg BID for 10 days
 - **Note:** Fluoroquinolones are not recommended for treatment of confirmed or suspected *N gonorrhoeae* because of high rates of resistance.
 - Enteric organisms confirmed or suspected; or, patient is allergic to cephalosporins or tetracyclines:
 - Ofloxacin 300 mg BID for 10 days
 - Levofloxacin 500 mg QD for 10 days
- Management of sex partners:
 - Refer sex partners for evaluation if the patient has confirmed or suspected *C trachomatis* or *N gonorrhoeae* epididymitis and sexual contact has occurred within 60 days from onset of symptoms.
 - At the current time, VA facilities are not authorized to evaluate or treat nonveteran sex partners.
 - VA facilities are strongly encouraged to report notifiable STDs to the local public health department, in accordance with established VA policies and procedures.
 - Patients should avoid sexual contact until they and their sex partners have completed therapy and no longer have symptoms.
- Follow-up: Symptoms should improve within 3 days of initiating therapy. If there is no improvement or if the symptoms persist after completion of antibiotics, reevaluate for the following:
 - Other causes of epididymitis (eg, fungi, mycobacteria)
 - Testicular abscess
 - Testicular infarction
 - Testicular tumor

Nephrolithiasis



BACKGROUND

- Renal calculi are common in the general population, affecting 12% of men and 5% of women.
- Stones result from supersaturation of urine with a normally soluble compound, with subsequent nucleation, crystal aggregation, and stone formation.
- Stones typically result from a combination of dietary, metabolic, genetic, and medical factors.
- Calculi most often are composed of calcium, but may form from uric acid or cystine.
- Stones also may be composed of drugs; IDV in particular may cause nephrolithiasis. Among HIV-infected patients who receive IDV, 5-15% develop stones. Other PIs (ATV, NFV) also have been reported as causes of stones.
- 50% of patients will have a recurrence within 10 years. It is important to define the underlying cause in order to determine preventive therapy.



EVALUATION

History	<p>Symptoms</p> <ul style="list-style-type: none">• Flank pain, frequently severe, radiating to groin• Undulating cramps• Gross hematuria• Nausea, vomiting <p>Ask about:</p> <ul style="list-style-type: none">• Duration, characteristics, location of pain• History of renal stones• UTIs• Family history of renal stones• Solitary or transplanted kidney• Medications: IDV, sulfa drugs, penicillins, quinolones• Presence of metabolic syndrome, diabetes mellitus
Differential diagnosis (partial)	<ul style="list-style-type: none">• Appendicitis• Biliary colic• Diverticulitis• Pancreatitis• Lumbar disc disease

	<ul style="list-style-type: none"> • UTI • Ectopic pregnancy • Abdominal abscess • Aortic aneurysm • Bowel ischemia
<p>Physical examination, laboratory evaluation, imaging</p>	<ul style="list-style-type: none"> • On physical examination, look for: <ul style="list-style-type: none"> • Costovertebral tenderness • Absence of peritoneal signs • Laboratory studies <ul style="list-style-type: none"> • Urinalysis (85% of patients will have hematuria) • CBC, electrolytes, creatinine, calcium, uric acid, phosphorus, parathyroid hormone levels (if serum calcium is elevated) • 24-hour urine collection for patients <30 years of age, multiple calculi, renal failure, renal transplant, family history of calculi, recurrent calculi; analyze for pH, calcium, oxalate, uric acid, sodium, phosphorus, citrate, magnesium, creatinine, total volume • Stone analysis (size, morphology, composition); if IDV or ATV suspected, may need to order specific testing • Imaging studies: <ul style="list-style-type: none"> • Abdominal X ray (calcium-containing stones are radiopaque; IDV stones are radiolucent) • Renal ultrasound • Intravenous urography (may be the only way to detect IDV-containing stones) • Helical CT without contrast (will not demonstrate IDV stones)

Rx MANAGEMENT

Acute

- In the absence of infection, most (80%) patients can be managed medically.
 - Stones <5 mm in diameter typically pass spontaneously.
 - Hydration and analgesia (see **Pain Medications**, p. 321) should be instituted promptly.
 - Consider use of medications that relax ureteral smooth muscle (eg, terazosin; nifedipine [use caution regarding interactions with PIs; see **Hyper-tension**, p. 171]).
 - For patients suspected of having an IDV stone, it is reasonable to discontinue IDV temporarily to lower urinary concentrations and allow dissolution. (To avoid the development of virologic failure and HIV resistance, IDV should be replaced by another appropriate ARV, or all ARVs should

be stopped temporarily.) Urine acidification may promote IDV stone dissolution.

- Indications for hospitalization include infection with concurrent obstruction, patients with a solitary or transplanted kidney, uncontrolled pain, intractable emesis, or comorbidities (eg, coronary artery disease) that may complicate management.
 - If infection is suspected, consult a urologist regarding drainage via nephrostomy tube placement.
 - Passed stones should be analyzed to determine their composition in order to design a preventive therapy regimen.
- Larger (>10 mm) stones and those located more proximally are less likely to pass spontaneously and frequently require surgical therapy; consult a urologist for percutaneous nephrostolithotomy, ureterorenoscopy, or shock wave lithotripsy.
- IDV stones typically are gelatinous and thus not amenable to lithotripsy; endoscopic stent placement is the procedure of choice for patients who do not respond to medical therapy alone.

Prevention

- All patients with a history of nephrolithiasis should maintain a daily fluid intake >2 L and restrict sodium intake.
- Targeted preventive therapy depends on identified metabolic abnormalities and stone analysis:
 - If hyperparathyroidism has been excluded, patients with hypercalciuria should restrict dietary calcium to 600-800 mg/day; consider use of a thiazide diuretic to decrease urinary calcium excretion.
 - Patients with hyperoxaluria should increase daily intake of calcium to 1-4 g (calcium citrate is the preferred agent) and avoid foods high in oxalate (chocolate, spinach, rhubarb, beets).
 - Patients with hyperuricosuria should be treated with potassium citrate (60-80 mEq/day), along with allopurinol 100-300 mg/day to decrease uric acid excretion.
 - Patients with recurrent UTI resulting from struvite stones should undergo stone removal.
 - Patients with IDV stones should maintain an adequate fluid intake (>1.5 L/day) if continued on IDV.



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Women's Health

KEY POINTS

- A Women Veterans Program Manager is available at every VA Medical Center to assist in providing care for women veterans.
- Nearly one third of people living with HIV in the United States are women.
- In the United States, HIV-infected women are less likely than HIV-infected men to receive ART.
- General preventive strategies and health maintenance are all part of routine care for HIV-infected women.
- Women should receive reproductive counseling.
- For pregnant women and women who may become pregnant, avoid use of EFV.
- Women with HIV have increased risk of developing abnormal cervical, vaginal, vulvar, and anal cytology, with possible progression to squamous carcinoma, especially if the CD4 count is <200 cells/ μ L.
- Women with HIV have higher rates of persistence and recurrence of herpes simplex virus, human papillomavirus (HPV), bacterial vaginosis, and candidal genital tract infections compared with their HIV-uninfected counterparts.
- Women with HIV are at increased risk of neuropsychiatric disease and should be screened accordingly.
- All women veterans, including those with HIV, should be screened for military sexual trauma and exposure to domestic violence.
- All women veterans, including those with HIV, should be screened for breast cancer and osteoporosis.



BACKGROUND

Epidemiology

- One half of the people living with HIV worldwide are women.

Veterans with HIV*

Women: 3%

*Veterans in the VA HIV Clinical Case Registry in care in 2007

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- In the United States, according to the CDC:
 - Nearly one third of people living with HIV are women.
 - Heterosexual transmission is the main mode of HIV acquisition among women (80% in recent years), followed by injection drug use.
 - Rates of HIV infection are increasing in rural and small metropolitan areas.
 - Women of color are disproportionately infected with HIV.
 - In 2005, the diagnosis rate of both HIV/AIDS and AIDS was 20 times higher for non-Hispanic black women than for non-Hispanic white women; 60% of HIV-infected women are African American.
 - The rate of both HIV/AIDS and AIDS was >5 times higher among Hispanic women than among non-Hispanic white women.
 - HIV-infected women are less likely than their male counterparts to be on ART, largely because of decreased access to health care and because of other priorities that compete for their attention.

Natural History

- Women generally have lower viral loads than men at the time of seroconversion.
- On average, HIV RNA levels are at least 50% lower in women than in men with the same CD4 cell counts and duration of HIV infection.
- From seroconversion, the time to the development of AIDS and overall mortality are the same for women and men despite the difference in HIV RNA levels.
- Virologic and CD4 responses to ART are the same for women and men.

Risks for Women with HIV

- Women tend to be diagnosed later in the course of HIV infection than men, and they tend to seek care at more advanced disease stages.
- Barriers to care include:
 - Child care or family care obligations, transportation limitations, lack of insurance, fear of disclosure (particularly to male partners, also to community and social networks), denial, and cultural mistrust of the health care system
 - Perception of their own need for medical care as being of low priority
- Depression: A prospective cohort study showed that women who self-reported chronic depressive symptoms were twice as likely to have CD4 declines and to die than women with mild or no depressive symptoms.

Pharmacologic Considerations for Women with HIV

- Limited pharmacokinetic studies show differences in ARV metabolism between women and men.
 - Women often have higher serum drug levels of certain ARVs, including EFV, NVP, IDV, LPV, and SQV.
 - Women have higher rates of adverse effects from certain ARVs, including:
 - Hepatotoxicity related to NVP, especially when NVP is initiated at CD4 counts of >250 cells/ μ L or during pregnancy
 - Rash related to NNRTIs and the PIs DRV and TPV
 - Nausea and vomiting related to PIs
 - ABC hypersensitivity (odds ratio: 1:4)
- There is little information on dosage adjustment of ARVs for women (pregnant or nonpregnant).
- Metabolism of ARVs may be altered during pregnancy.
- Some ARVs should not be used by pregnant women or those who may become pregnant, because of potential teratogenicity or other toxicity.
- Some ARVs have significant interactions with certain hormonal contraceptives; ARVs and contraceptives should be selected with this in mind (see **Potential ARV Interactions**, below).

Health maintenance: With prolonged survival in the era of ART, preventive strategies and health maintenance measures such as control of hypertension, smoking cessation, minimizing cardiovascular risk factors, and routine screening for osteoporosis and cancer (cervical, breast, and colon) are all part of routine care for HIV-infected women. See **Evaluation and Management**, below, as well as **Hypertension** (p. 171), **Dyslipidemia** (p. 143), and **Smoking Cessation** (p. 53) for further information on these topics.

This chapter will address these commonly encountered issues for HIV-infected women:

- Reproductive and hormonal issues
- Interactions of ARVs with hormonal contraceptives
- Screening for neuropsychiatric disorders
- Screening for military sexual trauma and domestic violence
- Screening for cancer, osteoporosis, and STD
- Cervical dysplasia
- Osteoporosis
- Genital tract infections



Note: A Women Veterans Program Manager is available at every VA Medical Center to assist in providing care for women veterans, including those with HIV infection.

HIV Prevention (see also **Prevention for Positives**, p. 39)

	Recommendations	Comments
Prevention of HIV transmission	<ul style="list-style-type: none"> Evaluate each patient's need for HIV prevention strategies on a regular basis Evaluate patient for high-risk behaviors (eg, alcohol misuse, substance use disorders) that may predispose to high-risk behaviors Encourage use of condoms (male or female) during all sexual encounters Other barriers: diaphragm, cervical cap (limited efficacy in preventing HIV transmission) Screen regularly for STDs, and treat as needed Use of nonoxynol-9 is not recommended: increased risk of HIV transmission resulting from vaginal irritation; lack of prevention of STDs 	<ul style="list-style-type: none"> If used correctly and consistently, condoms are effective for preventing transmission of HIV and other STDs, including HPV. Condoms may also be effective for contraception, but only if used optimally (see below). In some women, HIV viral load may be substantially higher in vaginal secretions than in blood; thus risk of sexual transmission of HIV may not be predicted by plasma viral load.

Reproductive and Hormonal Issues

Issue	Recommendations	Comments
Contraception	<ul style="list-style-type: none"> Condoms (male or female) during all sexual encounters; high failure rate if used suboptimally (consider second contraceptive method); if used correctly and consistently, effective also for prevention of HIV transmission Other barriers: diaphragm, cervical cap Spermicides (eg, nonoxynol-9) are not recommended: increased risk of HIV transmission resulting from vaginal irritation 	<ul style="list-style-type: none"> 50% of pregnancies in the United States are unplanned. On a regular basis, evaluate each woman's pregnancy intent and need for contraceptive information and methods. For women who intend or desire pregnancy, provide preconception counseling (see below).

	<ul style="list-style-type: none"> • Oral hormonal contraceptives: note drug-drug interactions with some ARVs (see Potential ARV Interactions, below) • Injectable contraceptives (medroxy-progesterone [DMPA, Depo-Provera]): appear to be safe and effective for women on ARVs (however, see Potential ARV Interactions, below) • Transdermal/patch: little information on interactions with ARVs • Intravaginal ring (NuvaRing): possibly improved contraceptive compliance; little information on interactions with ARVs • Intrauterine devices (IUDs), particularly the Mirena levonorgestrel-releasing (LNG) device and copper-T devices have been shown to be safe for use by HIV-infected women and do not increase HIV viral shedding 	<ul style="list-style-type: none"> • Avoid use of EFV with women who use inadequate or inconsistent contraception (risk of teratogenicity). • Interactions between oral hormonal agents and many ARVs may decrease contraceptive efficacy (see Potential ARV Interactions, below). Fewer data are available for drug-drug interactions with other formulations. • Possible adverse effects of hormonal contraceptives include thrombosis, myocardial infarction (estrogen/progesterone), stroke, menstrual irregularities, breast tenderness, weight gain, mood changes, loss of bone mineral density (DMPA), increased risk of breast cancer. • For women in whom hormonal methods are contraindicated (eg, history of thrombosis, thrombophilia, or cancer), the copper-T IUD may be safe and effective.
<p>Preconception</p>	<p>Preconception counseling is needed for all women who intend to become or who may become pregnant; preconception counseling and care includes:</p> <ul style="list-style-type: none"> • Education regarding HIV and pregnancy, risk of transmission (to fetus or uninfected partners), measures to reduce this risk • Initiation of folate supplementation (higher dosage required for women who take TMP-SMX; see Pregnancy, below) 	<ul style="list-style-type: none"> • Many HIV-infected women become pregnant, intentionally or unintentionally. It is important to discuss each patient's intentions and desire to bear children at entry to care and periodically thereafter.

- Screening tests: rubella titers, varicella titers in patients with no varicella history, HBV serologies, HCV antibody, *Toxoplasma* immunoglobulin G, cytomegalovirus, tuberculosis screening (purified protein derivative or Quantiferon), complete blood count; consider fasting glucose
 - Vaccinations as appropriate
 - Pap smear, STD screening (gonorrhea, chlamydia, syphilis, trichomoniasis)
 - Nutrition evaluation
 - Substance abuse and mental health screening and treatment as indicated
 - Referral to reproductive health specialist with experience in working with HIV-infected women (see **Pregnancy**, below)
 - Referral for prenatal genetic counseling
- Women with HIV infection have been noted to have increased rates of infertility compared with non-HIV infected women.
 - Tubal infertility is more common among women with HIV.
 - For women with difficulty conceiving, referral for evaluation of possible etiologies for infertility (including evaluation of endocrine, uterine, tubal, and male factors) should occur in advance of referral for assisted reproduction.

Assist women to become pregnant in ways that have lowest risk of HIV infection for partner (if HIV uninfected) and for fetus. **Note that VA does not provide in vitro fertilization or other assisted reproduction services; patients must be referred to a non-VA provider for such services, which cannot be covered by VA on a fee basis.**

- For an HIV-infected woman with an HIV-uninfected male partner, advise methods of conception that avoid risk of HIV transmission to the partner (eg, home or office artificial insemination using partner's semen)
- For an HIV-uninfected woman with an HIV-infected male partner, consider sperm washing, in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI); full disclosure of genetic and other risks of assisted reproduction should occur
- Sperm washing results in sperm that is reported to be >99.9% free of HIV virus

	<ul style="list-style-type: none"> • Note that legal issues in some states may limit access to reproductive services • Maximize ART efficacy, selecting ARVs that are appropriate for use during pregnancy (see below) • Avoid potential teratogens, including EFV, ribavirin, hydroxyurea, thalidomide, some antiepileptic drugs • Optimize control of other medical conditions (eg, hypertension, diabetes) 	
<p>Pregnancy</p>	<ul style="list-style-type: none"> • Detailed information on care of HIV-infected pregnant veterans is available at http://www.hiv.va.gov/vahiv?page=cm-306_pg_tx • Refer to an obstetrician who has expertise working with HIV-infected women; for centers that do not have such expertise available, consultation is available through the National Perinatal HIV Consultation and Referral Service (http://www.ucsf.edu/hivcntr/Hotlines/Perinatal.html); the number of the hotline for the service is 888-448-8765) • For pregnant women or women who may become pregnant, give folate (folate dosage should be 4-5 mg QD for women who take TMP-SMX, to overcome the folate-antagonist effects of TMP-SMX) • ART during pregnancy: <ul style="list-style-type: none"> • Test for HIV resistance before initiating ART • Give combination ART with goal of maximal virologic suppression • Recommended agents for use during pregnancy*: <ul style="list-style-type: none"> • ZDV + 3TC, combined with NVP or LPV/r • Alternative ARVs during pregnancy: <ul style="list-style-type: none"> • NRTIs: ABC,[#] ddl, FTC, d4T • NNRTIs: none • PIs: IDV/r, NFV, RTV, SQV/r 	<ul style="list-style-type: none"> • Goals include maximal suppression of HIV RNA to prevent HIV transmission and to optimize the patient's health. • Higher risk of perinatal transmission with: <ul style="list-style-type: none"> • High viral load • Low CD4 count • Advanced HIV infection • Poor nutrition • Drug use • STD • Vaginal delivery (if HIV RNA >1,000 copies/mL) • Invasive monitoring • Prolonged rupture of membranes • Chorioamnionitis • Without ART, risk of transmission is 25%; with PI-based ART, risk of transmission is 1% in the United States. • Pharmacokinetic changes during pregnancy may alter serum levels of some ARVs; check USPHSTF guidelines for recommended dosage adjustments; consult with pharmacist.

	<ul style="list-style-type: none"> • Insufficient data: TDF, ETR, ATV, DRV, FPV, TPV, ENF, RTV, MVC • Avoid use of EFV, DLV: risk of teratogenicity, especially during first trimester) 	<ul style="list-style-type: none"> • Many experts recommend increase in LPV/r dosage to 600/150 mg BID during 3rd trimester. • Some evidence suggests ART may increase rates of preeclampsia. • Consider scheduled cesarean section delivery if HIV viral load is >1,000 copies/mL near time of delivery.
Breast-feeding	<ul style="list-style-type: none"> • Breast-feeding is not recommended in the United States (to avoid risk of HIV transmission through breast milk). 	
Menstrual irregularities and menopause	<ul style="list-style-type: none"> • Evaluate menstrual irregularities as in HIV-uninfected women. Initial considerations include: <ul style="list-style-type: none"> • For abnormal bleeding, seek to determine source of bleeding (bladder, urethra, vagina, uterus), with further evaluation depending on source • Pregnancy test • Consider polycystic ovarian syndrome (PCOS) in women with amenorrhea or hypomenorrhea and features suggestive of PCOS (clinical or serum hyperandrogenism, glucose intolerance, obesity) • Consider menopause (check follicle-stimulating hormone [FSH] to confirm) • Consider checking FSH and prolactin for secondary causes of amenorrhea • Consider hypothyroidism (check TSH) • For intermenstrual bleeding, evaluate for estrogen or progestin breakthrough on hormonal contraceptives, complications of intrauterine device, polyps, genital tract cancers, genital tract infections such as endometritis 	<ul style="list-style-type: none"> • HIV-infected women more commonly experience irregular cycles and amenorrhea, but it is not entirely clear whether this is associated with HIV infection itself. Some research suggests associations between CD4 count and ovulatory status. • Confounders include weight loss, psychiatric medications, hormonal treatments, substance abuse, stress, and chronic disease. • Prolonged amenorrhea without ovarian failure in HIV-infected women is associated with low body mass index and low serum albumin. • Combined analysis of data from the HERS and WIHS cohorts showed that women on ART with good CD4 response had lower rates of menstrual irregularities than HIV-uninfected women.

	<ul style="list-style-type: none"> • For postcoital bleeding, evaluate for cervical malignancies and lesions, also for STDs • Treatment of menopausal symptoms: consider hormonal therapy as for HIV-uninfected women; keep in mind potential adverse effects, as well as drug-drug interactions between estrogens and some ARVs (see Potential ARV Interactions below) 	<ul style="list-style-type: none"> • In the WIHS study, the average age at onset of menopause was 48 for both HIV-infected women and HIV-uninfected women of similar demographics. • There is a blunted CD4 recovery to ART among postmenopausal women with HIV. This is postulated to be related to lower levels of estrogen and with decrease in thymic volume (associated with aging).
Sexual function	<p>Evaluate women's perceived level of and satisfaction with sexual function</p> <p>Evaluate for factors related to perceptions of suboptimal sexual function:</p> <ul style="list-style-type: none"> • Physical, sexual, emotional abuse • Relational problems • Depression • STDs • Medications • Pelvic pain • Constitutional symptoms • Peripheral and autonomic neuropathy • Hypogonadism • Other medical and psychiatric comorbidities 	<p>Sexual function in HIV-infected women is a neglected area of study.</p> <p>Discuss patient's concerns candidly.</p> <ul style="list-style-type: none"> • Patient-reported sexual dysfunction is associated with nonadherence to ART. • Sexual dysfunction may be a marker for depression, worsening health status including pain syndromes, or intimate partner violence. • A wide variety of medications, especially psychiatric, antiepileptic, and cardiovascular drugs, are associated with sexual dysfunction.

Abbreviations: HERS = Heart and Estrogen/Progestin Replacement Study; USPHSTF = U.S. Public Health Services Task Force; WIHS = Women's Interagency HIV Study

* Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States; November 2, 2007.

If possible, check for HLA-B*5701 before treatment with ABC.



Hormonal Contraception and ARVs

Drug interactions between oral contraceptive agents and many PIs and NNRTIs may affect the serum levels of either the hormonal agent or the ARV. In some cases, contraceptive efficacy or the potential for side effects may be affected significantly. Dosage adjustments may be required, and some combinations are contraindicated. See table below for details.

There are very few data on potential interactions between ARVs and nonoral hormonal contraceptives. Transdermal (patch) and transvaginal (intravaginal ring) contraceptive devices contain ethinyl estradiol (EE); thus caution should be used on a theoretical basis with ARVs that increase the serum estradiol levels. DMPA (Depo-Provera) is a progestin; thus, its interactions with ARVs may mirror those of norethindrone (NE). This may be cause for concern if DMPA is used with ARVs that increase NE levels, because DMPA is long-acting and has sustained serum levels.

There are no significant known interactions between hormonal contraceptives and NRTIs, integrase inhibitors, or CCR5 antagonists.

Potential Interactions between Oral Contraceptives and PIs or NNRTIs

Decreased EE or NE levels

PIs:

- ATV/r
- DRV/r
- LPV/r
- NFV
- RTV
- TPV/r

Risk of contraceptive failure; use alternative (or additional) contraceptive method (If oral contraceptive used with ATV/r, it should contain ≥35 mcg of EE.)

NNRTIs:

- NVP

Risk of contraceptive failure; use alternative (or additional) contraceptive method.

Increased EE or NE levels

PIs (without RTV):

- ATV
- FPV
- IDV

- **ATV:** Risk of EE or NE adverse effects (eg, deep vein thrombosis). Use alternative method of contraception or lowest effective dosage with careful monitoring for adverse effects. If given concurrently, oral contraceptive should contain ≤30 mcg of EE; however, doses <25 mcg have not been studied.
- **FPV:** Risk of EE or NE adverse effects; also, ↓ FPV levels; avoid, or use lowest effective dosage of EE/NE with careful monitoring for adverse effects and for ARV efficacy.
- **IDV:** No dosage adjustment.

NNRTIs: EFV	Risk of EE or NE adverse effects; alternative contraceptive method is recommended.
No data	
PIs: • SQV	Alternative method of contraception is recommended.
Mixed effects	
NNRTIs: • ETR	↑ EE, ↓ NE; no dosage adjustment.

Neuropsychiatric Disorders

Recommendations	Comments
<p>Screen for neuropsychiatric disorders in HIV-infected women</p> <ul style="list-style-type: none"> • Depression • Dementia • Posttraumatic stress disorder (PTSD) • Personality disorders <p>Perform neuropsychiatric testing as needed</p>	<p>Neuropsychiatric disorders are common in HIV-infected individuals:</p> <ul style="list-style-type: none"> • Direct effects of HIV on neuronal function • Underlying psychiatric disease • Affective disorders • Prior trauma • Social comorbidities • Personality disorders <p>Women with HIV are at increased risk of HIV-associated psychiatric disease, especially HIV-related dementia, but also at risk of underdiagnosis and undertreatment of depression.</p> <p>Neuropsychiatric testing is recommended to establish diagnosis.</p> <p>Owing to increased rates of depression and PTSD in women veterans, aggressive screening and treatment of depression in HIV-infected women is recommended.</p> <p>Substance abuse is often comorbid with PTSD and depression.</p> <p>For women with HIV infection, especially those with multiple responsibilities, psychosocial needs may be complex, requiring multidisciplinary team care. Research suggests that case management can improve outcomes, care, and treatment adherence.</p> <p>For further information, see Depression, p. 271.</p>

Military Sexual Trauma and Domestic Violence (Intimate Partner Violence)

Issue	Recommendations	Comments
<p>Military sexual trauma (MST)</p>	<ul style="list-style-type: none"> • Screen all veterans, including female veterans, for MST. • Refer veterans with MST to the designated MST Counselor or team; referral to a local Vet Center may be an appropriate alternative based on available services. 	<ul style="list-style-type: none"> • All VA Medical Centers have designated MST Coordinators. • 30-45% of female veterans have been exposed to MST. • Effects of MST include: <ul style="list-style-type: none"> • Avoidance of places or objects that recall memories of the traumatic incident • Anxiety • Depression • Suicidal thoughts • Misuse of alcohol and other substance • Recurring and intrusive thoughts and dreams about the trauma incident • Nonspecific health problems • Problems with interpersonal relationships
<p>Domestic violence</p>	<ul style="list-style-type: none"> • Consider screening with the HITS scale: <ul style="list-style-type: none"> • Hurt: How often does your partner physically hurt you? • Insult: How often does your partner insult or talk down to you? • Threaten: How often does your partner threaten you with physical harm? • Scream: How often does your partner scream or curse at you? <p>Each question is answered on a 5-point scale: 1 = never; 2 = rarely; 3 = sometimes; 4 = fairly often; 5 = frequently. The score ranges from 4 to a maximum of 20. A score of ≥ 10 is considered diagnostic of abuse.</p>	<ul style="list-style-type: none"> • Domestic violence is prevalent among both female veterans and women living with HIV infection. • Screening instruments such as the HITS scale have been validated. • There is weak evidence for the efficacy of interventions in the health care setting.

	<ul style="list-style-type: none"> • Look for evidence of physical abuse (bruises, fractures, injuries accompanied by implausible explanation). • If abuse is documented or suspected: <ul style="list-style-type: none"> • Consult Social Work Service • Refer the patient to community domestic violence agencies • Work with the patient to develop an emergency safety plan. 	
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Screening: Cancer, Osteoporosis, and STDs

Note: For other routine cancer screening, see **Cancer Screening**, p. 17.

Test	Recommendations	Comments
<p>Cervical cancer screening:</p> <ul style="list-style-type: none"> • Cervical Pap test (smear or liquid cytology) 	<ul style="list-style-type: none"> • Baseline • Repeat in 6 months • If both Pap results are normal and CD4 count is >200 cells/μL, repeat annually • If both Pap results are normal and CD4 count is <200 cells/μL, repeat every 6 months • If any Pap smear result is abnormal, additional testing should be done; see Cervical Dysplasia and Management of Abnormal Pap Smear Results, below 	<ul style="list-style-type: none"> • HIV-infected women are more likely than HIV-uninfected women to be infected with HPV, especially with oncogenic HPV types. • Dysplasia may involve the cervix, vulva, vagina, or anus. • Abnormalities on cervical colposcopy are seen in 64% of women with CD4 counts of <200 cells/μL and 34% of those with CD4 counts of >400 cells/μL. • HIV-infected women have decreased rates of clearance of HPV; as a result, they have an increased risk of disease progression and recurrence. • For management of abnormal results, see Cervical Dysplasia and Management of Abnormal Pap Smear Results, below.
<p>Vulvar and vaginal cancer screening:</p> <ul style="list-style-type: none"> • Visual and manual inspection 	<ul style="list-style-type: none"> • Evaluate at times of cervical Pap test • Suspicious lesions: colposcopy; biopsy 	<ul style="list-style-type: none"> • HIV-infected women have elevated rates of vulvar and vaginal neoplasia. • Lesions may be multifocal, extensive, and recurrent, and may have an unusual appearance; sometimes progressing rapidly, especially in women with CD4 counts of <200 cells/μL.

		<ul style="list-style-type: none"> Apparent condylomata that are resistant to treatment and unusual vulvar lesions should be referred for biopsy; also check RPR.
<p>Anal cancer screening:</p> <ul style="list-style-type: none"> Digital rectal examination (DRE) Anal Pap test 	<p>No national guidelines for anal cancer screening; consider:</p> <ul style="list-style-type: none"> Baseline Annual DRE and anal Pap screening if patient is sexually active and baseline result was normal Use polyester swab and liquid cytology method, if available 	<ul style="list-style-type: none"> Anal dysplasia and anal cancer rates among HIV-infected women are not fully known but appear to be higher than those for HIV-uninfected women. Anal dysplasia is seen in women with and without a history of receptive anal sex. ART has not been shown to prevent or alter the course of anal dysplasia. ASCUS, LSIL, HSIL: Refer for high-resolution anoscopy with biopsy. Screening was cost-effective in a small study; no large-scale clinical trials on cost-effectiveness have been conducted. See Anal Dysplasia, p. 83.
<p>Breast cancer screening:</p> <ul style="list-style-type: none"> Mammogram 	<ul style="list-style-type: none"> Age 40-69: every 1-2 years Age ≥ 70: discuss and take into account estimated life expectancy and presence of comorbid disease 	<ul style="list-style-type: none"> HIV-infected women do not appear to have elevated risk of breast cancer. see Cancer Screening, p. 17.
<p>Osteoporosis/osteopenia screening:</p> <ul style="list-style-type: none"> Dual-energy X-ray absorptiometry (DEXA) bone densitometry 	<ul style="list-style-type: none"> Baseline for patients at risk and all women >65 years of age Also consider for thin female smokers >40 years of age Every 1-2 years for patients with osteoporosis who are treated with bisphosphonates 	<ul style="list-style-type: none"> Age and previous fracture are the most significant risk factors. See Osteoporosis, below, for more information and treatment recommendations.
<p>STD screening:</p> <ul style="list-style-type: none"> RPR, VDRL Cervical GC and CT (NAAT or culture of first-void urine or cervical specimen) 	<ul style="list-style-type: none"> Perform at baseline, repeat according to risks or exposures (eg, every 3-6 months for women with new sex partners since previous examination) 	<ul style="list-style-type: none"> STDs should be treated to prevent health complications for the patient, and also to prevent perinatal transmission or transmission to sex partners.

<ul style="list-style-type: none"> • Rectal or pharyngeal testing for GC and CT, based on possible risks or exposures (NAAT or culture of swab) • <i>Trichomonas</i> (wet-mount examination or culture of vaginal secretions) • HBV, HCV • HSV IgG (type specific) 	<ul style="list-style-type: none"> • Inflammatory STDs may increase risk of HIV transmission to uninfected sex partners. • See Prevention for Positives, p. 39.
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Abbreviations: ASCUS = atypical squamous cells of undetermined significance; CT = *Chlamydia trachomatis*; GC = *Neisseria gonorrhoea*; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; NAAT = nucleic acid amplification test

Cervical Dysplasia and Management of Abnormal Pap Smear Results

Epidemiology and Diagnosis	Management and Treatment
<ul style="list-style-type: none"> • HPV prevalence is higher among HIV-infected women than among HIV-uninfected women. • In the WIHS cohort, prevalence of genital HPV among HIV-infected women is approximately 64%, compared with 30% among HIV-uninfected women. • HIV-infected women have increased persistence of HPV and greater likelihood of high-risk oncogenic types of HPV. • Women with low CD4 counts tend to harbor high-risk HPV types. • HIV-infected women are at greater risk of cervical dysplasia and cervical cancer. • The time between diagnosis of carcinoma in situ and development of invasive disease is shorter among HIV-infected women who are not on ART than among HIV-uninfected women (3.2 vs 15.7 years). • However, ART has not been shown consistently to prevent or alter the course of cervical dysplasia in HIV-infected women. <p>See Screening: Cancer, Osteoporosis, and STDs, above, for screening recommendations.</p>	<ul style="list-style-type: none"> • Most experts recommend more aggressive management of HIV-infected women than HIV-uninfected women. The American Society for Colposcopy and Cervical Pathology (ASCCP) recommends managing HIV-infected women no differently than HIV-uninfected women. • ASCUS: There is controversy about management of ASCUS in HIV-infected women: <ul style="list-style-type: none"> • Most authorities recommend that HIV-infected women with ASCUS be referred for colposcopy. • In HIV-infected women, there are insufficient data to recommend HPV DNA testing for oncogenic HPV types as part of management of ASCUS. • ASC-H (atypical squamous cells, cannot exclude HSIL), LSIL, HSIL, and atypical glandular cells: Refer all patients with these findings for colposcopy. Note that some laboratories use the cervical intraepithelial neoplasia (CIN) 1, 2, 3 classification; these patients should also be referred for colposcopy.

Osteoporosis

Epidemiology and Diagnosis	Management and Treatment
<p>Background</p> <ul style="list-style-type: none"> In small cohort studies, HIV-infected women had twice the rate of osteopenia (by DEXA) as HIV-uninfected women matched for age, race, and BMI. HIV infection itself appears to be independently associated with reduced bone mineral density. Exposure to ARVs, specifically PIs, has not been found to be associated with osteoporosis. <p>Risk factors</p> <ul style="list-style-type: none"> History of fracture as an adult Age Female sex Race (Asians and Caucasians at higher risk) Family history Low body weight (<58 kg, 127 lb) or weight loss Estrogen deficiency at early age (amenorrhea >1 year, early menopause) Lifestyle: current cigarette smoking, alcohol misuse, inadequate physical activity Poor health/nutrition (eg, low calcium intake) Medications (eg, corticosteroids, anti-convulsants, gonadotropin-releasing hormone [GnRH] agonists, lithium) Medical conditions (eg, hyperthyroidism, gastrectomy, COPD, hyperparathyroidism, multiple myeloma, celiac disease, eating disorder) Recurrent falls, dementia <p>Evaluation</p> <ul style="list-style-type: none"> DEXA screening for women with risk factors or age >65 (see above): <ul style="list-style-type: none"> Normal = T-score above -1 Osteopenia = T-score between -1 and -2.5 Osteoporosis = T-score less than -2.5 (a fracture-threshold) 	<p>Prevention (for all women)</p> <ul style="list-style-type: none"> Calcium* 1,000 mg per day for premenopausal women; 1,500 mg per day for postmenopausal women, in divided doses Vitamin D 400-800 IU QD (800-1,000 IU in women age >50 years) Exercise: 30 minutes of weight-bearing exercise ≥4 times per week Smoking cessation, limited alcohol intake, adequate diet, careful sun exposure Women taking calcium and vitamin D supplements in the Women's Health Initiative had a 1% gain in hip bone mineral density and a slight but statistically nonsignificant reduction in hip fracture (hazard ratio: 0.71; 95% confidence interval: 0.52-0.97 [for women with ≥80% adherence]). <p>Treatment</p> <p>Treat women with:</p> <ul style="list-style-type: none"> T-score below -2.0 in the absence of risk factors T-score below -1.5 + risk factors Age >70 + multiple risk factors <p>Treatment options</p> <ul style="list-style-type: none"> Bisphosphonates offer the most clinically significant benefit. Randomized controlled studies show a 56% reduction in hip fractures in patients treated with alendronate. Options include: <ul style="list-style-type: none"> Alendronate 70 mg PO once weekly Ibandronate 150 mg PO once monthly Zoledronic acid 5 mg IV once yearly <p>Plus:</p> <ul style="list-style-type: none"> Calcium* 1,500 mg per day in divided doses Vitamin D 800-2,000 IU QD Smoking cessation Limited alcohol intake Exercise: 30 minutes of weight-bearing exercise ≥4 times per week

* Calcium and other divalent cations may lower serum levels of integrase inhibitors; calcium should be taken ≥2 hours apart from integrase inhibitors.

Genital Tract Infections

Infection	Epidemiology and Diagnosis	Management
HSV	<ul style="list-style-type: none"> • Risk factor for HIV acquisition and transmission • Of HIV-infected women, 50-90% have concurrent HSV infection • In the HERS study, there was no difference in rates between HIV-infected and high-risk HIV-uninfected women • Chronic suppressive therapy with acyclovir may increase survival for HIV/HSV-coinfected women who do not take ARVs; this benefit is not demonstrated in patients on ART • Infection can be primary, nonprimary first episode, or recurrent • Most genital HSV infections occurring in HIV coinfection reflect reactivation syndromes; symptomatic episodes may be more severe, more frequent, and longer in duration than in HIV-negative women • Genital HSV in HIV-infected women ranges in appearance from small confined ulcers to painful extensive necrotic lesions accompanied by constitutional symptoms • Complications seen more commonly in advanced HIV infection include aseptic meningitis, sacral radiculopathy, transverse myelitis, scarring, rectovaginal fistulae <p>Diagnosis: swab base of lesion for testing via viral culture, direct fluorescent-antibody assay, HSV PCR, or Tzanck prep (less sensitive)</p> <p>Differential diagnosis includes: syphilis, chancroid, drug eruptions, Behçet syndrome</p>	<ul style="list-style-type: none"> • Initial episode or severe mucocutaneous outbreak: hospitalize and treat with IV acyclovir (5 mg/kg IV Q8H) for 7-14 days, changing to PO therapy when lesions improve • Episodic therapy for outbreaks: valacyclovir 1,000 mg BID, acyclovir 400 mg TID, or famciclovir 500 mg BID for 5-14 days • Suppressive therapy: consider for patients with frequent recurrences, especially those with CD4 counts of <100 cells/μL and severe protracted outbreaks: acyclovir 400 mg BID, valacyclovir 500 mg BID, or famciclovir 500 mg BID • During pregnancy, refer to OB/GYN specialist for management • Counsel use of latex barriers to prevent HSV transmission to uninfected partners
Genital ulcers	<ul style="list-style-type: none"> • Risk factor for HIV acquisition and transmission • Research indicates prevalence as high as 14% in an urban population, with recurrence rate of 19% 	<p>Initial episode:</p> <ul style="list-style-type: none"> • Attempt to establish a diagnosis: laboratory testing (viral, bacterial culture, serology) or biopsy

	<ul style="list-style-type: none"> • Only 40% of cases had identifiable pathogen • Differential diagnosis includes syphilis, chancroid, HSV (see above); may be caused by atypical pathogens identified (CMV, <i>Chlamydia trachomatis</i>, <i>Gardnerella vaginalis</i>) • In women, genital ulcers often are not noticed • Lesions may be large, requiring multiple admissions and surgical procedures 	<ul style="list-style-type: none"> • For severe or erosive lesions, prompt evaluation and management, possibly including hospitalization and surgery, may be needed to prevent scarring, vaginal or urethral stricture, or fistulae • Follow up carefully to evaluate for recurrence
Bacterial vaginosis (BV)	<ul style="list-style-type: none"> • Risk factor for HIV acquisition and transmission • HIV-infected women have increased persistence of BV, especially with CD4 counts of <200 cells/μL <p>Diagnosis (3 of 4 Amsel criteria):</p> <ul style="list-style-type: none"> • Homogeneous, thin, grayish-white discharge that smoothly coats the vaginal walls • Vaginal pH >4.5 • Positive whiff-amine test, defined as the presence of a fishy odor when 10% KOH is added to a sample of vaginal discharge • Clue cells on saline wet mount 	<ul style="list-style-type: none"> • Metronidazole 500 mg BID for 7 days <p>Alternatives:</p> <ul style="list-style-type: none"> • Topical vaginal therapy <ul style="list-style-type: none"> • Metronidazole gel 0.75%, 5 g QD for 5 days • Clindamycin cream 2%, 5 g QD for 7 days • Clindamycin 300 mg PO BID for 7 days (less evidence for efficacy; higher risk of <i>Clostridium difficile</i>)
Vaginal candidiasis	<ul style="list-style-type: none"> • HIV-infected women may have higher rates of persistence and recurrence (≥ 4 episodes per year) <p>Diagnosis: budding yeast and hyphae on 10% KOH wet mount of vaginal discharge</p>	<ul style="list-style-type: none"> • Single episode: <ul style="list-style-type: none"> • Topical azoles for 3-7 days • Fluconazole 150 mg PO for 1 dose • Itraconazole 200 mg PO BID for 1 day or QD for 3 days • Recurrent episodes (≥ 4 episodes per year): <ul style="list-style-type: none"> • Fluconazole 150 mg PO for 3 doses 72 hours apart, followed by fluconazole 150 mg PO once a week for 6 months
Pelvic inflammatory disease (PID)	<ul style="list-style-type: none"> • Among women with HIV infection, risk for severe morbidity and mortality is increased and PID may be more severe at time of presentation 	<ul style="list-style-type: none"> • Consider hospitalization in event of severe illness, pregnancy, or inability to take oral therapy

- A Kenyan study showed increased incidence of tuboovarian abscesses in HIV-infected women
- HIV-infected women with PID respond to the same antibiotics as HIV-uninfected women but may need surgical interventions more frequently
- Causative organisms include *Chlamydia trachomatis*, *Neisseria gonorrhoea*, *Streptococcus* spp, *Escherichia coli*, *Klebsiella* spp, *Proteus* spp, and BV flora
- Risk factors: multiple partners, partner with an STD or STD symptoms, prior STD, IUD in situ
- Clinical presentation: bilateral lower abdominal pain, often <2 weeks' duration, worse with coitus or jarring movements

Clinical diagnosis:

- Lower abdominal pain, plus one of the following:
 - Cervical motion tenderness or uterine/adnexal tenderness
 - Temperature >101°F (>38.3°C)
 - Leukocytosis
 - Abnormal cervical or vaginal mucopurulent discharge
 - Presence of WBCs on saline microscopy of vaginal secretions
 - Elevated erythrocyte sedimentation rate
 - Elevated C-reactive protein
- An adnexal mass suggests tuboovarian abscess
- Laparoscopic evaluation is recommended for:
 - Strongly suspected competing diagnosis (eg, appendicitis)
 - Acutely ill patients for whom outpatient treatment of PID has failed
 - Patients not clearly improving after 72 hours of inpatient treatment for PID

Outpatient treatment:

- Ceftriaxone 250 mg IM for 1 dose, plus doxycycline 100 mg PO BID for 14 days, with or without metronidazole 500 mg PO BID for 14 days
- Cefoxitin 2 g IM for 1 dose with probenecid 1 g PO for 1 dose, plus doxycycline 100 mg PO BID for 14 days, with or without metronidazole 500 mg PO BID for 14 days
- Consultation with OB/GYN is recommended as treatment failures, delayed diagnosis, and loss to follow-up are common

* STD treatments reflect current CDC guidelines.



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Neurology, Psychiatry, and Pain

Depression

KEY POINTS

- Depression can be a life-threatening disorder.
- Depression among HIV-infected persons is common and is associated with increased high-risk behavior, nonadherence to ART, and progression of immunodeficiency.
- Depression can be diagnosed and treatment can be initiated in the primary care setting.
- Potentially treatable causes of secondary depressive symptoms in HIV-infected persons should be investigated and treated.
- Antidepressant medication and psychotherapy both are effective for treating depression in HIV-infected persons.

Linking Primary Care and Mental Health Care Services in the Treatment of Depression

VA medical centers and community-based outpatient clinics are now integrating mental health services into primary care settings. The model on which these clinics are structured and their services are delivered varies from one facility to another; but primary care providers should be knowledgeable about when they should refer for mental health consultation and when they can successfully treat depressive symptoms themselves.



WHEN TO REFER

Indications for referring depressed patients to a mental health care provider:

- Disabling symptoms
- Suicidal thought with plan or intent
- Severe hopelessness or negativism
- Persistent agitation
- Psychotic symptoms
- Pronounced affective instability
- Suspected bipolar disorder
- 3 or more ineffective therapeutic trials of antidepressant medication

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- Complicated psychopharmacologic regimens requiring medications that the care provider is not experienced in prescribing
- Need for tricyclic antidepressants (TCAs)
- Maladaptive social functioning



BACKGROUND

- Lifetime prevalence of depression among HIV-infected persons in the United States is 20-40%, up to 2-fold higher than it is among HIV-uninfected persons. Among veterans, this percentage may even be higher (see box at right).
- Depression increases the risk of acquiring HIV infection and the likelihood of high-risk sexual behavior among persons already infected with HIV.
- Depression is associated with nonadherence to ART, progression of HIV disease, and decline in CD4 cell count.
- Treatment of depression improves adherence to ART.

Veterans with HIV*

Depression: 49%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to this condition



EVALUATION



SCREENING

Recommended Screening for Depression in Primary Care Settings

The VA recommends using the PHQ-2 and PHQ-9 instruments to screen for depression in the primary care setting, a use for which they are validated, and recommends that the result of screens be entered in the chart on the day they are administered. Telephone screening is acceptable, provided that positive screening results are addressed by appropriate risk assessments and interventions.

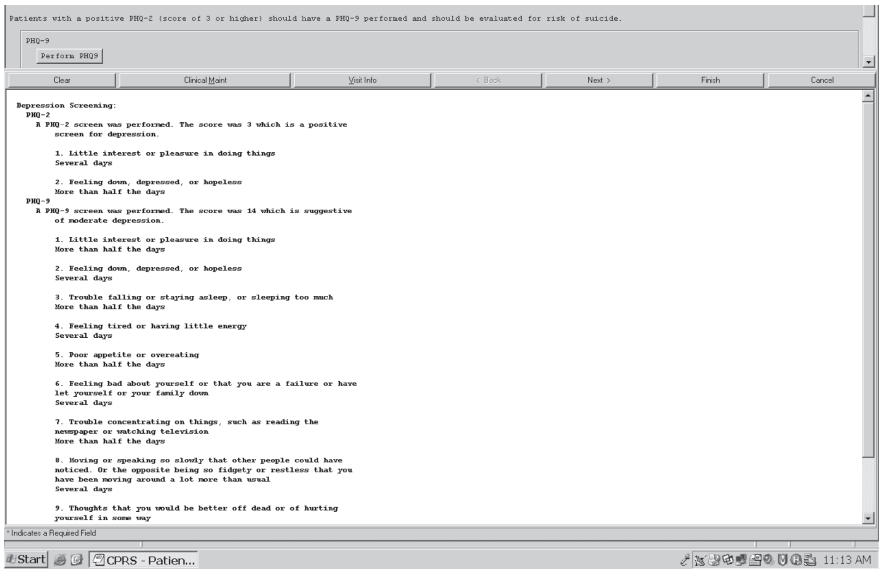
PHQ-2 and PHQ-9

The PHQ-2 is a 2-question screen. The maximum score is 6, and a positive score is 3. If the PHQ-2 result is negative, further screening is unnecessary. If the PHQ-2 result is positive, the patient must be screened on the same day with the PHQ-9, with responses to all questions and the summary score to be recorded

in the patient’s chart. Alternatively, the patient can be screened with the PHQ-9 alone, with responses to all questions and the summary score to be recorded in the patient’s chart.

Patients who screen positive for depression should be evaluated for risk factors that indicate a need for urgent intervention. Foremost in this process is an explicit assessment for the presence of suicidal ideation. After an evaluation of screening results and a discussion with the patient, the provider can decide whether the patient may benefit from urgent intervention or further specialized mental health evaluations.

- **Note:** The CPRS Clinical Reminder supporting the standard PHQ-2 and PHQ-9 tools will display the questions comprising these instruments when the “Perform PHQ-2” and “Perform PHQ-9” buttons are clicked, and it allows for documentation of depression screen results, as shown:



Acceptable screening is summarized as follows:

Screening Tool Used	PHQ-2 Result	PHQ-9 Result
If PHQ-2 initially used:	And result Negative, then:	Not required
If PHQ-2 initially used:	And result Positive, then:	Required on same day
If PHQ-9 initially used:	Not required	NA

The Patient Health Questionnaire – 2 (PHQ-2)

Patient Name: _____

Date of Visit: _____

Over the past two weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
		Total point score: _____		

Scoring the PHQ-2

PHQ-2 Score	Probability of Major Depressive Disorder (%)	Probability of Any Depressive Disorder (%)
1	15.4	36.9
2	21.1	48.3
3	38.4	75.0
4	45.5	81.2
5	56.4	84.6
6	78.6	92.9

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Patient Health Questionnaire – 9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3

7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3								
8. Moving or speaking so slowly that other people could have noticed, or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3								
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3								
Add columns:												
	0	+ ____	+ ____	+ ____								
= Total Score:												

<p>If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?</p> <table style="width: 100%; text-align: center;"> <thead> <tr> <th style="width: 25%;">Not difficult at all</th> <th style="width: 25%;">Somewhat difficult</th> <th style="width: 25%;">Very difficult</th> <th style="width: 25%;">Extremely difficult</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>					Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult									
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Scoring the PHQ-9	
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression
<p>Clinicians should be particularly alert to patients' responses to question 9, "Thoughts that you would be better off dead, or of hurting yourself in some way." Any affirmative response to question 9, or a PHQ-9 score of >9, requires that a suicide risk assessment be completed within 24 hours (see below).</p>	

The PHQ-9 is validated for use only with English-speaking persons of European origin; some experts feel it is less sensitive for depression in many patients with Asian or Latino backgrounds. As with all symptom questionnaires, assessment results should be interpreted and guided by clinical experience.

Depressive symptoms may be associated with illnesses other than major depression

Given the overlap between symptoms of depression and symptoms of other illnesses and medication side effects common among HIV-infected persons, all potentially treatable or reversible causes of depression (see list below) should be considered when HIV-infected persons present with depressive symptoms.

Screening	<ul style="list-style-type: none"> • PHQ-2 (see above) • PHQ-9 (see above)
History	<ul style="list-style-type: none"> • Relationship between onset of depression symptoms and major life stressors • Concurrent chronic disease • Medication history, including recent changes • Use of alcohol or other psychoactive drugs, whether legal or illegal • Past history of depression • Suicidal thoughts • Family history of mental illness
Physical examination	<ul style="list-style-type: none"> • Mini mental status • Neurologic screening • Signs of hypogonadism • Signs of hypothyroidism
Laboratory studies	<ul style="list-style-type: none"> • Serum electrolytes • BUN/creatinine • Calcium (for hypercalcemia) • CBC (for anemia) • TSH • Serum testosterone • Hepatitis serologies • RPR
Differential diagnosis	<ul style="list-style-type: none"> • Mood disorders <ul style="list-style-type: none"> • Major depression • Bipolar affective disorder • Dysthymia (minor depression) • Demoralization • Drug use • Alcohol use/abuse • Anemia • HIV-associated dementia, other dementia • Hypercalcemia • Renal failure • Hepatitis

- Hypothyroidism
- Hypogonadism
- Drug effects or side effects (eg, EFV, anabolic steroids, corticosteroids, sedative-hypnotics, beta-blockers, reserpine, interferon, alcohol, methamphetamine withdrawal)
- CNS infections
- CNS neoplasms

Assessment of suicide risk

Veteran suicide is emerging as a serious public health issue, and primary care providers are on the front line in identifying veterans with risk factors for suicide and ensuring they receive appropriate interventions. An affirmative response to questions about suicidality on screening instruments, such as the PHQ-9, should prompt further investigation. **When the PHQ-9 is used, a score >9 or any affirmative response to question 9 requires that a suicide risk assessment be performed within 24 hours;** ideally, this risk assessment should immediately follow a positive screening result for depression.

Such assessments may be performed by telephone, provided that the assessment is made by an acceptable provider, and that the results are appropriately documented. An acceptable provider is an MD, NP, DO, PsyD or PhD Psychologist, LCSW, APN, PA (or a trainee with appropriate cosignature), or other allied health care professional who, by virtue of educational background *and* approved credentialing, privileging, or scope of practice, has been determined by the facility to be capable of diagnosing and treating mental illness.

All VA medical centers now have a designated suicide prevention coordinator, whose role includes providing general consultation to clinicians concerning risk assessment, providing resources for suicidal individuals, and ensuring that high-risk patients receive education and support about approaches to reduce risks.

The CPRS contains a detailed suicide risk assessment template. To assess patients for suicide risk:

- **Look** for warning signs
- **Assess** for risk and protective factors
- **Ask** the questions

I. Look for warning signs

- Threatening to hurt or kill self
- Looking for ways to kill self; seeking access to pills, weapons, or other means
- Talking or writing about death, dying, or suicide

Any of the above warning signs requires immediate attention and referral. Consider hospitalization for safety until complete assessment may be made.

Additional warning signs include:

- Hopelessness
- Rage, anger, seeking revenge
- Acting reckless or engaging in risky activities, seemingly without thinking
- Feeling trapped – like there's no way out
- Increasing alcohol or drug abuse
- Withdrawing from friends, family, or society
- Anxiety, agitation, unable to sleep or sleeping all the time
- Dramatic changes in mood
- No reason for living, no sense of purpose in life

2. Assess for risk and protective factors

Factors that may increase risk for suicide

Current ideation, intent, plan, access to means

Previous suicide attempt or attempts

Alcohol or substance abuse

Previous history of psychiatric diagnosis

Impulsivity and poor self-control

Hopelessness – presence, duration, severity

Recent losses – physical, financial, personal

Recent discharge from an inpatient unit

Family history of suicide

History of abuse (physical, sexual, or emotional)

Comorbid health problems, especially a newly diagnosed problem or worsening symptoms

Age, gender, race (elderly or young adult, unmarried, white, male, living alone)

Same-sex sexual orientation

Transgender identity

Factors that may decrease risk for suicide

Positive social support

Spirituality

Sense of responsibility to family

Children in the home, pregnancy

Life satisfaction
Reality-testing ability
Positive coping skills
Positive problem-solving skills
Positive therapeutic relationship

3. Ask the questions

(Note: Asking about suicide does not induce patients to contemplate killing themselves.)

- Are you feeling hopeless about the present/future? If yes, ask ...
- Have you had thoughts about taking your life? If yes, ask ...
- When did you have these thoughts and do you have a plan to take your life?
- Have you ever had a suicide attempt?

Response to suicide risk

- **Assure the patient's immediate safety and determine the most appropriate treatment setting**
- Refer for mental health treatment or assure that follow-up appointment is made
- Consult with the facility suicide prevention coordinator
- Inform and involve someone close to the patient
- Limit access to means of suicide
- Increase contact and make a commitment to help the patient through the crisis
- Provide number of emergency department or urgent care center to the patient and significant others
- National Suicide Prevention Lifeline: 800-273-TALK (800-273-8255)

Rx MANAGEMENT

Patients with depressive symptoms who do not require referral to a mental health provider (see **When to Refer**, p. 271) may be managed safely in the primary care setting. There is evidence that treatment with SSRIs, SNRIs, TCAs, or stimulants is superior to placebo in relieving symptoms of depression in HIV-infected patients. However, a surprisingly high proportion of placebo recipients in clinical studies also experience symptom relief.

Psychotherapy of many kinds, including cognitive behavioral therapy, social support counseling, and individual psychodynamic therapy, is also effective in treating depression in HIV-infected patients. Comparison of methods is complicated by

differences in definitions of depression used in various studies and by the heterogeneity of various scoring instruments.

Interestingly, a study of the effect of treatment of depression on adherence to ART found that participants treated with psychotherapy or psychotherapy plus medication were more adherent to ART than those treated with medication alone, or with placebo.

An SSRI or an SNRI usually is recommended as initial pharmacotherapy for depression, because of their efficacy and safety profile. A patient requiring pharmacologic therapy with an agent (particularly a TCA or an MAOI) probably should be managed in collaboration with a psychiatrist.

Response to Pharmacotherapy

- Patients typically start responding to SSRIs in 2-4 weeks.
- Patients who show no improvement on maximal-dose therapy after 8 weeks should be switched to another medication or be referred to a psychiatrist.
- Suicidality may remain or emerge during the first several weeks of pharmacologic therapy, even as depression seems to decrease; close follow-up is recommended, with screening for suicidality (see above) as needed.

SSRI Discontinuation Syndrome

SSRIs and SNRIs should be tapered slowly rather than discontinued abruptly. Side effects associated with abrupt discontinuation include dizziness, irritability, anxiety, chills, myalgias, and nausea. Symptoms typically occur 1 day after discontinuing and can last up to 2 weeks. They remit when the drug is restarted. The discontinuation syndrome is more likely with venlafaxine and shorter-acting SSRIs, such as paroxetine, than with longer-acting agents, such as fluoxetine.

Commonly Used Antidepressant Medications

Generic Drug Name	Usual Starting Dosage/ Dosage Titration	Comments/ Drug Interactions
SSRIs		
<ul style="list-style-type: none">• Pros: Favored by some experts because of low potential for fatal overdose• Cons: Risk of discontinuation symptoms (see above) with certain agents if discontinued abruptly• Increased risk of suicidality among children and young adults with depression during first month of taking SSRIs• Most common side effects: sexual dysfunction, nausea, sweating, sleep disturbance• Contraindicated for use with monoamine oxidase inhibitors (MAOIs) or triptans because of risk of serotonin syndrome• Interactions with ARVs incompletely studied		

Citalopram	Start at 10-20 mg QD; may increase daily dosage after 7 days, if no adverse effects; maximum dosage: 60 mg QD	Metabolized by CYP 3A4; however, no significant change in citalopram levels when coadministered with RTV
Escitalopram	Start at 5-10 mg QD; may increase daily dosage after 7 days, but no evidence of increased efficacy; maximum dosage: 20 mg QD	Metabolized by mixture of enzymes, including CYP 3A4; however, no significant change in citalopram levels when coadministered with RTV
Fluoxetine	Start at 10-20 mg QD; not to exceed 80 mg QD Also available in weekly dose formulation: 90 mg once weekly	Metabolized by CYP 2D6, but no adjustment required when coadministered with RTV
Paroxetine	Start at 10-20 mg QD; may increase daily dosage by 10 mg every 7 days to maximum of 50 mg QD	DRV and FPV decrease paroxetine levels; titrate paroxetine to effect Must be tapered slowly when discontinuing to avoid rebound depression symptoms and discontinuation symptoms Slightly more sedating than other SSRIs
Sertraline	Start at 50 mg QD; may increase daily dosage by 25-50 mg every 7 days to maximum of 200 mg QD	DRV decreases sertraline levels; titrate sertraline to effect
SNRIs		
<ul style="list-style-type: none"> Increased presynaptic levels of serotonin and norepinephrine Most common side effects: GI events (nausea, diarrhea, constipation), dry mouth Other side effects: somnolence, insomnia, dizziness, nervousness, headache; sexual dysfunction can occur 		
Duloxetine	Start at 20 mg QD; may increase to BID, then to 60 mg QD or divided as 30 mg BID	Hepatically metabolized; not recommended for use in patients with hepatic impairment To discontinue, taper gradually

Venlafaxine Formulations		
Venlafaxine immediate release	Start at daily dosage of 75 mg divided BID (ie, 37.5 mg BID) or TID (ie, 25 mg TID) with food; may increase total daily dosage by up to 25 mg per dose every 4 days; maximum daily dosage: 375 mg divided TID (ie, 125 mg TID)	Metabolized by CYP 2D6 When stopping venlafaxine, it is essential to taper slowly to avoid discontinuation symptoms Postmarketing studies suggest that venlafaxine overdoses are more associated with fatal outcomes than are SSRI overdoses, but less than TCA overdoses; use lowest effective dosage of venlafaxine
Venlafaxine extended release (XR)	Start at 75 mg venlafaxine XR QD with food; may increase daily dosage by up to 75 mg every 4 days; maximum daily dosage: 225 mg	
Other		
Bupropion Formulations		
Bupropion		Inhibits CYP 2D6 EFV and TPV decrease bupropion levels; titrate bupropion to effect Side effects: restlessness, agitation, insomnia Bupropion increases seizure incidence (0.4% at 300 mg/day or higher); contraindicated in patients with elevated risk of seizures Sexual dysfunction unlikely
Bupropion immediate release	Start at 75-100 mg BID for 3 days, increase to 100 mg TID on day 4; maximum daily dosage: 450 mg divided TID	No single dose should exceed 150 mg, and doses should be taken at least 6 hours apart Dosage escalation should be delayed for agitation, motor restlessness, or insomnia
Bupropion SR	Start at 100-150 mg QAM; increase to usual dosage of 150 mg BID no earlier than day 4; maximum daily dosage: 400 mg divided BID (ie, 200 mg BID)	Doses of bupropion SR should be taken at least 8 hours apart Dosage escalation should be delayed for agitation, motor restlessness, or insomnia

Bupropion XR	Start at 150 mg QAM; increase to usual dose of 300 mg QAM no earlier than day 4; maximum dosage: 450 mg QD	Doses should be taken at least 24 hours apart Dosage escalation should be delayed in the event of agitation, motor restlessness, or insomnia
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Low Back Pain

KEY POINTS

- Low back pain (LBP) is a common complaint.
- When evaluating LBP, assess whether the patient has evidence of systemic disease or neurologic compromise. Assess for social or psychological distress that may contribute to chronic, disabling pain.
- **Check for red flags:** major trauma, age >50, unexplained fever, unexplained weight loss, injection drug use (IDU), immunosuppression, history of cancer, major muscle weakness, bladder or bowel dysfunction, unrelenting night pain, saddle anesthesia, decreased sphincter tone, focal neurologic deficit, duration >6 weeks, abdominal pulsating mass.
- Up to 90% of patients experiencing acute LBP without sciatica or systemic symptoms improve within 4 weeks.
- All patients with LBP should receive nonpharmacologic interventions, nonsteroidal antiinflammatory drugs (NSAIDs), or acetaminophen as indicated, and other interventions and medications as necessary.
- Follow up in 1-3 weeks and as needed. Reevaluate sooner in the event of worsening neurologic symptoms, bowel or bladder dysfunction, systemic symptoms, or failure to improve with initial management.



BACKGROUND

Epidemiology

- Back pain is common: In a 2002 U.S. National Health Interview Survey of 30,000 respondents, 26% of adults had back pain lasting at least a whole day during a 3-month period.
- Back pain is the second most common reason patients in the United States visit their physicians.
- Back pain can lead to chronic disability. Among patients who have had treatment for back pain, 72% have discontinued exercise and sports because of the

Veterans with HIV*

Lumbago, sciatica, or
backache: 25%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to these conditions

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

pain, 60% have experienced limitations on their activities of daily living, and 46% have reported refraining from sexual activity.

- The physiologic cause of LBP cannot be definitively established in 85% of patients. Among such patients, LBP has been attributed to disc degeneration or muscular and ligamentous sources.
- Of patients who have LBP:
 - 70% have lumbar strains or sprains
 - 10% have age-related degenerative processes of discs and facets
 - 4% have herniated discs
 - 3% have spinal stenosis
 - 4% have osteoporotic compression fractures
 - <1% have urgent situations (red flags)

Definitions

Acute: duration <6 weeks

Chronic: duration >6 weeks

LBP: pain does not radiate past the knee

Sciatica: pain radiates past the knee along the sciatic nerve (posterior/lateral lower extremity)

Radiculopathy: impairment of a nerve root, usually causing radiating pain, numbness, or muscle weakness that corresponds to a specific nerve root

Cauda equina syndrome: urinary retention with overflow incontinence, saddle anesthesia, bilateral sciatica, and leg weakness; usually caused by a tumor or massive midline disc herniation; represents a medical emergency

Spondylolisthesis: slipping forward of one vertebral body over another; patients may have back or leg pain; rarely, bladder or bowel symptoms or radiculopathic pain

Spondylosis: arthritis of the spine, with radiographically apparent disc space narrowing and arthritic changes at the facet joint; localized pain or spasms with spinal flexion

Spinal stenosis: local, segmental, or generalized narrowing of the central spinal canal by bone or soft tissue; transient tingling in the legs, pain with walking, improvement with rest and with leaning forward; pseudoclaudication with normal distal arterial pulses



EVALUATION

Check for red flags:

- Major trauma
- Age >50
- Duration >6 weeks
- Diabetes
- History of cancer
- Major muscle weakness

- Failure to improve with therapy
- Unexplained fever
- Unexplained weight loss
- IDU
- CD4 count <200 cells/μL
- Transplant recipient
- Steroid use
- Bladder or bowel dysfunction
- Unrelenting night pain
- Saddle anesthesia
- Decreased sphincter tone
- Focal neurologic deficit
- Abdominal pulsating mass

In general, evaluate whether the patient has evidence of systemic disease, neurologic compromise, or social or psychological distress that may contribute to pain. Identify modifiable risk factors that may affect the risk of LBP recurrence.

Risk factors	<ul style="list-style-type: none"> • Obesity • Older age • Female sex • Physically or psychologically strenuous work • Sedentary work • Job dissatisfaction • Smoking • Low educational attainment • Psychological factors: somatization, anxiety, depression, substance abuse
History	<ul style="list-style-type: none"> • Mechanism of onset, trauma • Location of symptoms, involvement of legs • Duration (acute <6 weeks, chronic >6 weeks) • Character of pain: mechanical, radicular, claudicatory • Limitations on activity • Neurologic symptoms: distribution, bowel or bladder symptoms, weakness, saddle anesthesia • Constitutional symptoms: fever, weight loss • Night pain • Previous spinal surgeries • IDU • Smoking history • Cancer • Corticosteroid use • Work-related injuries or repetitive stress • Psychological stressors, symptoms of anxiety, depression, substance abuse

Example history-taking questions	<ul style="list-style-type: none"> • What are your symptoms? (ask about red-flag symptoms) • How do these symptoms limit you? How long can you sit, stand, etc? • When did the current limitations begin? • What do you hope we can accomplish during this visit?
Physical examination	<ul style="list-style-type: none"> • Observation of gait, position changes, and stance • Inspection of back and posture (scoliosis = lateral asymmetry; kyphosis = posterior convexity; lordosis = lumbar concavity) • Range of motion, including lumbar flexion (limited in ankylosing spondylosis) • Palpation of the spine (vertebral tenderness suggests fracture or infection) • Straight leg raising (SLR): sensitive but not specific for radiculopathy; pain with lifting leg of affected side (from lying position) from 10° to 60° • Cross-SLR: specific but not sensitive for radiculopathy; pain with lifting leg opposite affected side (from lying position) from 10° to 60° • Neurologic assessment of L5-S1 nerve roots: L5 injury corresponds to numbness in the medial foot and web space between first and second toes; S1 injury corresponds to reduced ipsilateral ankle reflex, reduced sensation along the posterior calf and lateral foot; reduced ability to walk on tiptoes for 3 steps • Evaluation for malignancy and infection if history and examination suggest a systemic disease (sites of interest include lymph nodes, prostate, breasts) • Inconsistent, incongruous, or contradictory physical signs in patients with chronic pain may point to psychological distress
Imaging	<p>Imaging is not necessary in the first 4-6 weeks of symptoms unless the patient has red flag symptoms or has any of the following:</p> <ul style="list-style-type: none"> • Progressive neurological findings • Constitutional symptoms • History of traumatic onset • History of malignancy • Age ≤ 18 or ≥ 50 years • Infection risk: IDU, severe immunosuppression, prolonged corticosteroid use, skin or urinary tract infection, indwelling urinary catheter • Osteoporosis <p>If there is no clinical improvement after 6 weeks, obtain plain antero-posterior and lateral X rays of the lumbosacral spine to evaluate for tumor, infection, instability, spondyloarthropathy, or spondylolisthesis.</p>

	<p>Computed tomography (CT) or magnetic resonance imaging (MRI) is indicated if there are progressive neurologic deficits or a high suspicion of cancer or infection, and should be considered for patients with >12 weeks of persistent LBP.</p>
<p>Differential diagnosis: Red flags for specific conditions and suggested initial workup</p>	<ul style="list-style-type: none"> • Cancer: history of cancer, unexplained weight loss, age >50, pain >6 weeks, night pain <i>Evaluation:</i> check CT or MRI of spine, check complete blood count (CBC) and erythrocyte sedimentation rate (ESR), and perform directed evaluation for suspected malignancy (eg, prostate-specific antigen and prostate examination, mammogram, serum protein electrophoresis, urine protein electrophoresis) • Infection/osteomyelitis or Pott disease: fever, IDU (consider sacroiliac or vertebral osteomyelitis), tuberculosis exposure risk, recent urinary tract infection, skin infection, pneumonia, corticosteroid use, transplant, diabetes, rest pain <i>Evaluation:</i> MRI of the spine, CBC, ESR, urinalysis, blood and urine cultures • Cauda equina syndrome: urinary retention or incontinence, saddle anesthesia, decreased anal sphincter tone, bilateral lower extremity weakness/numbness <i>Evaluation:</i> immediate surgical consultation • Fracture: corticosteroid use, age >70, osteoporosis, recent trauma <i>Evaluation:</i> plain X rays or CT, orthopedic consultation • Acute abdominal aneurysm: pulsating abdominal mass, vascular disease, resting or night pain, age >60 <i>Evaluation:</i> ultrasound or CT to evaluate aorta, surgical consultation • Significant herniated nucleus pulposus: major muscle weakness <i>Evaluation:</i> MRI of the spine and surgical consultation

Rx MANAGEMENT

- Up to 90% of patients with LBP without sciatica or systemic symptoms improve within 4 weeks of starting treatment.
- Recurrences are common, occurring in up to 40% of patients within 6 months after initial resolution.
- Goals of management are to reduce pain and disability using conservative measures and to identify patients with more serious conditions that need further care.
- All patients with LBP should get nonpharmacologic interventions and move up the analgesic and intervention “ladder”:
 - acetaminophen or NSAIDs +/- adjuvants →
 - weak opioids +/- adjuvants →
 - strong opioids +/- adjuvants

- Acetaminophen and NSAIDs are first-line medications for most LBP.
- For chronic and subacute back pain, studies suggest that antiepileptic drugs, muscle relaxants, benzodiazepines, and opiates show insufficient evidence of effectiveness to be recommended as treatment.

Intervention	Comments
Nonpharmacologic	
<ul style="list-style-type: none"> • Patient education • Activity modification • Exercise • Physical therapy • Self-application of heat or cold to back • Manipulation 	<ul style="list-style-type: none"> • Patient education topics include expectations for rapid recovery, avoiding worry, coping with having a sore back, methods of symptom control, activity modifications, recognition of certain red-flag symptoms, and follow-up. • Limited bed rest: <48 hours. Patients who go on longer bed rest have less improvement in pain and function than those who remain ambulatory. • Activity modification should be minimal for acute back pain: Modifications might include limiting prolonged unsupported sitting, avoiding heavy lifting, and avoiding bending or twisting the back when lifting. • Maintain or start aerobic conditioning exercises, including swimming, walking, and stationary biking. • Avoid physical therapy for 2 weeks after onset of acute back pain. • Conduct workplace ergonomics evaluation if the back pain is related to work activities. • Manipulation may be helpful in the first month of symptoms for selected patients who do not have radiculopathy or severe or progressive neurologic deficits. Refer to practitioners with specific training in manipulation (eg, osteopathic physicians).
Pharmacologic (for dosages and additional information, see Pain Medications, p. 321)	
Acetaminophen	<ul style="list-style-type: none"> • First-line analgesic because of its safety profile. • Use for patients who cannot tolerate NSAIDs. • Possible adverse effects include hepatotoxicity (especially if taken with alcohol) and nephrotoxicity (with chronic overdose).
NSAIDs (eg, ibuprofen, naproxen)	<ul style="list-style-type: none"> • First-line analgesic; may be combined with acetaminophen. • Avoid use for patients with peptic ulcer disease or cirrhosis.

<p>Tricyclic antidepressants (TCAs) (eg, amitriptyline, nortriptyline)</p>	<ul style="list-style-type: none"> • Consider for neuropathic pain; also consider as an adjunct for any type of LBP unresponsive to acetaminophen and NSAIDs. • Anticholinergic and other adverse effects, especially at higher doses.
<p>Muscle relaxants (nonbenzodiazepines)</p> <ul style="list-style-type: none"> • Cyclobenzaprine • Baclofen 	<ul style="list-style-type: none"> • May be useful as adjunctive therapy for acute back pain but not recommended for chronic or subacute back pain.
<p>Epidural steroid injections Medications may include corticosteroids, lidocaine, and opioids</p>	<ul style="list-style-type: none"> • For short-term relief of radicular pain; consider after failure of conservative treatment, as means of avoiding surgery. • Refer to back pain specialist or orthopedist.
<p>Opiate analgesics</p> <p>Options include:</p> <ul style="list-style-type: none"> • Tramadol (not a typical opiate; exact mechanism of action is unknown; acts in part as a central opioid agonist) <p>Weak opioids</p> <ul style="list-style-type: none"> • Codeine • Hydrocodone + acetaminophen • Oxycodone + acetaminophen <p>Strong opioids</p> <ul style="list-style-type: none"> • Morphine • Oxycodone • Hydromorphone • Fentanyl transdermal 	<ul style="list-style-type: none"> • Consider opioids for patients who have severe pain refractory to the interventions listed above (nonpharmacologic and pharmacologic) or cannot receive those therapies. • For very short-term use in severe acute exacerbations, and for severely disabling chronic back pain; start with weak opioids; assess safety, efficacy, and usage; titrate up and move to strong opioids as needed. • Use the lowest effective dosage. • If needed for acute flares, limit use to a designated short period of time. • If needed for chronic pain, try to use a sustained-release opioid with scheduled dosing around the clock, with shorter-acting opioids for breakthrough pain as needed. • Risk of dependence, overdose: monitor closely. • Adverse effects include oversedation, hypotension, respiratory depression, central nervous system stimulation or somnolence, dizziness, constipation, nausea, and pruritus. • Note that tramadol 37.5 mg + acetaminophen 325 mg has shown pain relief equivalent to codeine 30 mg + acetaminophen 325 mg but with fewer side effects (major side effect: headache). • Chronic opioid therapy should incorporate an opioid use agreement that includes functional goals for outcome, not reduced pain intensity alone.



WHEN TO REFER

Refer immediately to Orthopedic Surgery or Neurosurgery for:

- Cauda equina syndrome
- Spinal cord compression
- Progressive or severe neurologic deficit

Consider referral to Orthopedic Surgery or Neurosurgery for patients with persistent LBP or sciatica caused by:

- Disc herniation
- Spinal stenosis
- Spondylolisthesis

Consider referral to Physiatry for patients who are not improving:

- Chronic back pain <6 weeks
- Chronic sciatica <6 weeks
- Chronic pain syndrome
- Recurrent back pain

Consider referral to Neurology for:

- Chronic sciatica >6 weeks
- Atypical chronic leg pain (negative SLR)
- New or progressive neuromotor deficit

Consider referral to Rheumatology for patients with persistent symptoms to:

- Rule out inflammatory arthropathy
- Rule out fibrositis/fibromyalgia
- Rule out metabolic bone disease (eg, osteoporosis)

Prevention

- Conduct ergonomic evaluation of work areas and implement ergonomic design of job tasks.
- Exercise has shown benefit in reducing the perception of back pain.

Follow-Up

- Follow up in 1-3 weeks with a phone call or visit and as needed. Follow-up is necessary when there is worsening of neurologic symptoms, bowel or bladder dysfunction, presence of systemic symptoms, or failure to improve with initial management.



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Peripheral Neuropathy

KEY POINTS

- HIV-associated peripheral sensory neuropathy (HIV-SN) includes distal sensory polyneuropathy (DSP) and ARV toxic neuropathy.
- Patients typically present with bilateral tingling, numbness, or neuropathic pain starting in their toes and spreading proximally; the pain frequently is described as burning or aching and is worse on the soles.
- **For a very simple and brief evaluation:** Ask about distal numbness and check ankle reflexes. Screening for numbness and delayed or absent ankle reflexes has the highest sensitivity and specificity among the clinical evaluation tools.
- Treat suspected ARV toxic neuropathy by withdrawing the offending drug, if possible.
- Treat the pain of HIV-SN with analgesics, anticonvulsants, and topical medication; if severe, treat with long-acting narcotics.



BACKGROUND

- HIV-SN is a “dying-back” neuropathy, affecting the most distal fibers first, involving myelinated and unmyelinated axons of all sizes. On pathologic examination, this pattern of loss is indistinguishable from other toxic neuropathies.
- Patients typically present with bilateral tingling, numbness, or neuropathic pain that starts in the toes and spreads proximally; the pain frequently is described as burning or aching and is worse on the soles. It also may be described as shocklike or knifelike.
- HIV-SN includes:
 - DSP caused by HIV infection itself
 - ARV toxic neuropathy resulting from exposure to ARVs, particularly d4T, ddI, and ddC (the “dNRTIs” or “d-drugs”). The onset can occur as early as 9 weeks after starting the offending agent.

Veterans with HIV*

Peripheral neuropathy: 19%

*Veterans in the VA HIV Clinical Case Registry in care in 2007 who had an ICD-9 code corresponding to this condition

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

- DSP is thought to be related to chronic immune activation, leading to macrophage overproduction of proinflammatory cytokines and chemokines in the peripheral nervous system.
- ARV toxic neuropathy is thought to be associated with mitochondrial toxicities of the dNRTIs.
- Many other drugs and conditions may cause peripheral neuropathy (PN) or compound the condition.

Epidemiology

- A recent study showed the prevalence of HIV-SN was 42% among patients at an outpatient clinic in Australia; 92% of patients with sensory neuropathy were on ARVs.
- The risk of PN is higher for patients with advanced HIV infection.
 - The annual incidence of DSP among patients with CD4 counts of <200 cells/ μ L is 7%. In two studies from the 1980s, 30% of patients hospitalized with advanced AIDS had DSP in the absence of ART.
 - The prevalence is lower among patients with less-advanced HIV disease.

Prevention

Prevention and early intervention are vitally important in avoiding or reversing symptoms of neuropathy.

- Initiate ART according to usual guidelines to avoid increased risk of HIV-SN resulting from advanced HIV disease.
- Avoid ARVs (particularly d4T and ddI) associated with neurotoxicity.
- If possible, avoid non-ARV medications that may cause PN.
- Avoid treatment regimens that have additive neurotoxicity (eg, ddI for a patient who is receiving isoniazid).
- With patients who develop ARV toxic neuropathy, discontinue the causative ARV if a reasonable substitution can be made.



EVALUATION

DSP and ARV toxic neuropathy are clinically indistinguishable, although the timing of symptom onset may help to differentiate the etiology.

Risk factors

- Increasing age
- Exposure to d4T, ddI, or ddC
- Advanced untreated HIV (low CD4 count nadir, high HIV RNA)
- Alcohol use
- Nutritional deficiencies (eg, vitamin B12)

- Other neurotoxic medications, eg:

Dapsone	Thalidomide
Hydroxyurea	Isoniazid
Metronidazole	Linezolid
Vincristine	Ribavirin
- Diabetes, impaired glucose tolerance



SCREENING

Quick Screen

Ask about distal numbness and check ankle reflexes.

- Use the **ACTG Brief Peripheral Neuropathy Screen (BPNS)** (see p. 301). This is a validated screening tool for scaling the degree of PN. It includes subjective and objective information, and takes <10 minutes to administer.
- HIV-SN can be diagnosed when a patient exhibits **≥1 symptom specified in the BPNS and 1 of the following: diminished ankle reflexes, reduced vibration sense at the first toe.**
- Serial assessment of BPNS scores allows tracking of symptom severity and response to treatment.

History

- Ask about numbness, pain, location/distribution of symptoms, character or quality of pain, other neurologic symptoms, duration, exposure to dNRTIs and other neurotoxic drugs.
- **Numbness** has a sensitivity of 86% and a specificity of 81% for the clinical diagnosis of HIV-SN. Asking about numbness has greater sensitivity for the diagnosis of HIV-SN than asking about pain.

Physical examination

Perform a thorough neurologic examination.

Characteristics of HIV-SN:

- Reduced or absent **ankle Achilles tendon reflexes**; this has a sensitivity of 84% and a specificity of 98% for HIV-SN.
- **Distal sensory loss** (temporal progression: loss of vibratory sense occurs first, followed by loss of temperature sensation, followed by pain).
- Findings usually are bilateral and symmetric.

Differential diagnosis

- Alcohol toxicity
- Non-ARV medication toxicity
- Nutritional deficiency (eg, vitamin B12)
- Diabetes, impaired glucose tolerance
- Hypothyroidism
- Other HIV-associated neuropathies, including:

	<p>Inflammatory demyelinating polyradiculoneuropathy</p> <p>Cauda equina syndrome</p> <p>Neuromuscular weakness syndrome</p> <p>Diffuse infiltrative lymphocytosis syndrome (DILS)</p> <p>Autonomic neuropathy</p> <p>Mononeuritis</p> <p>Polyradiculitis</p> <ul style="list-style-type: none"> • Cryoglobulinemia (especially in hepatitis C virus-infected patients) • Syphilis • Herpes zoster radiculitis • Plantar fasciitis, musculoskeletal conditions, tarsal or carpal tunnel compression <p><i>Note: Patients with foot pain or numbness may have ≥1 source of symptoms.</i></p>
<p>Findings that suggest a different diagnosis</p>	<ul style="list-style-type: none"> • Prominent weakness (consider inflammatory demyelinating polyneuropathies, HIV-associated neuromuscular weakness syndrome, especially with d4T use – check lactic acid levels) • Neuropathy in the hands more so than in the feet (consider carpal tunnel syndrome) • Proximal features (consider inflammatory demyelinating polyneuropathies) • Marked asymmetry (consider mononeuritis multiplex, especially with foot drop) • Sphincter dysfunction (consider progressive polyradiculoneuropathy, especially caused by cytomegalovirus) • Cranial nerve involvement (consider progressive polyradiculoneuropathy) • Tenderness or deformity in plantar foot or joints (consider plantar fasciitis, gout)
<p>Laboratory evaluation</p>	<p>Screen for:</p> <ul style="list-style-type: none"> • Diabetes (fasting glucose; consider HbA1c) • Vitamin B12 deficiency (check B12 level; if low, check methylmalonic acid levels and intrinsic factor antibody titers) • Hypothyroidism (TSH, T4) • Syphilis (RPR or VDRL) • Renal failure (serum creatinine, blood urea nitrogen; consider serum protein electrophoresis) • Hepatitis C (HCV IgG/PCR)
<p>Further evaluation</p>	<ul style="list-style-type: none"> • Electromyography and nerve conduction velocity studies are not needed unless the symptoms are complex or there are atypical findings.

- Sensory threshold testing is used primarily in research settings.
- Punch biopsy for pathologic evaluation of epidermal nerve density may be useful in differentiating HIV-SN and other causes.
- Consider referral of patients to neurologist or podiatrist if the diagnosis is unclear.

Rx MANAGEMENT

- Goals: relieve pain, halt progression of symptoms.
- Patients taking neurotoxic medications: discontinue these if possible.
- Patients not on ART: consider initiation, if low CD4 cell count or high HIV viral load.
- Pharmacologic treatment often is multimodal, involving several types of medications.
 - Consider starting with an anticonvulsant such as gabapentin or pregabalin and titrating to effect.
 - Add or use antidepressants, especially for patients with comorbid depression.
 - Add or use topical agents for patients who cannot tolerate systemic pain medications.
 - For breakthrough pain, add topical agents or NSAIDs.
 - For severe or recalcitrant symptoms, consider adding a long-acting opioid.



WHEN TO REFER

Refer to a pain specialist or neurologist if symptoms are not controlled with initial trials of medication.

Intervention	Comments
Pharmacologic	
Discontinuation of offending drug (eg, switching from dNRTIs, avoiding combinations with additive neurotoxicity)	<ul style="list-style-type: none"> • Differentiate DSP and ARV toxic neuropathy by timing of symptom onset. • Prompt discontinuation of a neurotoxic medication may prevent progression of symptoms, and may allow reversal of symptoms. • Before discontinuing an offending drug, carefully weigh risks and potential benefits. • Consider dosage reduction of d4T, if discontinuation is not possible. • With ARV toxic neuropathy caused by a dNRTI, symptoms often improve within 3 months (though they may be permanent).

<p>Initiation of ART</p> <ul style="list-style-type: none"> • Avoid dNRTIs 	<ul style="list-style-type: none"> • Initiation of ART can improve non-ARV-associated DSP for patients with advanced HIV who have uncontrolled viremia and low CD4 counts.
<p>Medications (for dosages and additional information, see Pain Medications, p. 321)</p>	
<p>Mild analgesics</p> <ul style="list-style-type: none"> • Acetaminophen • NSAIDs 	<ul style="list-style-type: none"> • Use as first-line therapy for mild symptoms. • Can use in combination with tricyclic antidepressants (TCAs), anticonvulsants, and topical adjuncts. • Avoid use or limit dosages for patients with underlying liver or renal disease.
<p>Anticonvulsants</p> <ul style="list-style-type: none"> • Gabapentin • Pregabalin • Lamotrigine 	<ul style="list-style-type: none"> • Gabapentin: considered first-line for its tolerability. • Pregabalin: sometimes better tolerated than gabapentin. Little evidence of efficacy for HIV-SN. • Lamotrigine: has shown the greatest efficacy in clinical trials for HIV-SN. • To discontinue these agents, taper slowly over course of ≥ 7 days.
<p>Antidepressants: TCAs and others</p> <ul style="list-style-type: none"> • Amitriptyline • Nortriptyline • Other potential agents include venlafaxine and duloxetine; these have shown limited efficacy or are inadequately studied in people with HIV infection 	<div data-bbox="291 857 966 922" style="background-color: #e6f2ff; padding: 5px;"> <p>! POTENTIAL ARV INTERACTIONS</p> </div> <ul style="list-style-type: none"> • Consider for patients with comorbid depression. • Small studies have shown limited or negative results with antidepressants. • Monitor serum TCA levels to avoid cardiotoxicity at higher dosage levels. • Drug interactions: RTV and other PIs may increase the level of TCAs; start at low dosage, increase slowly.
<p>Topical anesthetics</p> <ul style="list-style-type: none"> • Capsaicin patch or cream • Lidocaine patch 	<ul style="list-style-type: none"> • A single capsaicin patch application can provide some degree of pain relief for up to 12 weeks. • Topical lidocaine has not shown significant benefit over placebo, and is expensive. Consider brief trial for patients with incomplete pain relief on other therapies.

<p>Opiate analgesics</p> <p>Long-acting narcotics preferred:</p> <ul style="list-style-type: none"> • Transdermal fentanyl • Long-acting morphine • Methadone • Long-acting oxycodone 	<ul style="list-style-type: none"> • For moderate to severe HIV-SN with an inadequate response to the therapies listed above. • Titrate carefully. (For more information, see Pain Medications, p. 321.) • Methadone: acts on NMDA receptors; may give adjunctive benefit. Caution: start at low dosage and titrate slowly because of its long half-life; consult with pharmacist. • Transdermal fentanyl is appropriate only for patients already on stable dosage of other opiates: start at equianalgesic (or lower) dosage.
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Brief Peripheral Neuropathy Screening Tool

NIAID Adult AIDS Clinical Trials Group

I. Elicit Subjective Symptoms

Ask the subject to rate the severity of each symptom listed in Question 1 on a scale of 01 (mild) to 10 (most severe) for right and left feet and legs. Enter the score for each symptom in the columns marked R (right lower limb) and L (left lower limb). If a symptom has been present in the past, but not since the last visit, enter “00 – Currently Absent.” If the symptom has never been present, enter “11 – Always Been Normal.”

Always Been Normal	Currently Absent	Mild	←—————→								Severe
11	00	01	02	03	04	05	06	07	08	09	10

Symptoms

- Pain, aching, or burning in feet, legs
- “Pins and needles” in feet, legs
- Numbness (lack of feeling) in feet, legs

R	L

2. Grade Subjective Symptoms

Use the single highest severity score from Question 1 above to obtain a subjective sensory neuropathy score. If all severity scores are “00” or “11,” the subjective sensory neuropathy score will equal “0.”

Subjective Sensory Neuropathy Score

(based on highest severity rating)

01 – 03 = grade of 1

04 – 06 = grade of 2

07 – 10 = grade of 3

11 or 00 = grade of 0

R	L

3. Evaluate Perception of Vibration

Compress the ends of a 128-Hz tuning fork just hard enough that the sides touch. Place the vibrating tuning fork on a bony prominence on the subject's wrist or hand to be sure that he/she can recognize the vibration or "buzzing" quality of the tuning fork. Again, compress the ends of the tuning fork just hard enough that the sides touch. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of one great toe and begin counting the seconds. Instruct the subject to tell you when the "buzzing" stops. Repeat for the other great toe.

Vibration perception

- Great toe DIP joint perception of vibration in seconds
- Vibration perception score (see below)

0 = felt >10 seconds (normal)

1 = felt 6-10 seconds (mild loss)

2 = felt <5 seconds (moderate loss)

3 = not felt (severe loss)

8 = unable to or did not assess

R	L

4. Evaluate Deep Tendon Reflexes

With the subject seated, the examiner uses one hand to press upward on the ball of the foot, dorsiflexing the subject's ankle to 90 degrees. Using a reflex hammer, the examiner then strikes the Achilles tendon. The tendon reflex is felt by the examiner's hand as a plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon is struck. Use reinforcement by having the subject clench his/her fist before classifying the reflex as absent.

Ankle Reflexes Score

0 = absent

1 = hypoactive

2 = normal deep tendon reflexes

3 = hyperactive

4 = clonus

8 = unable to or did not assess

R	L



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Gonzalez-Duarte A, Robinson-Papp J, Simpson DM. Diagnosis and management of HIV-associated neuropathy. *Neurol Clin*. 2008 Aug;26(3):821-32.

McArthur JC, Brew BJ, Nath A. Neurological complications of HIV infection. *Lancet Neurol*. 2005 Sep;4(9):543-55.

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Drug Tables

Common Medications: ARV Interactions

For information on potential ARV interactions with the following medications, see the specified chapters:

Acid-lowering medications (see **GERD**, p. 155)

Fluticasone (see **Asthma**, p. 97; **COPD**, p. 107)

Hormonal contraceptives (see **Women’s Health**, p. 249)

Lipid-lowering medications (see **Lipid-Lowering Medications**, p. 315)

PDE5 (see **Urology**, p. 227)

Psychoactive medications: antidepressants, sedatives, antipsychotics (see **Psychoactive Medications**, p. 327)

St. John’s wort (see **Food and Supplements**, p. 313)

Medication	ARV Interactions	Comments
Antiepileptic Medications: Carbamazepine, phenytoin, and phenobarbital may ↓ PI and NNRTI levels substantially.		
Carbamazepine CYP450 inducer	PIs: may ↓ PI levels <ul style="list-style-type: none"> • ATV: ↑ carbamazepine levels • DRV: ↑ carbamazepine levels; ↓ DRV levels • RTV: ↑ carbamazepine levels • TPV: ↑ carbamazepine levels; ↓ TPV levels Other PIs: may also ↑ carbamazepine levels	Avoid concomitant use if possible; use alternative antiepileptics. Two-way interactions also affect PI and NNRTI levels.
	NNRTIs: may ↓ NNRTI levels <ul style="list-style-type: none"> • EFV: ↓ carbamazepine AUC 27%; ↓ EFV levels • ETR: expect ↓ ETR levels 	Avoid use with EFV, if possible; use alternative antiepileptics. Do not use concurrently with ETR.
	MVC: ↓ MVC levels	If used concurrently, give MVC 600 mg BID.
Phenobarbital CYP450 inducer	PIs: may ↓ PI levels <ul style="list-style-type: none"> • DRV: ↓ phenobarbital levels • RTV: ↓ phenobarbital levels • TPV: ↓ phenobarbital levels and ↓ TPV levels 	Avoid concomitant use if possible; use alternative antiepileptics. Two-way interactions also affect PI and NNRTI levels.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

	<p>NNRTIs: may ↓ NNRTI levels</p> <ul style="list-style-type: none"> • EFV and NVP: ↓ phenobarbital levels • ETR: ↓ ETR levels 	<p>Avoid with EFV and NVP, if possible; use alternative antiepileptics.</p> <p>Do not use concurrently with ETR.</p>
	<p>MVC: ↓ MVC levels</p>	<p>If used concurrently, give MVC 600 mg BID.</p>
<p>Phenytoin CYP450 inducer</p>	<p>PIs: may ↓ PI levels</p> <ul style="list-style-type: none"> • DRV: ↓ phenytoin levels • FPV: ↓ phenytoin levels • LPV/r: ↓ LPV C_{min} 46%, ↓ RTV C_{min} 47%; ↓ phenytoin C_{min} 34% • NFV: ↓ M8 levels 20-30%, ↓ phenytoin C_{min} 39% • RTV: anticipate ↓ phenytoin levels • TPV: ↓ TPV levels 	<p>Avoid if possible; use alternative antiepileptics.</p> <p>Two-way interactions also affect PI and NNRTI levels.</p>
	<p>NNRTIs: may ↓ NNRTI levels</p> <ul style="list-style-type: none"> • EFV: ↓ phenytoin levels, ↓ EFV levels • ETR: ↓ ETR levels 	<p>Avoid use with EFV if possible.</p> <p>Do not use concurrently with ETR.</p>
	<p>MVC: ↓ MVC levels</p>	<p>If used concurrently, give MVC 600 mg BID.</p>
<p>Valproate</p>	<p>PIs</p> <ul style="list-style-type: none"> • LPV/r: ↑ LPV C_{max} 33%, ↑ AUC 75%, may ↓ valproate levels • RTV and TPV: ↓ valproate levels 	<p>Titrate to effect.</p>
	<p>NNRTIs: no significant changes in NNRTI or valproate levels</p>	
<p>Lamotrigine</p>	<ul style="list-style-type: none"> • LPV/r: ↓ lamotrigine levels 50% • RTV: ↓ lamotrigine levels 	<p>Titrate to effect.</p>
<p>Antifungal Medications</p>		
<p>Fluconazole Inhibitor of CYP 2C9</p>	<p>PIs</p> <ul style="list-style-type: none"> • ATV/r: no significant change • TPV: ↑ TPV levels 	<p>TPV: Avoid fluconazole >200 mg daily.</p>

	NNRTIs <ul style="list-style-type: none"> NVP: 100% ↑ in NVP levels EFV: no significant change ETR: potential ↑ in ETR levels 	Avoid use with NVP. EFV, ETR: dosage adjustment not required.
Itraconazole Inhibitor and substrate of CYP 3A4	PIs: ↑ PI levels and ↑ itraconazole levels <ul style="list-style-type: none"> LPV/r: ↑ itraconazole levels 	Avoid itraconazole dosages >200 mg daily with patients who take PIs.
	NNRTIs <ul style="list-style-type: none"> EFV: ↓ itraconazole levels ETR: ↓ itraconazole levels and ↑ ETR levels NVP: ↓ itraconazole levels and ↑ NVP levels 	If used concomitantly, consider monitoring itraconazole levels and adjust itraconazole dosage as necessary. Avoid with ETR.
	MVC: ↑ MVC levels	MVC 150 mg BID
Ketoconazole: Inhibitor and substrate of CYP 3A4	PIs: may ↑ PI levels and ↑ itraconazole levels <ul style="list-style-type: none"> ATV/r, FPV/r: ↑ ketoconazole levels DRV/r: ↑ ketoconazole levels, ↑ DRV levels LPV/r: ↑ ketoconazole levels; may ↑ or ↓ LPV/r levels 	Avoid ketoconazole dosages >200 mg daily with patients who take RTV-boosted PIs.
	NNRTIs <ul style="list-style-type: none"> EFV: no data NVP: ↓ ketoconazole levels; ↑ NVP levels ETR: ↓ ketoconazole levels and ↑ ETR levels 	Not recommended for use with NVP. Dosage adjustment for ETR not established.
	MVC: ↑ MVC levels	MVC 150 mg BID
Posaconazole Inhibitor of CYP 3A4	PIs <ul style="list-style-type: none"> RTV: ↑ RTV levels ATV: ↑ ATV levels 	Monitor laboratory values frequently for signs of toxicity.
	NNRTIs <ul style="list-style-type: none"> EFV: ↓ posaconazole levels ETR: ↑ ETR levels 	Consider alternative antifungal or monitor posaconazole level. Monitor for ETR-related adverse effects.
Terbinafine: Inhibitor of CYP 2D6	PIs: no significant changes	No dosage adjustments necessary.
	NNRTIs: no significant changes	No dosage adjustments necessary.

Voriconazole CYP 3A4, CYP 2C9, and CYP 2C19 inhibitor; CYP 2C19 substrate	PIs: limited data <ul style="list-style-type: none"> • RTV: voriconazole AUC ↓ 39% with RTV 100 mg BID 	Not recommended for use with RTV 100 mg QD or BID unless benefit outweighs risk. If used, consider monitoring voriconazole levels.
	NNRTIs <ul style="list-style-type: none"> • EFV: substantial ↓ voriconazole and ↑ EFV; similar effect expected for NVP • ETR: ↑ voriconazole and ↑ ETR 	Contraindicated at standard dosages; use voriconazole 400 mg BID and EFV 300 mg QD. Dosage adjustments for ETR and voriconazole not established; use alternative antifungal or monitor voriconazole level and ETR adverse effects.
	MVC: anticipated ↑ MVC levels	MVC 150 mg BID
Calcium Channel Blockers (CCBs)		
Amlodipine	<ul style="list-style-type: none"> • FPV, RTV, and SQV: ↑ amlodipine levels • IDV: ↑ amlodipine C_{max} and AUC 89% 	Incompletely studied. PIs may inhibit metabolism of CCBs, increasing risk of adverse effects including hypotension, conduction block, and bradycardia.
Diltiazem	<ul style="list-style-type: none"> • ATV: ↑ diltiazem C_{max} 200% • IDV: ↑ diltiazem C_{max} 25% • SQV/r: ↑ diltiazem levels • EFV: ↓ diltiazem AUC 70% • NVP: ↓ diltiazem levels 	NNRTIs may induce metabolism of CCBs, reducing their effect. Avoid use in patients with CHF. Avoid immediate-release forms.
Methadone		
	PIs <ul style="list-style-type: none"> • ATV: ↓ total methadone AUC 6%; ↑ R-methadone AUC 3%, C_{min} 11% • DRV/r: ↓ methadone AUC 16% • FPV: ↓ methadone AUC 18% • LPV/r: ↓ methadone AUC 53% • NFV: ↓ methadone AUC 47% • SQV/r: ↓ methadone AUC • TPV/r: ↓ methadone AUC 48% 	Most PIs ↓ methadone levels, particularly LPV/r, NFV, and TPV. Of NNRTIs, EFV and NVP ↓ methadone, whereas ETR is anticipated to have no effect. DLV ↑ methadone levels. Monitor for methadone efficacy, and signs and

		symptoms of opiate withdrawal. Titrate dosage cautiously as needed.
	NNRTIs <ul style="list-style-type: none"> DLV: ↑ methadone AUC EFV: ↓ methadone AUC 60% ETR: no change in methadone level anticipated NVP: ↓ methadone AUC 46% 	<p>With DLV, monitor for methadone toxicity; may need to decrease methadone dosage.</p> <p>With EFV, ETR, and NVP, monitor for methadone efficacy and signs and symptoms of opiate withdrawal. Titrate methadone dosage cautiously as needed.</p>
Warfarin		
	PIs <ul style="list-style-type: none"> FPV, IDV, SQV, ATV: ↑ warfarin levels LPV/r: may ↑ or ↓ warfarin levels RTV: may ↓ warfarin levels DRV: ↓ warfarin levels TPV: no change in warfarin levels 	<p>Start at low dosage; monitor INR closely. Adjust warfarin dosage as indicated.</p> <p>Monitor INR closely, may need increased warfarin dosage.</p>
	NNRTIs <ul style="list-style-type: none"> EFV: warfarin levels may ↑ or ↓ NVP: ↓ warfarin levels (anticipated) ETR: ↑ warfarin levels (anticipated) 	<p>Monitor INR closely, adjust dosage as indicated.</p>



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Also see product labeling for the individual ARVs.

Food and Supplements: ARV Interactions

ARVs: Food Requirements

ARV Class	No Food Restrictions	Take with Food	Take on Empty Stomach
NRTI	3TC ABC d4T FTC TDF ZDV		ddl: gastric acid impairs absorption; take 30 minutes before or 2 hours after a meal (if coadministered with TDF, may be taken with food)
NNRTI	DLV NVP	ETR: take after a meal	EFV: fat increases absorption and may increase the risk of EFV adverse effects
PI	FPV LPV/r (tablets) TPV	ATV DRV NFV RTV SQV	IDV: heavy meals interfere with absorption; if unboosted, IDV should be taken 1 hour before or 2 hours after a meal; may be taken with a light, nonfatty, snack; if boosted with RTV, IDV may be taken with or without food
Integrase Inhibitor	RAL		
Entry Inhibitor	ENF MVC		

ARV Interactions with Specific Foods, Nutritionals, Herbs

Calcium (other divalent cations): May interfere with activity of integrase. Separate dosing by 2 hours.

Garlic: Capsules ↓ SQV (unboosted) levels. Avoid.

Grapefruit juice: ↑ SQV levels. Separate dosing by 2 hours.
↓ IDV levels. Monitor virologic response.

St. John's wort: ↓ levels of all NNRTIs and PIs. Avoid with PIs and NNRTIs.
↓ levels of MVC; increase MVC dosage to 600 mg BID.

Vitamin E: ↑ risk of bleeding associated with TPV. Avoid.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

Lipid-Lowering Medications: ARV Interactions

PIs and NNRTIs can affect hepatic metabolism of HMG-coenzyme A reductase inhibitors (statins). ARVs do not generally affect the metabolism of other classes of lipid-lowering agents.

PIs	NNRTIs
<p>Most PIs inhibit the metabolism of most statins and can significantly increase serum statin levels, thus increasing the risk of toxicity, including myopathy and rhabdomyolysis.</p>	<p>NNRTI effects vary according to specific NNRTI.</p>
<p>The degree to which statin metabolism is affected by PIs varies according to the statin as well as the specific PI.</p>	<p>EFV generally induces statin metabolism, resulting in lower serum statin levels.</p>
<p>In general, the potential for inhibition of statin metabolism is as follows: simvastatin and lovastatin > atorvastatin >> fluvastatin, pravastatin, rosuvastatin.</p>	<p>NVP has not been studied well in combination with statins, but its interactions with statins would be expected to be similar to those of EFV.</p>
<p>Fluvastatin and rosuvastatin have few recognized interactions with PIs.</p>	<p>ETR has not been studied thoroughly in combination with statins. Its interactions are expected to depend on the specific statin.</p>
	<p>DLV inhibits hepatic cytochrome P450 metabolism. Thus, DLV increases statin levels and the risk of statin-related adverse effects.</p>

Medical providers should consult with a clinical pharmacist or review published information on drug interactions before prescribing statins for patients taking PIs or NNRTIs, as dosage adjustments are frequently required and some combinations are contraindicated.

Other classes of ARVs (NRTIs, fusion inhibitors, chemokine coreceptor antagonists, and integrase inhibitors) do not have recognized interactions with statins. Other types of lipid-lowering medications are not metabolized by hepatic cytochrome P450 and are not affected by ARVs.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

Lipid-Lowering Medication	Considerations
Statins	
<ul style="list-style-type: none"> • Atorvastatin 	<ul style="list-style-type: none"> • Hepatic metabolism including CYP 3A4 metabolism. • PIs: significant \uparrow in atorvastatin levels with most PIs (C_{\max} \uparrow 100-300%). • Start with lowest dosage (10 mg). Monitor antilipid activity and titrate the statin dosage cautiously. • TPV/r: atorvastatin C_{\max} \uparrow 760%. Consider alternative statin. If prescribed, use lowest possible dosage, monitor carefully. • EFV: \downarrow in atorvastatin levels (\downarrow AUC 58%); may need \uparrow dosage. • ETR: \downarrow in atorvastatin levels (\downarrow AUC 37%); may need \uparrow dosage.
<ul style="list-style-type: none"> • Fluvastatin 	<ul style="list-style-type: none"> • Metabolized by CYP 2C9 (75%), CYP 3A4 (20%). • Not well studied; no known significant interactions with most PIs; theoretic risk of \downarrow NFV levels. • ETR, DLV may \uparrow fluvastatin.
<ul style="list-style-type: none"> • Lovastatin 	<ul style="list-style-type: none"> • Extensively metabolized by CYP 3A4. • PIs: substantial \uparrow in statin levels, high risk of adverse effects. • Do not use in patients taking PIs or DLV.
<ul style="list-style-type: none"> • Pravastatin 	<ul style="list-style-type: none"> • Renal excretion and some hepatic metabolism. • PIs: variable effects; moderate \uparrow pravastatin AUC and C_{\max} with most. No dosage adjustment of pravastatin is required. Exceptions: <ul style="list-style-type: none"> • DRV/r: pravastatin AUC \uparrow 80-500%. Consider alternative statin. If prescribed, use lowest possible dosage, monitor carefully. • SQV + RTV: pravastatin AUC \downarrow 35- 50%. May need to \uparrow pravastatin dosage to reach lipid goals. • NFV: pravastatin AUC \downarrow 46%. May need to \uparrow pravastatin dosage to reach lipid goals. • EFV: pravastatin AUC \downarrow 40%. May need to \uparrow pravastatin dosage to reach lipid goals.
<ul style="list-style-type: none"> • Rosuvastatin 	<ul style="list-style-type: none"> • Metabolized by CYP 2C9 and CYP 2C19. Mostly excreted in bile. • No significant interactions expected with most PIs or NNRTIs; studies under way. Exceptions: <ul style="list-style-type: none"> • DRV/r: rosuvastatin expected to \uparrow. Use lowest possible dosage (5 mg/day), monitor carefully. • LPV/r: rosuvastatin C_{\max} \uparrow 466%. Consider alternative statin. If prescribed, use lowest possible dosage (5 mg/day), monitor carefully. • TPV/r: rosuvastatin C_{\max} \uparrow 123%. Use lowest possible dosage (5 mg/day), monitor carefully.

<ul style="list-style-type: none"> • Simvastatin 	<ul style="list-style-type: none"> • Extensively metabolized by CYP 3A4. • PIs: substantial ↑ in simvastatin levels, high risk of adverse effects (eg, simvastatin C_{max} and AUC ↑ 3,000% with SQV + RTV). • Do not use in patients taking PIs or DLV. • EFV: ↓ simvastatin AUC >50%. May need to ↑ simvastatin dosage to reach lipid goals.
<p>Fibrates</p>	<ul style="list-style-type: none"> • No significant interactions with ARVs expected.
<p>Bile Acid Sequestrants</p>	<ul style="list-style-type: none"> • No drug interactions with ARVs, but may interfere with absorption of ARVs. Avoid in patients who take ARVs.
<p>Ezetimibe</p>	<ul style="list-style-type: none"> • Not metabolized by hepatic P450 system; no significant interactions with ARVs.
<p>Niacin</p>	<ul style="list-style-type: none"> • Not metabolized by hepatic P450 system; no significant interactions with ARVs.
<p>N-3 (Omega-3) Fatty Acids</p>	<ul style="list-style-type: none"> • Not metabolized by hepatic P450 system; no significant interactions with ARVs.

Recommendations for Coadministration of PIs and NNRTIs with Statin Medications

Generally safe to begin treatment with usual starting dosage
 Caution; start with low dosage, monitor effects
 Coadministration is contraindicated

	ATV	DRV/r	FPV	IDV	LVP/r	NFV	RTV	SQV	TPV	EFV	ETR
Atorvastatin									Atorvastatin C_{max} ↑ >760%	May need ↑ atorvastatin dosage	May need ↑ atorvastatin dosage
Fluvastatin						Possible ↓ in NFV levels				May need ↑ fluvastatin dosage	May ↑ fluvastatin levels
Lovastatin										May need ↑ lovastatin dosage	May need ↑ lovastatin dosage
Pravastatin		↑ pravastatin AUC up to 500%	May need ↑ pravastatin dosage					SQV + RTV: May need ↑ pravastatin dosage		May need ↑ pravastatin dosage	
Rosuvastatin					↑ rosuvastatin C_{max} 466%					May need ↑ rosuvastatin dosage	
Simvastatin										May need ↑ simvastatin dosage	May need ↑ simvastatin dosage

Note: NVP in combination with statins has not been well studied; its interactions would be expected to be similar to those of EFV. DLV's interactions would be expected to be similar to those of PIs.



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Pain Medications: Dosage and Indications

(please refer to **Osteoarthritis, Low Back Pain, Peripheral Neuropathy**)

Medication	Standard Dosage	Comments
Acetaminophen	<p>1 g Q6H PRN or 650 mg Q4H PRN</p> <p>Maximum dosage: 4 g per 24 hours or 2 g per 24 hours in patients with comorbid liver disease</p>	<ul style="list-style-type: none"> • First-line analgesia in noninflammatory mild OA, LBP, mild PN because of safety profile • Possible adverse effects: hepatotoxicity (especially if taken with alcohol), nephrotoxicity (with chronic overdose): monitor liver and renal function when using maximal dosages • Use caution and consider reducing total dosage for patients with comorbid liver disease or excessive alcohol intake
NSAIDs	<p>Ibuprofen</p> <ul style="list-style-type: none"> • 600-800 mg TID PRN for pain • Take with food • Schedule around the clock for inflammatory condition (eg, inflammatory OA) or persistent symptoms • Can titrate up as tolerated and based on risks to 800 mg TID • Maximum dosage: 3,200 mg/day in divided doses or 1,800 mg/day for patients at increased risk of adverse effects 	<ul style="list-style-type: none"> • For persistent noninflammatory and inflammatory OA, LBP, mild PN • Possible adverse effects: GI bleeding, abdominal pain, rash and hypersensitivity, renal and hepatic impairment, platelet aggregation abnormalities • Avoid use in patients with peptic ulcer disease or cirrhosis • Avoid ibuprofen in patients with history of aspirin-induced asthma • Increased bleeding risk with concurrent warfarin; if used, monitor closely • Increased risk of renal impairment in patients on diuretics and those with baseline renal dysfunction, congestive heart failure, or cirrhosis

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

	<p>Alternative NSAIDs</p> <p>Naproxen: 250-500 mg BID Sulindac: 150-200 mg BID Celecoxib: 200 mg QD Meloxicam: 7.5 mg QD</p> <p>For chronic pain, use for 2 weeks at initial dosage and reevaluate efficacy; titrate up as needed and if safe; if not effective after a 4-week trial, consider changing NSAID, or adding or changing to another intervention</p>	<ul style="list-style-type: none"> • To minimize risks, use the lowest effective dosage and try to use for short periods of time • COX-2 inhibitors, such as celecoxib, have higher risk of cardiovascular events but fewer GI side effects than nonselective COX inhibitors • Indomethacin is associated with increased joint destruction; avoid using for OA or LBP
<p>Antidepressants: TCAs and others</p>	<p>Amitriptyline</p> <p>Start at 10-25 mg QHS; titrate upward every 3 days by 25 mg to achieve symptom relief, if tolerated; maximum daily dosage is 150 mg (use lower dosages for older patients)</p> <p>Nortriptyline</p> <p>Start at 10-25 mg QHS; titrate upward every 3 days by 25 mg to achieve symptom relief, if tolerated; maximum daily dosage is 150 mg (use lower dosages for older patients)</p>	<ul style="list-style-type: none"> • Consider for patients with comorbid depression • Consider for neuropathic pain; also as an adjunct in any type of LBP unresponsive to acetaminophen and NSAIDs • Small studies of PN have shown limited or negative results with antidepressants • Drug interactions: RTV and other PIs may increase the level of TCAs; start at low dosage, increase slowly • Monitor serum TCA levels to avoid cardiotoxicity at higher dosage levels • Possible TCA adverse effects: anticholinergic (dry mouth, dizziness, constipation, urinary retention, blurred vision, orthostatic hypotension), extrapyramidal symptoms, incoordination; risk of cardiac conduction abnormalities and overdose at higher dosages • For neuropathic pain, other potential agents include venlafaxine and duloxetine; these are inadequately studied in people with HIV infection or show limited efficacy

<p>Anticonvulsants</p>	<ul style="list-style-type: none"> • Gabapentin: start at 300 mg QHS; may increase every few days, as tolerated, to achieve symptom relief; first increase to BID, then TID, then increase by 300 mg per dose to maximum of 1,200 mg TID • Pregabalin: start at 25-50 mg TID; may increase by 25-50 mg per dose every few days as tolerated to achieve symptom relief; maximum dosage: 200 mg TID • Lamotrigine: start at 25 mg every other day; titrate slowly to 200 mg BID over the course of 6-8 weeks 	<ul style="list-style-type: none"> • Consider for PN • Gabapentin: considered first-line for HIV-SN (See Peripheral Neuropathy, p. 295) <ul style="list-style-type: none"> • Common adverse effects include nausea, constipation, fatigue, somnolence, dizziness, truncal ataxia, weight gain • To discontinue, taper over course of ≥ 7 days • Pregabalin: sometimes better tolerated than gabapentin <ul style="list-style-type: none"> • Uncertain efficacy in HIV-related PN • Possible adverse effects include somnolence, constipation, dizziness, ataxia, and weight gain • To discontinue, taper over course of ≥ 7 days • Lamotrigine: has shown the greatest efficacy in clinical trials for HIV-SN <ul style="list-style-type: none"> • Possible adverse effects: rash (including Stevens-Johnson syndrome), cytopenias, dizziness • To discontinue, taper slowly • Drug interactions: LPV/r may decrease lamotrigine levels; may need to increase lamotrigine dosage for therapeutic effect
<p>Muscle relaxants (nonbenzodiazepines)</p>	<p>Cyclobenzaprine (Flexeril)</p> <p>5-10 mg TID; start with 5 mg doses for elderly patients and those with hepatic impairment; maximum dosage is 30 mg per 24 hours</p> <p>Baclofen</p> <p>5-10 mg TID or QID; start with 5 mg doses for elderly patients and those with renal impairment; maximum dosage is 80 mg QD in divided doses</p>	<ul style="list-style-type: none"> • May be useful as adjunctive therapy for acute back pain but not recommended for chronic or subacute back pain • Common adverse effects include drowsiness, dry mouth, and dizziness • Severe adverse effects include arrhythmias, altered mental status, and seizures

Opiate analgesics

Options include:

Tramadol (not a typical opiate; exact mechanism of action is unknown; acts in part as a central opioid agonist)

Start with 50 mg QAM PRN pain, titrate upward by 50 mg/day every 3 days to 50 mg Q6H

Maximum dosage: 400 mg/day, or 300 mg/day if >70 years of age; to discontinue, taper dosage in the same way

In renal insufficiency with CrCl <30, reduce dose frequency to Q12H, and maximum dosage to 200 mg/day

Weak opioids

- **Codeine**

15-30 mg every 4-6 hours; titrate up by 15 mg every 2-3 days to achieve pain relief, if tolerated

Maximum dose: 60 mg; take with food

- **Hydrocodone + acetaminophen**

5 mg/500 mg fixed-dose tablet, 1-2 tablets Q6H PRN pain

Maximum dosage: 12 tablets per 24 hours; 6 tablets for elderly patients and those with liver disease

- **Oxycodone + acetaminophen**

5 mg/325 mg fixed-dose tablet (other dosages available), 1-2 tablets Q6H PRN pain

- Use opioids for patients who have severe pain refractory to other interventions (pharmacologic or nonpharmacologic) or who cannot receive those interventions
- Start with weak opioids, assess safety, efficacy, and usage; titrate up and move to stronger opioids as needed
- Use the lowest effective dosage
- Use opioids cautiously in elderly patients
- If needed for acute flares, try to limit use to a designated short period of time
- If needed for chronic pain, try to use a sustained-release opioid (eg, sustained-release morphine) around the clock, plus shorter-acting opioids (eg, hydrocodone) for breakthrough pain as needed
- Opioid therapy for chronic pain should use a fixed-dose schedule, not PRN dosing
- Methadone may have utility for neuropathic pain owing to its action on NMDA receptors; start at low dosage and titrate slowly because of its long half-life; consult with pharmacist
- Risk of dependence, overdose; monitor closely
- Adverse effects include oversedation, hypotension and respiratory depression, central nervous system stimulation or somnolence, dizziness, constipation, nausea, pruritus
- Codeine and morphine can cause urticarial reactions (hives)
- For patients with renal and hepatic impairment, use low dosages and monitor carefully
- When prescribing opioids, remember to also give treatment for constipation (docusate and senna)

Maximum dosage: 12 tablets per 24 hours; 6 tablets for elderly patients and those with liver disease

Strong opioids

- **Morphine (immediate release)**

10-30 mg every 3-4 hours PRN pain

- **Morphine (sustained release)**

15-30 mg Q12H as scheduled doses; if pain control is inadequate, consider dosing Q8H; may titrate up by 15-30 mg PRN pain

- **Oxycodone (immediate release)**

5-30 mg Q4H PRN pain

- **Oxycodone (sustained release)**

10 mg Q12H as scheduled doses; titrate up by 10-20 mg PRN; monitor carefully

- **Methadone**

Consult with pharmacist

- **Hydromorphone**

2-4 mg Q4H PRN

- **Fentanyl transdermal**

12-100 mcg patch Q72H; a small proportion of patients will need dosing Q48H to maintain a stable blood level

Appropriate only for patients already on stable dosage of other opiates; start at equianalgesic (or lower) dosage; consult with pharmacist; use for chronic severe pain

- Note that tramadol 37.5 mg + acetaminophen 325 mg has shown pain relief equivalent to codeine 30 mg + acetaminophen 325 mg but with fewer adverse effects (major adverse effect: headache)
- Chronic opioid therapy should incorporate an opioid use agreement that includes functional goals for outcome, not reduction of pain intensity alone

<p>Topical anesthetics</p>	<p>Capsaicin</p> <ul style="list-style-type: none"> • 0.025% or 0.075% cream; apply to skin over affected joint(s) or limb TID-QID • High-dose capsaicin topical dermal patch; apply for 30-90 minutes <p>Lidocaine dermal patch 5%</p> <p>Apply 1-3 patches over affected area for 12 hours QD; must be removed for 12 hours</p>	<p>Capsaicin</p> <ul style="list-style-type: none"> • For noninflammatory and inflammatory OA, HIV-SN • For OA or neuropathy, apply to skin over affected joint or area • May take several days to achieve pain relief; initial application usually accompanied by sensation of heat or burning • For neuropathy, a single capsaicin patch application can provide pain relief for up to 12 weeks <p>Lidocaine</p> <ul style="list-style-type: none"> • Topical lidocaine may be used for neuropathic pain, but for HIV-SN it has not shown significant benefit over placebo, and is expensive; consider brief trial in patients with incomplete pain relief on other therapies
<p>Colchicine</p>	<p>0.6 mg BID</p>	<ul style="list-style-type: none"> • For inflammatory OA with refractory symptoms • Avoid use for patients with renal or hepatic disease • Use in conjunction with NSAIDs • Consider for patients with refractory inflammatory OA, as many have calcium pyrophosphate crystals in the synovial fluid

Abbreviations: CrCl = creatinine clearance; GI = gastrointestinal; HIV-SN = HIV sensory neuropathy; LBP = low back pain; OA = osteoarthritis; PN = peripheral neuropathy; TCAs = tricyclic antidepressants

Psychoactive Medications: ARV Interactions

Class of Medication	Interactions	Comments
Antidepressants		
SSRI	<p>Citalopram, escitalopram:</p> <ul style="list-style-type: none"> • RTV causes no change in levels <p>Fluoxetine:</p> <ul style="list-style-type: none"> • RTV: \uparrow RTV AUC 19%, no change in C_{max} <p>Paroxetine:</p> <ul style="list-style-type: none"> • DRV/r: paroxetine AUC and C_{min} \downarrow 38% • FPV/r: paroxetine AUC \downarrow 58% <p>Sertraline:</p> <ul style="list-style-type: none"> • DRV/r: sertraline AUC and C_{min} \downarrow 48% 	<p>Interactions with ARVs are incompletely studied.</p> <p>RTV may \uparrow SSRI levels; this usually is not significant but there are case reports of SSRI toxicity. Start at low dosage, monitor for adverse effects.</p> <p>No dosage adjustment of citalopram or escitalopram required.</p> <p>Start fluoxetine at low dosage, use lowest effective dosage; monitor for adverse effects.</p> <p>Titrate paroxetine to effect.</p> <p>Titrate sertraline to effect.</p>
SNRI	<p>Venlafaxine, duloxetine:</p> <ul style="list-style-type: none"> • No data; PIs may \uparrow SNRI levels 	<p>Start at low dosage, use lowest effective dosage; monitor for adverse effects.</p>
Tricyclic (TCA)	<p>Amitriptyline, nortriptyline, imipramine, desipramine, and others:</p> <ul style="list-style-type: none"> • NFV, RTV known to \uparrow TCA levels; other PIs may \uparrow TCA levels 	<p>Start at low dosage, use lowest effective dosage; monitor for adverse effects.</p>

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<http://www.pbm.va.gov/NationalFormulary.aspx>). Consult VA pharmacists for alternatives.

<p>Other antidepressants</p>	<p>Bupropion:</p> <ul style="list-style-type: none"> • EFV: ↓ bupropion AUC 55% • TPV: ↓ bupropion AUC 46% <p>Mirtazapine:</p> <ul style="list-style-type: none"> • No data; RTV may ↑ mirtazapine levels <p>Nefazodone:</p> <ul style="list-style-type: none"> • RTV may ↑ nefazodone levels • Nefazodone may ↑ MVC levels <p>Trazodone:</p> <ul style="list-style-type: none"> • RTV: ↑ trazodone AUC >200% • DRV, IDV, LPV/r: ↑ trazodone AUC <p>St. John's wort:</p> <ul style="list-style-type: none"> • Substantial ↓ in levels of most PIs, NNRTIs, and MVC 	<p>Monitor for efficacy; may need increased dosage.</p> <p>Start at low dosage, use lowest effective dosage; monitor for adverse effects.</p> <p>Start at low dosage, use lowest effective dosage; monitor for adverse effects.</p> <p>MVC dosage: 150 mg BID</p> <p>Start at low dosage, use lowest effective dosage; monitor for adverse effects.</p> <p>Do not coadminister.</p>
<p>Sedatives, Hypnotics</p>		
<p>Benzodiazepine</p>	<p>Midazolam:</p> <ul style="list-style-type: none"> • SQV/r: ↑ oral midazolam AUC 1,144% • Other PIs: large ↑ in serum midazolam levels expected <p>Triazolam:</p> <ul style="list-style-type: none"> • RTV: ↑ triazolam half-life 1,200%; ↑ AUC 20% • Other PIs: large ↑ in serum triazolam levels expected <p>Alprazolam:</p> <ul style="list-style-type: none"> • RTV: ↑ alprazolam half-life 200% <p>Diazepam:</p> <ul style="list-style-type: none"> • All PIs: ↑ diazepam levels • ETR: ↑ diazepam levels 	<p>Avoid midazolam and triazolam for patients taking PIs. For procedures, may consider single-dose IV midazolam with close monitoring.</p> <p>Avoid for patients taking PIs.</p> <p>Start at low dosage, use lowest effective dosage; monitor for adverse effects.</p> <p>Alternatives:</p> <p>Consider use of the following benzodiazepines: lorazepam, oxazepam, temazepam (these benzodiazepines are metabolized via non-CYP450 pathways; lower potential for interactions). Start at low dosage, use lowest effective dosage; monitor for adverse effects.</p>

Other	Zolpidem: • RTV: ↑ zolpidem AUC 27%	Start at low dosage, use lowest effective dosage; monitor for adverse effects.
Antipsychotics: Few data on interactions between ARVs and antipsychotics		
	Olanzapine: • RTV: ↓ olanzapine AUC 53%, half-life ↓ 50%	Start at low dosage, use lowest effective dosage; monitor for adverse effects.
	Pimozide: • PIs and EFV may ↑ pimozide levels	Contraindicated with PIs and with EFV.



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Index

Primary Care of Veterans with HIV

Page numbers followed by *t* or *f* indicate tables or figures, respectively

A

- Abacavir, 76, 221*t*, 251
- Abbreviations, xii
- Abdominal aneurysm, 289
- Abuse. *See also* Alcohol use and misuse;
Substance use
 - alcohol, 3–4
 - domestic violence, 260–261
 - military sexual trauma, 260
 - substance, 70
- Acamprosate, 13, 15
- ACE inhibitors, 138, 176, 177*t*, 180*t*
- Acetaminophen
 - in combination with opioids, 209, 324–325
 - dosage and indications for, 321, 324
 - for low back pain, 289–290, 291
 - for osteoarthritis, 208, 209
 - for peripheral neuropathy, 300
- Acid-suppressive agents, 161–164, 167
- Acne, 119
- ACTG Brief Peripheral Neuropathy Screen, 297, 301–302
- Activity modification, 290
- Acute renal failure, 211, 219–220
- Acyclovir, 223*t*, 265
- Addiction, 70
- Adrenergic agonists, beta
 - ARV interactions with, 105
 - for asthma treatment, 100, 101, 102, 103, 104, 105
 - for COPD treatment, 112
 - long-acting, 104, 105
 - short-acting, 100, 101, 103, 104
- Adrenergic blockers
 - alpha, 182–183*t*, 232
 - alpha-/beta, 179–180*t*
 - beta, 176, 177*t*, 179*t*
- Airflow obstruction, in asthma, 99
- Albumin/creatinine ratio, 139, 212, 214
- Albuterol, 103, 112
- Alclometasone, 122
- Alcohol use and misuse, 3–15
 - alcohol abuse, 3–4
 - alcohol dependence, 3–4
 - and diabetes, 131, 132
 - epidemiology of, 5
 - and hypertension, 176*t*
 - key points of, 3
 - and liver disease, 187, 188, 194
 - management of, 7–8, 11–12
 - pharmacotherapy for, 13, 14–15
 - recommended limits for, 3, 4–5
 - referrals for, 13
 - resources for, 176*t*
 - risk assessment for, 41, 42–43
 - risky drinking, 3
 - screening for, 5–7, 9–10
 - in women, 264
- Alcoholic liver disease, 188
- Alcoholics Anonymous, 7, 8
- Aldosterone antagonists, 177*t*, 181–182*t*
- Alendronate, 264
- Alfuzosin, 232
- Alkaline phosphatase, 187, 188
- Alpha-/beta-blockers, 179–180*t*
- Alpha₁-antitrypsin deficiency, 109
- Alpha-fetoprotein, 198
- 5-alpha-reductase inhibitors, 232, 233
- Alprazolam, 328
- Alprostadil, intraurethral, 239
- ALT (alanine transaminase), 187, 188
- Amitriptyline, 300, 322, 327
- Amlodipine, 181*t*, 310
- Amphotericin B, 224*t*
- Anabolic steroids, 94
- Anal dysplasia, 83–88
 - evaluation of, 84–86
 - key points of, 83
 - management of, 86–88
 - overview of, 83–84

- prevention of, 88
- screening for, 85–86
- and squamous cell cancer of the anus, 83–84, 88
- in women, 262
- Analgesics
 - dosage and indications for, 321–322, 324
 - for low back pain, 289–290, 291
 - opiate, 208–209, 324–325
 - for osteoarthritis, 208–209
 - for peripheral neuropathy, 300
- Anal intraepithelial neoplasia, 86, 87–88
- Anal pap tests, 85–86, 262
- Androgen deficiency, 89–94
 - causes of, 90
 - definition of, 89
 - and erectile dysfunction, 237
 - evaluation of, 91–92
 - key points of, 89
 - management of, 92–94
 - mechanisms of, 89–90
 - overview of, 89–90
 - referrals for, 94
 - symptoms of, 90, 91
- Anesthetics, topical, 300, 326
- Aneurysm, abdominal, 289
- Angiotensin converting enzyme (ACE)
 - inhibitors, 138, 176, 177t, 180t
- Angiotensin receptor blockers, 138, 176, 177t, 180–181t
- Ankle reflexes, 297, 302
- Antabuse (disulfiram), 14–15
- Antacids, 162, 164, 167
- Anti-adrenergic agents, 182–183t
- Antibiotics, 113, 241
- Anticholinergic bronchodilators, 103, 112
- Anticonvulsants, 300, 323
- Antidepressants, 280–283
 - ARV interactions with, 327–328
 - bupropion, 282–283, 328
 - dosage and indications for, 322
 - SNRIs, 280, 281–282
 - SSRIs, 280–281, 327
 - tricyclic, 291, 300, 322, 327
- Antiepileptic medications, 300, 307–308, 323
- Antifungal medications, 121, 308–310
- Antihypertensive medications, 176, 177t, 178–183t
- Antipsychotic medications, 329
- Antiretroviral drug interactions
 - with acid-lowering medications, 167
 - with alfuzosin, 232
 - with alpha-/beta blockers, 179t
 - with alprazolam, 328
 - with amitriptyline, 327
 - with amlodipine, 181t, 310
 - with antacids, 167
 - with antidepressants, 327–328
 - with antiepileptic medications, 307–308
 - with antifungal medications, 121, 308–310
 - with antihypertensives, 178–183t
 - with antipsychotics, 329
 - with asthma medications, 105
 - with atenolol, 179t
 - with benzodiazepines, 328
 - with beta agonists, 105
 - with beta-blockers, 179t
 - with buprenorphine, 74, 76
 - with bupropion, 62, 328
 - with calcium channel blockers, 181t, 310
 - with carbamazepine, 307
 - with carvedilol, 179t
 - with corticosteroids, 105, 114
 - with desipramine, 327
 - with diazepam, 328
 - with diltiazem, 181t, 310
 - with duloxetine, 327
 - with fluconazole, 308–309
 - with fluoxetine, 327
 - with fluticasone, 105, 114
 - with food, 313
 - with GHB, 76, 77
 - with hormonal contraceptives, 258–259
 - with H2RAs, 167
 - with hypnotics, 328–329
 - with imipramine, 327
 - with itraconazole, 309
 - with ketoconazole, 309
 - with lamotrigine, 308
 - with leukotriene receptor antagonists, 105
 - with lipid-lowering medications, 152, 315–318
 - with MDMA, 76
 - with methadone, 73, 76, 310–311
 - with methamphetamine, 74–75
 - with metoprolol, 179t

- with midazolam, 328
 - with mirtazapine, 328
 - with montelukast, 105
 - with nefazodone, 328
 - with nifedipine, 181t
 - with nortriptyline, 327
 - with olanzapine, 329
 - with paroxetine, 327
 - with PDE5 inhibitors, 238
 - with phenobarbital, 307–308
 - with phenytoin, 308
 - with pimozone, 329
 - with posaconazole, 309
 - with proton pump inhibitors, 167
 - with salmeterol, 105
 - with sedatives, 328–329
 - with sertraline, 327
 - with SNRIs, 327
 - with SSRIs, 327
 - with St. John's wort, 313, 328
 - with statins, 152, 315–318
 - with supplements, 313
 - with terbinafine, 309
 - with theophylline, 105, 114
 - with trazodone, 328
 - with triazolam, 328
 - with tricyclic antidepressants, 300, 327
 - with valproate, 308
 - with venlafaxine, 327
 - with voriconazole, 310
 - with warfarin, 311
 - with zafirlukast, 105
 - with zolpidem, 329
- Antiretroviral therapy. *See also* Antiretroviral drug interactions
- abbreviations for, xii
 - and comorbid conditions, x
 - and depression, 272, 280
 - and diabetes, 131
 - and dyslipidemia, 144, 152
 - and gastroesophageal reflux disease, 168
 - and hypertension, 172
 - and liver disease, 188
 - during pregnancy, 255–256
 - and renal disease, 217–218, 220–225
 - and smoking, 54
 - and substance abuse, 71
 - toxicities associated with, ix, 188, 194
 - for women, 250, 251
- Anus, cancer of, 83–84, 85, 86, 88, 262
 - Anxiety, and erectile dysfunction, 237
 - Arthritis
 - osteoarthritis, 203–209
 - rheumatoid, 205
 - of the spine, 286
 - Arthroscopic surgery, 209
 - ARV toxic neuropathy, 295, 296
 - ASC-H (atypical squamous cells/cannot exclude HSIL), 31t, 86, 87–88, 263
 - Ascites, 195
 - ASCUS (atypical squamous cells of undetermined significance), 30, 86, 87, 263
 - Aspirin, 138
 - AST (aspartate transaminase), 187, 188
 - Asthma, 97–105
 - acute, 102–104
 - chronic, 100–102
 - epidemiology of, 98
 - evaluation of, 98–100
 - key points of, 97
 - management of, 100–105
 - medications for, 103–105
 - occupational, 99
 - referrals for, 102
 - symptoms of, 97, 98
 - vs. COPD, 97, 110
 - Atazanavir
 - food requirements for, 313
 - interactions with
 - antacids, 167
 - antiepileptics, 307
 - antifungal medications, 308, 309
 - calcium channel blockers, 310
 - corticosteroids, 105, 114
 - H2RAs, 167, 168
 - methadone, 310
 - oral contraceptives, 258
 - protein pump inhibitors, 167, 168
 - statins, 318
 - warfarin, 311
 - and renal disease, 221, 223t
 - Atenolol, 179t
 - Atorvastatin, 151, 152, 316, 318
 - Atrophy, defined, 125
 - AUDIT-C questions, 5, 6–7
 - Autoimmune hepatitis, 189, 195
 - Avascular necrosis, 205

- B**
- Back pain, low, 285–292
 - acute, 286
 - cauda equina syndrome, 286, 289
 - chronic, 286
 - differential diagnosis of, 289
 - epidemiology of, 285–286
 - evaluation of, 286–289
 - key points of, 285
 - management of, 289–291
 - prevention of, 292
 - radiculopathy, 286
 - referrals for, 292
 - sciatica, 285, 286
 - spinal stenosis, 286
 - spondylolisthesis, 286
 - spondylosis, 286
 - treatment follow-up for, 292
 - Baclofen, 291
 - Bacterial vaginosis, 266
 - Barium studies
 - double-contrast enema, 22t
 - esophagram, 160
 - Barrett esophagus, 156, 157–158, 160, 161
 - Beclomethasone, 104
 - Bed rest, for back pain, 290
 - Behavior modification
 - for alcohol misuse, 7–8, 11–12
 - for benign prostatic hypertrophy, 231
 - for diabetes, 130–131, 132
 - for dyslipidemia, 149
 - for gastroesophageal reflux disease, 162, 164–165
 - for hypertension, 175–176t
 - of sexual practices, 40–41, 46–48, 49
 - for smoking cessation, 57–59
 - for substance abuse, 73–76
 - Benazepril, 180t
 - Benign prostatic hypertrophy, 228–233
 - evaluation of, 228–231
 - key points of, 227
 - management of, 231–233
 - referrals for, 233
 - Benzodiazepines, 328
 - Beta-adrenergic agonists
 - ARV interactions with, 105
 - for asthma treatment, 100, 101, 102, 103, 104, 105
 - for COPD treatment, 112
 - long-acting, 104, 105
 - short-acting, 100, 101, 103, 104
 - Beta-blockers, 176, 177t, 179t
 - Biguanides, 133
 - Bile acid sequestrants, 152, 317
 - Biliary cirrhosis, primary, 189
 - Bilirubin, 188
 - Biopsy, liver, 192
 - Bisphosphonates, 264
 - Bleeding
 - menstrual irregularities, 256–257
 - variceal/GI, 196
 - Blood pressure. *See also* Hypertension
 - and diabetes, 139, 177t
 - home monitoring, 177
 - measuring, 173
 - Bone densitometry, 262, 264
 - Breast cancer screening, 24–27
 - effectiveness of, 26
 - epidemiology, 25–26
 - methods for, 26
 - positive results in, 27
 - recommendations for, 17, 25, 26–27, 262
 - reminders for, 27
 - Breast examinations, 25, 26, 262
 - Breastfeeding, 256
 - Brief interventions
 - for alcohol misuse, 7–12
 - for preventing HIV transmission, 41, 46–50
 - for smoking cessation, 55–59, 110
 - for substance abuse, 72–75
 - Bronchitis, chronic, 107, 108. *See also* Chronic obstructive pulmonary disease
 - Bronchodilators, 103, 112
 - Bronchoprovocation testing, 100
 - Bronchospasm. *See* Asthma
 - Bullae, 124
 - Buprenorphine, 73–74, 76
 - Bupropion
 - ARV interactions with, 62, 328
 - for depression treatment, 282–283
 - for methamphetamine abuse, 74
 - for smoking cessation, 60–66, 67
 - Bursitis, 205
- C**
- Calcium, 264, 313
 - Calcium channel blockers, 176, 177t, 181t, 310

- Calcium pyrophosphate dehydrate deposition, 205
- Cancer
 - anal, 83–84, 85–86, 88, 262
 - breast, 24–27, 262
 - cervical, 27–31, 261, 263
 - colorectal, 18–24
 - hepatocellular carcinoma, 197–199
 - and low back pain, 289
 - prostate, 31–34
 - risk of, and HIV, 17, 18, 28, 31
 - screening for, 17–34
 - vaginal, 261–262
 - vulvar, 261–262
- Candesartan, 180t
- Candidiasis
 - onychomycosis, 121
 - vaginal, 266
- Cannabis, 76
- Capsaicin, 207, 300, 326
- Carbamazepine, 307
- Carcinoma, hepatocellular, 17, 197–199
- Cardiovascular disease
 - and diabetes, 128, 131
 - and dyslipidemia, 143–144, 145
 - and hypertension, 171, 177t
 - risk factors for, 145
- Carvedilol, 179t
- Cauda equina syndrome, 286, 289
- Ceftriaxone, 241
- Celecoxib, 322
- Cervical cancer screening, 27–31
 - effectiveness of, 29
 - epidemiology and pathogenesis, 28
 - methods for, 29
 - positive results of, 29–31, 263
 - recommendations for, 17, 29, 261
 - reminders for, 29
- Cervical intraepithelial neoplasia, 28, 30
- Change
 - assessing readiness for, 47, 49, 55, 72
 - stages of, 47, 49
- Child-Turcotte-Pugh classification, 193
- Chlamydia, 45t
- Chlorthalidone, 179t
- Cholangitis, primary sclerosing, 189
- Cholesterol
 - HDL, 144, 150
 - LDL, 143, 144, 146, 147–148, 149–150
 - total, 143, 144, 148
- Chronic kidney disease, 215–218
 - and ART, 217–218
 - evaluation of, 215–217
 - management of, 217–218
 - referrals for, 217
 - risk factors for, 211, 216
 - stages of, 215t
- Chronic obstructive pulmonary disease (COPD), 107–114
 - acute exacerbations of, 112
 - chronic, stable, 111–112
 - epidemiology of, 107–108
 - evaluation of, 108–110
 - key points of, 107
 - management of, 110–114
 - medications and therapies for, 112–114
 - referrals for, 112
 - and smoking, 57, 106, 110
 - types of, 108
 - vs. asthma, 97, 110
- Cialis (tadalafil), 238
- Cidofovir, 224t
- Cimetidine, 163, 167
- Cirrhosis, 192–194. *See also* Liver disease
 - clinical features of, 187–188, 192
 - compensated, 192
 - decompensated, 192
 - definitions, 185, 192
 - diagnostic tests for, 192–193
 - primary biliary, 189
 - staging and classification of, 193–194
- Citalopram, 281, 327
- Clinical breast examination, 25, 26
- Clobetasol, 122
- Clonidine, 182t
- Club drugs, 70, 76–78
- Cocaine, 71, 75
- Codeine, 209, 291, 324
- Colchicine, 208, 326
- Colonoscopy, 19, 21–22t
- Colorectal cancer screening, 18–24
 - epidemiology and pathogenesis, 18–19
 - methods for, 19, 20–22t
 - positive results of, 24
 - recommendations for, 17, 18, 19, 22–24
 - reminders for, 24
- Colposcopy, 30, 31
- Comorbid conditions
 - related to alcohol misuse, 5
 - related to diabetes, 128
 - related to dyslipidemia, 143–144

- related to HIV infection, ix–x
 - related to hypertension, 171, 174–175t
 - related to liver disease, 186–187
 - related to smoking, 54
 - related to substance abuse, 71
 - Condoms, 50, 252
 - Condylomata, 87
 - Confidentiality, patient, 43
 - Contraception, 50, 252–253, 258–259
 - Coronary heart disease
 - and diabetes, 128, 131
 - and dyslipidemia, 143–144, 145
 - and hypertension, 171, 177t
 - risk factors for, 145
 - Corticosteroids
 - ARV interactions with, 105, 114
 - for asthma treatment, 103–104
 - for COPD treatment, 112
 - epidural injections of, 291
 - intraarticular injection of, 208
 - for psoriasis treatment, 122
 - Cough, with COPD, 109, 112
 - Counseling
 - for alcohol misuse, 7–8
 - for HIV transmission prevention, 46–50
 - preconception, 253–255
 - for smoking cessation, 58–59, 110
 - CPRS reminders
 - for breast cancer screening, 27
 - for cervical cancer screening, 29
 - for colorectal cancer screening, 24
 - for depression screening, 273
 - for prostate cancer screening, 33–34
 - Creatinine, serum, 212
 - Creatinine clearance, 212, 221–222t
 - Cromolyn, 104
 - Crust, skin, 125
 - Crystal Meth Anonymous, 75
 - Cyclobenzaprine, 291, 323
 - Cytology
 - anal, 86–88
 - cervical, 30–31, 263
- D**
- Darunavir
 - food requirements for, 313
 - interactions with
 - antidepressants, 327, 328
 - antiepileptics, 307, 308
 - antifungals, 309
 - corticosteroids, 105, 114
 - methadone, 310
 - oral contraceptives, 258
 - statins, 316, 318
 - warfarin, 311
 - DASH diet, 175t
 - Date-rape drug (Rohypnol), 70, 77
 - Degenerative joint disease. *See* Osteoarthritis
 - Delavirdine, 311, 315, 316, 317
 - Dementia, 128, 259
 - Dependence
 - alcohol, 3–4
 - physical, 70
 - substance, 70
 - Depo-Provera (medroxyprogesterone), 253, 258
 - Depression, 271–283
 - and ART adherence, 272, 280
 - associated with other illnesses, 276–277
 - and erectile dysfunction, 237
 - and HIV infection, 272
 - key points of, 271
 - management of, 279–283
 - medications for, 280–283, 322, 327–328
 - mental health services for, 271
 - prevalence of, 272
 - referrals for, 271–272
 - screening for, 272–277
 - and smoking cessation, 67
 - and suicide, 277–279
 - in women, 250, 259
 - Dermatitis, seborrheic, 115, 116, 117
 - Dermatologic conditions, 115–125
 - according to clinical status, 116
 - epidemiology of, 115–116
 - evaluation and management of, 117–123
 - folliculitis, 115, 117–119
 - HPV-associated warts, 115, 123
 - key points of, 115
 - onychomycosis, 115, 119–121
 - psoriasis, 115, 122
 - seborrheic dermatitis, 115, 116, 117
 - terminology for, 124–125
 - Dermatophytes, 119
 - Desipramine, 327
 - Desonide, 122

- DEXA bone density screening, 262, 264
- Dextroamphetamine, 74
- Diabetes, 127–140
 - complications of, 128
 - definitions of, 128–129
 - evaluation of, 129–130
 - and hypertension, 139, 177t
 - key points of, 127
 - management of, 130–139
 - and alcohol intake, 131, 132
 - ART regimens in, 131
 - behavior modification in, 130–131, 132
 - diet in, 131, 132, 133, 140
 - exercise in, 131, 132, 140
 - insulin in, 135–136, 137f
 - monitoring and prevention strategies in, 138–140
 - oral medications in, 131, 133–135
 - other therapies in, 138
 - patient education in, 131, 133
 - self-monitoring of blood glucose in, 131, 138–139
 - treatment goals, 131
 - weight loss in, 130, 132, 140
 - medications that increase risk of, 129
 - overview of, 128
 - referrals for, 139
 - risk factors for, 128, 129
 - screening for, 129–130
 - Type 2, 131, 132f, 137f
- Diazepam, 328
- Didanosine, 221t, 295, 313
- Diet
 - in diabetes management, 131, 132, 133, 140
 - in GERD management, 162, 164
 - in hypertension management, 175t
 - resources for, 176t
- Digital rectal exam, 19, 32, 33, 262
- Diltiazem, 181t, 310
- Diphtheria immunization, 38
- Distal sensory polyneuropathy, 295, 296
- Distal subungual onychomycosis, 119
- Disulfiram, 14–15
- Diuretics
 - potassium-sparing, 181–182t
 - thiazide, 176, 177t, 178–179t
- Domestic violence, 260–261
- Dosing
 - for antihypertensives, 178–183t
 - for atazanavir, 168
 - for insulin, 136
 - for NRTIs, 221–222t
 - for pain medications, 321–326
 - for PDE5 inhibitors, 238
 - terminology for, xii
- Doxazosin, 182t, 231–232
- Doxycycline, 241
- Drugs. *See* Medications; Substance use
- Duloxetine, 281, 300, 327
- Dutasteride, 233
- Dyslipidemia, 143–152
 - and ART, 144, 152
 - and coronary heart disease, 143–144, 145
 - evaluation of, 145–148
 - and HIV infection, 144
 - hypertriglyceridemia, 146, 148, 150
 - key points of, 143
 - LDL cholesterol goals and treatment, 147
 - management of, 148–152
 - medications for, 149–152, 315–318
 - overview of, 143–144
 - screening for, 144
- Dyspnea, with COPD, 108, 112
- E**
- Ecstasy (MDMA), 70, 77
- Education, patient
 - in diabetes management, 131, 133
 - for HIV transmission prevention, 46
 - for low back pain, 290
- Efavirenz
 - food requirements for, 313
 - interactions with
 - antidepressants, 328
 - antiepileptics, 307, 308
 - antifungals, 309, 310
 - antipsychotics, 329
 - calcium channel blockers, 310
 - methadone, 311
 - oral contraceptives, 259
 - statins, 315, 316, 317, 318
 - warfarin, 311
- Emphysema, 107, 108. *See also* Chronic obstructive pulmonary disease
- Emtricitabine, 221t
- Encephalopathy, hepatic, 196–197
- Endoscopic therapies, 166
- Enema, barium, 22t

Eosinophilic folliculitis, 115, 117–118
Epididymitis, 239–241
 acute, 239, 241
 chronic, 239
 evaluation of, 240
 key points of, 227
 management of, 241
 overview of, 239–240
Epidural steroid injections, 291
Erectile dysfunction, 233–239
 causes of, 234
 evaluation of, 235–237
 key points of, 227
 management of, 237–239
 medications associated with, 234
 overview of, 233–234
 refractory, 238
Erosion, skin, 125
Escitalopram, 281, 327
Esomeprazole, 163
Esophagitis, 156, 162
Esophagogastroduodenoscopy, 156, 160
Esophagram, barium, 160
Esophagus. *See also* Gastroesophageal
 reflux disease
 Barrett, 156, 157–158, 160, 161
 lower sphincter dysfunction, 156
Etravirine
 food requirements for, 313
 interactions with
 antiepileptics, 307, 308
 antifungals, 309, 310
 benzodiazepines, 328
 methadone, 311
 oral contraceptives, 259
 statins, 315, 316, 318
 warfarin, 311
Excoriation, 125
Exenatide, 135
Exercise
 asthma induced by, 104
 for back pain, 290
 and diabetes, 131, 132, 140
 and erectile dysfunction, 237
 and hypertension, 176t
 and osteoarthritis, 207
 resources for, 176t
 tolerance for, 109
 for women, 264
Eye examinations, 139
Ezetimibe, 152, 317

F

Famotidine, 163
Fecal occult blood testing, 19, 20t, 21t
Feet
 examination of, 139
 osteoarthritis in, 206
Fenofibrate, 151
Fentanyl transdermal, 209, 291, 301, 325
Fibrates, 151, 316
Finasteride, 233
Fingernails, fungal infections of, 115, 119–121
Fissures, 125
Fixed-dose combinations, 176
Flexeril (cyclobenzaprine), 323
Fluconazole, 308–309
Flunisolide, 104
Flunitrazepam, 70, 77
Fluocinonide, 122
Fluoroquinolones, 241
Fluoxetine, 280, 281, 327
Fluticasone, 104, 105, 114
Fluvastatin, 151, 316, 318
Folate, 255
Follicle-stimulating hormone, 89–90, 92
Folliculitis, 115, 117–119
Food interactions with ARVs, 313
Forced expiratory volume (FEV₁)
 in asthma, 99, 101–102
 in COPD, 107, 111, 113
Forced vital capacity (FVC)
 in asthma, 99, 101–102
 in COPD, 107, 111
Formoterol, 104
Fosamprenavir, interactions with
 antidepressants, 327
 antiepileptics, 308
 antifungals, 309
 calcium channel blockers, 310
 methadone, 310
 oral contraceptives, 258
 statins, 318
 warfarin, 311
Foscarnet, 224t
Fosinopril, 180t
Fractures, 289

G

Gabapentin, 300, 322
Gamma-hydroxybutyrate (GHB), 70, 76,
 77

- Garlic, interactions with, 313
 - Gastroesophageal reflux disease, 155–168
 - acute, 161–165
 - Barrett esophagus, 156, 157–158, 160, 161
 - chronic, 165–166
 - complicated, 156, 157
 - diagnostic tests for, 159–160
 - dietary and lifestyle modifications for, 162, 164–165
 - evaluation of, 156–161
 - extraesophageal, 158–159
 - key points of, 155
 - management of, 161–166
 - medications for
 - acid-suppressive agents, 161–164, 167
 - antacids, 162, 164, 167
 - ARV interactions with, 167
 - dosage recommendations, 168
 - prokinetic agents, 162, 164
 - nonerosive reflux disease, 156, 162
 - overview of, 155–156
 - referrals for, 166
 - surgery and endoscopic treatments for, 166
 - symptoms of, 155–156, 157, 158–159
 - Gastrointestinal bleeding, 196
 - Gemfibrozil, 151
 - Genital tract infections
 - bacterial vaginosis, 266
 - chlamydia, 45
 - genital ulcers, 265–266
 - gonorrhea, 45
 - herpes simplex virus, 45, 265
 - pelvic inflammatory disease, 266–267
 - sexually transmitted, 42, 44–45, 262–263
 - syphilis, 45
 - trichomoniasis, 45
 - vaginal candidiasis, 266
 - warts, 115, 123
 - GHB (gamma-hydroxybutyrate), 70, 76, 77
 - Gleason score, 32
 - Glipizide, 133–134
 - Glomerular filtration rate, 212–213, 215–216t, 219
 - Glucocorticoids, 112
 - Glucose, blood
 - impaired fasting, 129
 - self-monitoring, 131, 138–139
 - testing, 129
 - tolerance test, 128, 129
 - Glyburide, 133–134
 - Glycopyrrolate, 112
 - Gonorrhea, 45t
 - Gout, 205
 - Grapefruit juice, interactions with, 313
 - Gum, nicotine polacrilex, 60–66, 67
 - Gynecological issues
 - contraception, 252–253, 258–259
 - genital tract infections, 265–267
 - menopause, 256–257
 - menstrual irregularities, 256–257
 - preconception counseling, 253–255
 - pregnancy, 45, 255–256
 - sexual function, 257
- ## H
- H2 receptor antagonists (H2RAs), 161–162
 - ARV interactions with, 167
 - atazanavir dosages with, 168
 - for chronic GERD, 166
 - dosages for, 163–164
 - and relapse of GERD symptoms, 165
 - Hands, osteoarthritis in, 204, 206
 - HbA1c, 131, 132, 138
 - HDL cholesterol, 144, 150
 - Heart disease
 - and diabetes, 128, 131
 - and dyslipidemia, 143–144
 - and hypertension, 171, 177t
 - risk factors for, 145
 - Heart failure, 171, 177t
 - Heartburn, 155, 156, 158
 - Hemodialysis, 218
 - Hemorrhage, variceal, 196
 - Hepatic encephalopathy, 196–197
 - Hepatitis, autoimmune, 189, 195
 - Hepatitis A immunization, 38
 - Hepatitis B
 - and hepatocellular carcinoma, 17
 - immunization for, 37, 38
 - laboratory findings in, 189, 190
 - and liver disease, 186, 189, 190, 195
 - prevalence of, 186
 - treatment of, 195
 - Hepatitis C
 - and hepatocellular carcinoma, 17
 - laboratory findings in, 189, 191

- and liver disease, 186, 189, 191, 195
 - and liver transplantation, 200
 - prevalence of, 186
 - treatment of, 195
 - Hepatocellular carcinoma, 17, 197–199
 - Hepatotoxicity, and ARVs, 188, 194
 - Herniated nucleus pulposus, 289
 - Heroin, 73–74
 - Herpes simplex virus, 45t, 265
 - High-resolution anoscopy, 87
 - Hips, osteoarthritis in, 204, 206
 - HITS scale, 260
 - HIV-associated nephropathy, 212, 217, 218–219
 - HIV-associated sensory neuropathy, 295–296, 297
 - HIV infection
 - and alcohol misuse, 3, 5
 - and anal dysplasia, 83–84
 - and androgen deficiency, 89, 90
 - and cancer risk, 17, 18, 28, 31
 - comorbid conditions related to, ix–x
 - and COPD, 108
 - and depression, 272
 - and dermatologic conditions, 115–116
 - and dyslipidemia, 143, 144
 - epidemiology of, 39–40
 - and epididymitis, 240
 - and erectile dysfunction, 233–234
 - and liver disease, 186–187
 - and peripheral neuropathy, 295, 296
 - preventing transmission of, 39–50
 - follow-up for, 50
 - key points of, 39
 - patient evaluation in, 41, 42–45
 - patient management in, 41, 46–50
 - patient support in, 50
 - pregnancy screening, 45
 - risk assessment in, 41, 42–44
 - with safer sexual behaviors, 40–41, 46–48, 49
 - and STDs, 42, 44–45, 262–263
 - in women, 252
 - and renal disease, 211–212, 217, 218–219
 - and smoking, 54
 - and substance abuse, 70–71
 - transmission routes for, 40, 250
 - in women, 249–251
 - HMG-CoA reductase inhibitors, 151, 315–318
 - HSIL (high-grade squamous intraepithelial lesion), 31t, 86, 87–88
 - Human papillomavirus
 - and anal dysplasia, 83–84
 - and cervical dysplasia, 28, 29, 263
 - immunization for, 38
 - warts associated with, 115, 123
 - Hydralazine, 182t
 - Hydrochlorothiazide, 138, 179t
 - Hydrocodone, 209, 291, 324
 - Hydrocortisone, 122
 - Hydromorphone, 209, 325
 - Hypertension, 171–183
 - and ART, 172
 - definitions of, 173–174t
 - evaluation of, 172–175
 - key points of, 171
 - lifestyle modifications for, 175–176t
 - management of, 175–183
 - medications for
 - ACE inhibitors, 177t, 180t
 - aldosterone antagonists, 177t, 181–182t
 - angiotensin receptor blockers, 177t, 180–181t
 - anti-adrenergic agents, 182–183t
 - ARV interactions with, 178–183t
 - beta-blockers, 177t, 179t
 - calcium channel blockers, 177t, 181t, 310
 - classes of, 177t
 - direct vasodilators, 182–183t
 - drug dosing for, 178–183t
 - mixed alpha-/beta-blockers, 179–180t
 - potassium-sparing diuretics, 181–182t
 - thiazide diuretics, 177t, 178–179t
 - portal, 192
 - rationale for detecting and treating, 171–172
 - referrals for, 178
 - screening for, 172–173
 - treatment for, 172, 173–174t, 177
 - Hypertriglyceridemia, 146, 148, 150
 - Hypnotics, 328–329
 - Hypogonadism, 89, 237
- I**
- Ibandronate, 264
 - Ibuprofen, 321

Imaging

- for asthma, 99
- for back pain, 288–289
- for COPD, 109
- for epididymitis, 240
- for liver disease, 192–193
- for nephrolithiasis, 243
- for osteoarthritis, 206

Imipramine, 327

Immunizations, 37–38, 140

Impaired fasting glucose, 129

Impaired glucose tolerance, 128, 129

Indinavir

- interactions with
 - antidepressants, 328
 - calcium channel blockers, 310
 - grapefruit juice, 313
 - oral contraceptives, 258
 - statins, 318
 - theophylline, 105, 114
 - warfarin, 311
- and nephrolithiasis, 242, 243–244
- and renal disease, 221, 223t

Infections. See also HIV infection

- epididymitis, 239–241
- and low back pain, 289
- sexually transmitted, 42, 44–45
- spontaneous bacterial peritonitis, 196

Infectious monoarticular disease, 205

Influenza immunization, 37, 38, 140

Injections

- of medications, 208, 291
- in substance use, 70, 71

Insulin, 128, 135–136, 137f

International Index of Erectile Function (IIEF-5), 235–236

International Prostate Symptoms Score, 228, 229–231

Interventions, brief

- for alcohol misuse, 7–12
- for preventing HIV transmission, 41, 46–50
- for smoking cessation, 55–59, 110
- for substance abuse, 72–78

Intrauterine devices, 253

Intravaginal ring, 253, 258

In vitro fertilization, 254

Ipratropium, 103, 112

Irbesartan, 180t

Itraconazole, 309

J

Joint aspiration, 206–207

Joint pain. See Osteoarthritis

K

Ketamine hydrochloride, 70, 78

Ketoconazole, 309

Kidney disease, chronic, 211, 213, 215–218. See also Renal disease

Kidney stones. See Nephrolithiasis

Knees, osteoarthritis in, 204, 206

L

Labetalol, 180t

Lamivudine, 221t

Lamotrigine, 300, 308, 323

Lansoprazole, 163

LDL cholesterol

- and cardiovascular disease, 143, 144
- elevated, drug treatments for, 149–150
- thresholds for treatment of, 147–148
- treatment goals for, 147–148

Lesions, skin, 124–125. See also Dermatologic conditions

Leukotriene receptor antagonists, 104, 105

Levalbuterol, 103, 112

Levitra (vardenafil), 238

Levofloxacin, 241

Lichenification, 125

Lidocaine, 300, 326

Lifestyle modification

- for dyslipidemia, 149
- for GERD management, 162, 164–165
- for hypertension, 175–176t

Lipid-lowering medications, 149–152, 315–318

Lipids, fasting, 139, 144

Lisinopril, 180t

Liver biopsy, 192

Liver disease, 185–201

- abdominal imaging in, 192–193
- and alcohol misuse, 187, 188, 194
- and ARVs, 188
- causes of, 186–187
- cirrhosis, 185, 187–188, 189, 192–194
- clinical features of, 187–188
- comorbidities associated with, 186–187

- complications of, 195–199
 - end-stage, 186, 194
 - epidemiology of, 186
 - evaluation of, 187–194
 - and hepatitis, 186–187, 189, 190, 191
 - hepatocellular carcinoma, 197–199
 - key points of, 185
 - laboratory findings in, 187, 188–191, 192
 - liver transplantation, 200–201
 - management of, 194–197
 - nonalcoholic fatty liver disease, 189
 - staging and classification of, 193–194
 - Liver function testing, 139, 187, 188
 - Liver transplantation, 200–201
 - Long-acting beta-agonists, 104, 105
 - Lopinavir/ritonavir, interactions with
 - antidepressants, 328
 - antiepileptics, 308
 - antifungals, 309
 - corticosteroids, 105, 114
 - methadone, 310
 - oral contraceptives, 258
 - statins, 316, 318
 - warfarin, 311
 - Losartan, 181t
 - Lovastatin, 316, 318
 - Lozenges, nicotine polacrilex, 60–66
 - LSIL (low-grade squamous intraepithelial lesion), 31t, 86, 87
 - Lumbago, 285
 - Luteinizing hormone, 89–90, 92
- M**
- Macules, 124
 - Mammography, 25, 26–27
 - Manipulation, for back pain, 290
 - Maraviroc, interactions with
 - antidepressants, 328
 - antiepileptics, 307–308
 - St. John's wort, 313, 328
 - Marijuana, 76
 - Mast cell inhibitors, 104
 - MDMA (methylenedioxymethamphetamine), 70, 76, 77
 - Measles immunization, 38
 - Medications. *See also* Antiretroviral drug interactions; Antiretroviral therapy; Substance use
 - for alcohol misuse relapse prevention, 13, 14–15
 - antidepressants, 280–283, 322, 327–328
 - antiepileptic, 300, 307–308, 323
 - antifungals, 121, 308–310
 - antihypertensive, 176, 177t, 178–183t
 - antipsychotics, 329
 - for asthma treatment, 103–105
 - for benign prostatic hypertrophy, 231–233
 - for COPD, 112–114
 - for diabetes, 133–138
 - and diabetes risk, 129
 - dosing terminology for, xii
 - for dyslipidemia, 149–152, 315–318
 - for erectile dysfunction, 237–239
 - for folliculitis, 117–119
 - for gastroesophageal reflux, 161–165, 167–168
 - for onychomycosis, 119–121
 - for osteoarthritis, 207–209
 - for pain, 290–291, 321–326
 - for peripheral neuropathy, 300–301
 - for psoriasis, 122
 - for seborrheic dermatitis, 117
 - for smoking cessation, 58, 59, 60–67
 - for substance abuse, 73–76
 - testosterone replacement therapy, 92–94
 - Medroxyprogesterone, 253, 258
 - MELD score, 194
 - Meloxicam, 322
 - Meningococcus immunization, 38
 - Menopause, 256–257
 - Menstrual irregularities, 256–257
 - Mental health, 42, 271–272. *See also* Depression
 - Metformin, 131, 133
 - Methadone, 73, 76, 301, 310–311, 325
 - Methamphetamine, 71, 74–75
 - Methylenedioxymethamphetamine (MDMA), 70, 76, 77
 - Methylprednisolone, 112
 - Metoclopramide, 162, 164
 - Metoprolol, 179t
 - Microalbuminuria, 213, 214
 - Midazolam, 328
 - Military sexual trauma, 260
 - Mirtazapine, 328
 - Mixed alpha-/beta-blockers, 179–180t
 - MMR immunization, 37, 38
 - Model for end-stage liver disease (MELD) score, 194

Modification of Diet in Renal Disease
(MDRD) Study equation, 212–213

Mold infections, in nails, 119, 121

Montelukast, 104, 105

Morbidity and mortality

- due to comorbid conditions, ix
- due to liver disease, 186
- due to renal disease, 211

Morphine, 209, 291, 301, 325

Motivation, to quit smoking, 68

Mumps immunization, 38

Muscle relaxants, 291, 323

Myocardial infarction, 171

N

N-3 (omega-3) polyunsaturated fatty acids, 151, 317

Nails, fungal infections of, 115, 119–121

Naloxone, 74

Naltrexone, 13, 14, 74, 75

Nandrolone, 94

Naproxen, 322

Narcotics Anonymous, 73, 75, 76

Necrosis, avascular, 205

Nedocromil, 104

Nefazodone, 328

Nelfinavir

- food requirements for, 313
- interactions with
 - antiepileptics, 308
 - antifungals, 309
 - methadone, 310
 - oral contraceptives, 258
 - statins, 316, 318
 - tricyclic antidepressants, 327

Nephrolithiasis, 242–244

- evaluation of, 242
- key points of, 227
- management of, 243–244
- overview of, 242–243

Nephropathy, HIV-associated, 212, 217, 218–219

Neuropathy, peripheral, 295–302

- ARV toxic, 295, 296, 299–300
- distal sensory polyneuropathy, 295, 296, 299–300
- epidemiology of, 296
- evaluation of, 296–298
- HIV-associated sensory neuropathy, 295–296, 297

key points of, 295

management of, 298–301

prevention of, 296

referrals for, 299

screening for, 297, 301–302

symptoms of, 295

Neuropsychiatric disorders, in women, 259. *See also* Depression

Nevirapine, interactions with

- antiepileptics, 308
- antifungals, 309
- calcium channel blockers, 310
- methadone, 311
- oral contraceptives, 258
- statins, 315
- warfarin, 311

Niacin, 152, 316

Nicotine

- replacement therapies for, 59, 60–67
- withdrawal from, 59, 67

Nifedipine, 181t

Nizatidine, 164

NNRTIs (nonnucleoside reverse transcriptase inhibitors)

- and dyslipidemia, 144
- interactions with
 - antiepileptics, 307–308
 - antifungals, 121
 - food and supplements, 313
 - methadone, 76
 - oral contraceptives, 258, 259
 - St. John's wort, 313, 328
 - statins, 315–318

Nodules, skin, 124

Nonalcoholic fatty liver disease, 189

Nonbenzodiazepines, 291, 323

Nonerosive reflux disease, 156, 162

Noninvasive positive pressure ventilation, 113

Nortriptyline, 67t, 300, 322, 327

NRTIs (nucleoside reverse transcriptase inhibitors)

- and diabetes, 128, 129
- and dyslipidemia, 144
- interaction with food and supplements, 313
- interaction with methadone, 76
- and renal disease, 220, 221–222t

NSAIDs (nonsteroidal anti-inflammatory drugs)

dosage and indications for, 321–322
for low back pain, 289–290
for osteoarthritis, 208
for peripheral neuropathy, 300
Numbness, distal, 295, 297
NuvaRing (intra vaginal ring), 253, 258

O

Obesity

and diabetes, 128, 130
and erectile dysfunction, 237
and osteoarthritis, 207

Occult blood testing, 19, 20t, 21t

Ofloxacin, 241

Olanzapine, 329

Omalizumab, 104

Omeprazole, 163, 167

Onychomycosis, 115, 119–121

Opioids

abuse of, 73–74
dosage and indications for, 324–325
for low back pain, 289, 291
for osteoarthritis, 208–209
for peripheral neuropathy, 301

Opportunistic illnesses, 157, 162

Oral contraceptives, 253, 258–259

Oral glucose tolerance test, 128, 129

Organ injury, ix, 174–175t

Osteoarthritis, 203–209

classification of, 203–204
definitions of, 203–204
diagnostic criteria for, 204
differential diagnosis of, 205
evaluation of, 205–207
key points of, 203
medications for, 207–209
nonpharmacologic interventions for, 207
surgery for, 209

Osteomyelitis, 289

Osteonecrosis, 205

Osteoporosis/osteopenia screening, 262, 264

Oxandrolone, 94

Oxycodone, 209, 291, 301, 324–325

Oxygen therapy, 113

P

Pain, low back, 285–292

Pain medications

dosage and indications for, 321–326

for low back pain, 289–290, 291

for osteoarthritis, 207–209

for peripheral neuropathy, 300–301

and substance abuse disorders, 78–79

Pantoprazole, 163

Pap smear

anal, 85–86, 262

cervical, 28, 29, 261, 263

Papules, 124

Paroxetine, 67t, 280, 281, 327

Patches, skin, 124

Patient education

in diabetes management, 131, 133

for HIV transmission prevention, 46

for low back pain, 290

PDE5 inhibitors, 237–238

Peak expiratory flow rate, 99–101, 102, 103

Pelvic inflammatory disease, 266–267

Penile self-injectable drugs, 239

Pentamidine, 224t

Peripheral vascular disease, 128

Peritonitis, spontaneous bacterial, 196

Personality disorders, 259

Pertussis immunization, 38

pH monitoring, ambulatory, 160

Phenobarbital, 307–308

Phenytoin, 308

PHQ-2 and PHQ-9 questionnaires,
272–275, 277

Physical dependence, 70

Physical therapy, 290

Pimozide, 329

Pioglitazone, 134–135

Pirbuterol, 112

Pityrosporum folliculitis, 118

Plaques, skin, 124

Pneumococcus immunization, 37, 38, 140

Polycystic ovarian syndrome, 256

Portal hypertension, 192

Posaconazole, 309

Posttraumatic stress disorder, 259

Pott disease, 289

Pravastatin, 151, 152, 316, 318

Prazosin, 183t

Prednisone, 103

Pregabalin, 300, 323

Pregnancy

antiretroviral therapy during, 255–256

preconception counseling, 253–255

screening for, 45

- Prehypertension, 171, 173t
 - Primary biliary cirrhosis, 189
 - Primary sclerosing cholangitis, 189
 - Problem-solving skills, for smoking cessation, 58
 - Prokinetic agents, 162, 164
 - Propranolol, 179t
 - Prostate, benign hypertrophy of, 228–233
 - evaluation of, 228–231
 - key points of, 227
 - management of, 231–233
 - referrals for, 233
 - Prostate cancer screening, 31–34
 - effectiveness of, 33
 - epidemiology, 32
 - methods for, 32
 - positive results for, 34
 - recommendations for, 17, 31, 33
 - reminders for, 33–34
 - and testosterone replacement therapy, 93
 - treatment for, 32–33
 - Prostate-specific antigen, 32, 93–94
 - Prostatectomy, 32–33
 - Protease inhibitors
 - and diabetes, 128, 129, 131
 - and dyslipidemia, 144, 152
 - potential interactions with
 - antidepressants, 300, 327
 - antiepileptics, 307–308
 - antifungals, 121
 - antipsychotics, 329
 - benzodiazepines, 328
 - buprenorphine, 76
 - food and supplements, 313
 - inhaled corticosteroids, 105, 114
 - methadone, 76
 - oral contraceptives, 258, 259
 - St. John's wort, 313, 328
 - statins, 152, 315–318
 - Protein/creatinine ratio, 214
 - Proteinuria, 212, 213–215
 - Proton pump inhibitor therapy
 - ARV interactions with, 167
 - atazanavir dosages with, 168
 - dosage for, 163
 - for gastroesophageal reflux disease, 159–160, 161–163
 - Proximal subungual onychomycosis, 120
 - Pseudomonal folliculitis, 118
 - Psoriasis, 115, 122
 - Psychoactive medications
 - antidepressants, 280–283, 322, 327–328
 - antipsychotics, 329
 - ARV interactions with, 327–329
 - sedatives and hypnotics, 328–329
 - Psychotherapy, 237, 279–280
 - Pulmonary function testing, 99–100, 109
 - Pustules, 124
- Q**
- Questionnaires
 - AUDIT-C, 5, 6–7
 - IIEF-5, 235–236
 - PHQ-2 and PHQ-9, 272–275, 277
- R**
- Rabeprazole, 163
 - Race, and HIV infection, 250
 - Radiation therapy, 33
 - Radiculopathy, 286
 - Ramipril, 180t
 - Ranitidine, 164, 167
 - Rectum, examination of, 19, 32, 33, 262
 - Referrals
 - for alcohol misuse, 13
 - for androgen deficiency, 94
 - for asthma, 102
 - for benign prostatic hypertrophy, 233
 - for COPD, 112
 - for depression, 271–272
 - for diabetes, 139
 - for GERD, 166
 - for HIV transmission prevention, 50
 - for hypertension, 178
 - for liver transplantation, 200–201
 - for low back pain, 292
 - for peripheral neuropathy, 299
 - for renal disease, 217
 - Reflexes, ankle, 297, 302
 - Regurgitation, 155, 158
 - Relapse
 - of alcohol misuse, 13–15
 - of tobacco use, 67–68
 - Renal calculi. *See* Nephrolithiasis
 - Renal disease, 211–225
 - acute renal failure, 211, 219–220
 - ARVs for patients with, 220–222
 - caused by ARVs, 222–225

- chronic kidney disease, 215–218
- and diabetes, 128
- HIV-associated nephropathy, 218–219
- and HIV infection, 211
- and hypertension, 171
- key points of, 211
- overview of, 211–212
- referrals for, 217
- risk factors for, 211–212
- screening for, 212–215

Renal function

- in chronic kidney disease, 215–216
- estimating, 212–213
- and NRTI dosing, 221–222t

Renal replacement therapy, 218

Reproductive issues

- contraception, 252–253, 258–259
- preconception counseling, 253–255
- pregnancy, 45, 255–256
- sexual function, 257

Retinopathy, 128

Rheumatoid arthritis, 205

Risk assessments

- for alcohol misuse, 41, 42–43
- for HIV transmission, 41, 42–48, 49
- for suicide, 277–279

Risk factors

- for anal dysplasia, 84
- for asthma, 98
- for back pain, 287
- for breast cancer, 25–26
- for cardiovascular disease, 145
- for cervical cancer, 28
- for colorectal cancer, 19, 22–24t
- for COPD, 108
- for diabetes, 128, 129
- for GERD, 158
- for hepatocellular carcinoma, 197
- for HIV transmission, 40–41, 47t
- for osteoarthritis, 205
- for osteoporosis, 264
- for peripheral neuropathy, 296–297
- for renal disease, 211–212, 216
- for suicide, 278

Ritonavir

- food requirements for, 313
- interactions with
 - antidepressants, 300, 327, 328
 - antiepileptics, 307, 308
 - antifungals, 309, 310
 - antipsychotics, 329

- calcium channel blockers, 310
- corticosteroids, 105, 114
- oral contraceptives, 258
- sedatives/hypnotics, 328–329
- statins, 316, 318
- theophylline, 105, 114

Rohypnol (flunitrazepam), 70, 77

Rosiglitazone, 134–135

Rosuvastatin, 151, 316, 317

Rubella immunization, 38

S

Salmeterol, 104, 105

Saquinavir

- food requirements for, 313
- interactions with
 - benzodiazepines, 328
 - calcium channel blockers, 310
 - food, 313
 - methadone, 310
 - oral contraceptives, 259
 - statins, 316, 318
 - warfarin, 311

Scales, skin, 125

Scars, 124

Sciatica, 285, 286

Screening

- for alcohol misuse, 5–7, 9–10
- for anal dysplasia, 85–86
- for cancer, 17–34
 - anal, 85–86, 262
 - breast, 24–27, 262
 - cervical, 27–31, 261, 263
 - colorectal, 18–24
 - hepatocellular carcinoma, 198–199
 - prostate, 31–34
 - vaginal, 261–262
 - vulvar, 261–262
- cost-benefits of, x
- for depression, 272–277
- for diabetes, 129–130
- for dyslipidemia, 144
- for HIV transmission risk behaviors, 42–44
- for hypertension, 172–173
- importance of, ix
- for osteoporosis/osteopenia, 262, 264
- for peripheral neuropathy, 297, 301–302
- for pregnancy, 45

- for renal disease, 212–215
- for sexually transmitted diseases, 42, 44–45, 262–263
- for substance abuse, 71
- Seborrheic dermatitis, 115, 116, 117
- Sedatives, 328–329
- Self-monitoring of blood glucose, 131, 138–139
- Sensory loss, 297
- Serosorting, 43
- Sertraline, 281, 327
- Sex partners, 241
- Sexual behaviors
 - and erectile dysfunction, 237
 - modifying, 40–41, 46–48, 49
 - risk assessment of, 41, 42–43, 47t, 49
- Sexual function
 - erectile dysfunction, 227, 233–239
 - in women, 257
- Sexual trauma, military, 260
- Sexually transmitted diseases, 42, 44–45, 262–263
- Short-acting beta-agonists, 100, 101, 103, 104
- Shoulders, osteoarthritis in, 206
- Sigmoidoscopy, flexible, 19, 20–21t
- Sildenafil, 238
- Simvastatin, 317, 318
- Sitagliptin, 135
- Skin lesions, 124–125. *See also* Dermatology conditions
- Smoking cessation, 53–68
 - and asthma, 100
 - and COPD, 57, 110
 - and diabetes, 138
 - effectiveness of programs for, 54
 - evaluation for, 55–56
 - and GERD, 164
 - and hypertension, 175
 - key points of, 53
 - management of, 57–68
 - overview of, 54
 - patient relapse, 67–68
 - pharmacologic interventions for, 58, 59–67
 - for women, 264
- SNRIs (serotonin-norepinephrine reuptake inhibitors), 280, 281–282, 327
- Social support, for smoking cessation, 59, 67
- Sperm washing, 254
- Spermicides, 252
- Spinal stenosis, 286
- Spine, 206, 286
- Spirometry, 99, 109
- Spiroolactone, 182t
- Spondylolisthesis, 286
- Spondylosis, 286
- Spontaneous bacterial peritonitis, 196
- Sputum production, 109, 112
- Squamous cell cancer of the anus, 83–84, 85, 86, 88
- SSRIs (selective serotonin reuptake inhibitors), 280–281, 327
- St. John's wort, 313, 328
- Stages of change theory, 47, 49
- Staphylococcal folliculitis, 115, 118
- Statins, 151, 315–318
- Stavudine, 222t, 295
- Steatohepatitis, 189
- Steroids, anabolic, 94
- Stroke, 128, 171, 177t
- Substance use, 69–79. *See also* Alcohol use and misuse; Smoking cessation
 - and antiretroviral therapy, 71
 - definitions of, 70
 - epidemiology of, 70–71
 - and HIV infection, 71
 - key points of, 69
 - management of, 71–79
 - and ARV interactions, 76
 - brief interventions, 72
 - cannabis, 76
 - club drugs, 76–78
 - cocaine, 75
 - heroin and other opioids, 73–74
 - methamphetamine, 74–75
 - and pain management, 78–79
 - screening for, 71
 - substance abuse, 70
 - substance dependence, 70
 - types of, 69–70
- Suicide, 277–279
- Sulfonylureas, 131, 133
- Sulindac, 322
- Supplements, interactions with ARVs, 313
- Support
 - for alcohol use goals, 11, 12
 - for HIV transmission prevention, 50
 - for smoking cessation, 59, 67

Surgery, 166, 209
Syphilis, 45t

T

Tadalafil, 238
Tamsulosin, 232
Telmisartan, 181t
Tenofovir, 220–221, 222–223t
Terazosin, 183t, 231–232
Terbinafine, 309
Testes, 239, 240
Testosterone
 deficiency of, 89–94
 measuring, 91–92
 replacement therapy, 92–93, 237
Tetanus immunization, 38
Theophylline, 104, 105, 113, 114
Thiazide diuretics, 176, 177t, 178–179t
Thiazolidinediones, 132, 134–135
Tipranavir, interactions with
 antidepressants, 328
 antiepileptics, 307, 308
 antifungals, 308
 methadone, 310–311
 oral contraceptives, 258
 statins, 316, 318
 vitamin E, 313
 warfarin, 311
TMP-SMX, 224–225t
Tobacco use, 53–54. *See also* Smoking cessation
Toenails, fungal infections of, 115, 119–121
Tolerance
 drug, 70
 for exercise, 109
 glucose, 128, 129
Tramadol, 209, 291, 324
Transdermal administration of drugs
 for contraception, 253, 258
 fentanyl, 209, 291, 301, 325
 nicotine replacement, 60–66, 67
Transplantation, liver, 200–201
Trazodone, 328
Treatment programs, substance abuse, 72
Triamcinolone, 104, 122
Triamterene, 182t
Triazolam, 328
Trichomoniasis, 45t
Tricyclic antidepressants, 291, 300, 322, 327

Triglycerides, 144, 146, 148, 150
Tumors, 124

U

Ulcers
 genital, 265–266
 skin, 125
Urine, protein in, 212, 213–215
Urology, 227–244
 benign prostatic hypertrophy, 227, 228–233
 epididymitis, 227, 239–241
 erectile dysfunction, 227, 233–239
 nephrolithiasis, 227, 242–244

V

Vacuum devices, for erectile dysfunction, 239
Vagina
 bacterial vaginosis, 266
 cancer of, screening for, 261–262
 candidiasis of, 266
Valproate, 308
Valsartan, 181t
Vardenafil, 238
Varenicline, 59, 60–66
Variceal hemorrhage, 196
Varicella immunization, 37, 38
Vascular disease, peripheral, 128
Vasodilators, 182–183t
Vegetating, defined, 125
Venlafaxine, 67t, 280, 282, 300, 327
Verapamil, 181t
Vesicles, 124
Viagra (sildenafil), 238
Violence, domestic, 260–261
Vitamin D, for women, 264
Vitamin E, interactions with, 313
Voriconazole, 310
Vulvar cancer screening, 261–262

W

Warfarin, 311
Warts, HPV-associated, 115, 123
Weight
 gain of, and smoking cessation, 68
 loss of
 and diabetes, 130, 132, 140
 and erectile dysfunction, 237

- and GERD, 164
 - and hypertension, 176t
 - and osteoarthritis, 207
 - resources for, 176t
- Wheals, 124
- White superficial onychomycosis, 120
- Withdrawal
- from alcohol, 8, 13
 - nicotine, 59, 67
- Women
- alcohol drinking limits for, 4, 5, 9
 - anal cancer screening in, 262
 - androgen deficiency in, 89, 90, 92–93
 - bacterial vaginosis in, 266
 - barriers to care for, 250
 - breast cancer screening in, 24–27, 262
 - breastfeeding by, 256
 - cervical cancer screening in, 27–31, 261, 263
 - contraception for, 252–253, 258–259
 - depression in, 250
 - domestic violence in, 260–261
 - genital herpes simplex virus in, 265
 - genital ulcers in, 265–266
 - health issues for, 249
 - HIV in, 40, 249–251
 - HPV immunization for, 38
 - menopause in, 256–257
 - menstrual irregularities in, 256–257
 - military sexual trauma in, 260
 - neuropsychiatric disorders in, 259
 - osteoporosis/osteopenia screening in, 262, 264
 - pelvic inflammatory disease in, 266–267
 - preconception counseling for, 253–255
 - pregnancy in, 45, 255–256
 - sexual function in, 257
 - STD screening in, 45t, 262–263
 - vaginal cancer screening in, 261–262
 - vaginal candidiasis in, 266
 - ovular cancer screening in, 261–262
- X**
- X-rays, chest, 99, 109
- Y**
- Yeast infections
- of nails, 119
 - vaginal, 266
- Yohimbine hydrochloride, 239
- Z**
- Zafirlukast, 104, 105
- Zalcitabine, 295
- Zidovudine, 222t
- Zoledronic acid, 264
- Zolpidem, 329
- Zoster immunization, 37

