Primary Care Management

This is a PDF version of the following document:
Section 1: Basic HIV Primary Care
Topic 5: Primary Care Management

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Topic Overview

With the advent of potent antiretroviral therapies, the life expectancy of individuals with HIV has increased dramatically, and HIV clinical care has transitioned to a chronic disease model. In recent years, proportionately fewer individuals with HIV experience AIDS-related complications compared with non-AIDS serious illnesses, such as cardiovascular disease and non-AIDS-defining malignancies.[1] Consequently, clinicians who provide primary care to persons with HIV infection should have knowledge and skills recognize and manage common primary care conditions, as well as to delivery of evidence-based prevention measures. This review will explore several common topics in the primary care management of persons with HIV.
Cardiovascular Risk

Cardiovascular Risk in Persons with HIV

Cardiovascular and cerebrovascular disease are of special importance for individuals with HIV, with evidence showing a 1.5- to 2-fold greater risk of cardiovascular disease in persons with HIV when compared with those without HIV.[2,3] The increased cardiovascular risk conferred by HIV has now been demonstrated across many different cohorts.

- **Global Burden of Atherosclerotic Cardiovascular Disease in People Living with HIV:** In this systematic review and meta-analysis that included 793,635 persons with HIV, investigators reported that individuals with HIV are twice as likely to develop cardiovascular disease as those without HIV.[4]
- **Kaiser Observational Study:** A Kaiser observational study of over 4,000 patients demonstrated that persons with HIV had higher rates of both myocardial infarction and hospitalization for coronary heart disease compared to persons without HIV (Figure 1).[5]
- **Veterans Aging Cohort Study:** The Veterans Aging Cohort Study analyzed data from nearly 90,000 veterans and showed an increased myocardial infarction risk among veterans with HIV across all age groups (Figure 2).[2] This study also found that low CD4 cell counts and high HIV RNA levels increased the risk of myocardial infarction.[2]

The increased risk of atherosclerotic disease in persons with HIV is potentially mediated by (1) traditional risk factors, such as dyslipidemia, obesity, and cigarette smoking, (2) metabolic alterations related to antiretroviral therapy (e.g. insulin resistance, and dyslipidemia), and (3) factors linked to HIV itself, including immune activation and inflammation.[3,6,7] In addition, cardiovascular disease in persons with HIV disproportionately affects Hispanics and non-Hispanic blacks.[8,9,10] Studies using carotid ultrasound, computed tomography (CT), and positron emission tomography (PET) imaging have shown an increased prevalence of atypical, non-calcified, vulnerable coronary plaques as well as increased arterial inflammation.[11,12,13] Rates of heart failure, stroke, pulmonary hypertension, and sudden cardiac death are also higher for people with HIV, even those taking antiretroviral therapy with suppressed HIV RNA levels.[7] Consequently, many experts now consider HIV as an independent cardiovascular disease risk factor, especially with more advanced immunosuppression.

Cardiovascular Risk and Antiretroviral Therapy

In contrast to broad evidence correlating increased cardiovascular risk with HIV, the relationship between antiretroviral therapy and cardiovascular disease risk has remained controversial. The overall benefits of antiretroviral therapy clearly outweigh the risks; in the Strategies for Management of Antiretroviral Therapy (SMART) trial, continuous antiretroviral therapy compared to intermittent (CD4-count driven) antiretroviral therapy decreased all-cause mortality, death from opportunistic infections, and death from major cardiovascular disease.[14] Nevertheless, studies examining individual drug and class effects have raised concerns regarding the contribution of protease inhibitors and abacavir to cardiovascular risk, although results have been conflicting.[2,15,16,17,18] The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study found that recent abacavir use conferring the highest relative rate of myocardial infarction (relative rate of 1.89, even after controlling for traditional cardiovascular risk factors); in the D:A:D study, the abacavir effect appeared to be reversible after the drug was stopped.[19,20] For persons with HIV, based on the cumulative findings from studies involving abacavir and risk of cardiovascular disease, most experts would avoid abacavir in those with cardiovascular disease and many would avoid abacavir based on significant cardiovascular risk factors alone.
Hypertension

Overview

Hypertension is the most common diagnosis seen in primary care, and untreated hypertension increases the risk of myocardial infarction, stroke, renal failure, and death. According to the National Health and Nutrition Examination Survey (NHANES), from 2011 to 2014, the age-adjusted prevalence of hypertension among persons aged 20 years and older was 34%.[21] The 2017 Hypertension Guideline revised the definition for hypertension as any systolic blood pressure of at least 130 mm Hg or any diastolic BP of at least 80 mm Hg (Figure 3).[22] The 2017 Hypertension Guideline also notes the importance of obtaining accurate blood pressure measurements and steps required before and during the measurement include:[22]

- The patient should avoid smoking, caffeine ingestion, or exercise for at least 30 minutes prior to the blood pressure measurement.
- The patient should empty their bladder and sit quietly for at least 5 minutes before the blood pressure measurement.
- Have the patient sit with legs on floor and support the patient's arm used to obtain for the blood pressure.
- Ensure the blood pressure cuff is at the level of the patient's heart.
- Use a correct size of blood pressure cuff.
- Have the patient sit still during the blood pressure measurement.
- The patient's blood pressure value should be based on an average of at least 2 careful readings obtained on at least 2 occasions.

Baseline Evaluation of Persons with Hypertension

The initial evaluation of patients with hypertension has three primary objectives: (1) to assess lifestyle and other risk factors that may affect prognosis and guide treatment of hypertension, (2) to reveal identifiable secondary causes of hypertension (such as renovascular or thyroid disease), and (3) to identify the presence or absence of target-organ damage and cardiovascular disease.[22] The 2017 Hypertension Guideline recommends a baseline evaluation for all persons with hypertension that should include an electrocardiogram, complete blood count, sodium, potassium, creatinine with estimated glomerular filtration rate, calcium, thyroid stimulating hormone, urinalysis, a lipid profile, and a fasting blood glucose.[22]

Current Guidelines for the Management of Hypertension

The 2017 Hypertension Guideline addresses thresholds for treatment initiation and blood pressure goals (Table 1); in addition the guidelines provide recommendations regarding medication treatment approaches.[22] For persons with stage 1 hypertension, the American College of Cardiology ASCVD Risk Estimator should be used to determine the estimated 10-year risk for heart disease and stroke. The key points from these guidelines are summarized below:

- For adults with hypertension the recommended blood pressure treatment goal is less than 130/80 mm Hg.
- Lifestyle modification is the foundation for cardiovascular risk reduction, and counseling should be provided to all persons with hypertension and continued throughout the management of the disease. Major aspects of lifestyle changes include (1) use the Dietary Approach to Stop Hypertension (DASH), (2) lose excess body weight, (3) reduce dietary intake of sodium, (4) increase dietary intake of potassium, (5) incorporate a weekly routine of physical activity that includes aerobic exercise, dynamic resistance training, and isometric resistance training, and (6) reduce consumption of alcohol.
- First-line initial pharmacotherapy for stage 1 hypertension, when indicated based on a
10-year risk for heart disease and stroke 10% or greater, should consist of a thiazide-type diuretic, calcium-channel blocker, angiotensin-converting-enzyme inhibitor, or angiotensin-receptor blocker.

- Initial pharmacotherapy with stage 2 hypertension and an average blood pressure more than 20 mm Hg systolic/10 mm Hg diastolic above their target blood pressure should consist of simultaneous administration of two agents of different classes (thiazide-type diuretic, calcium-channel blocker, angiotensin-converting-enzyme inhibitor, or angiotensin-receptor blocker). This strategy should be used with caution in older individuals.
- For blacks with hypertension who do not have heart failure or chronic kidney disease, the preferred initial therapy is with either a thiazide-type diuretic or a calcium-channel blocker.
- For all patients with chronic kidney disease (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio in the first morning void]), the antihypertensive regimen should include an angiotensin-converting-enzyme inhibitor (or an angiotensin-receptor blocker if the angiotensin-converting-enzyme inhibitor is not tolerated).
- Avoid the simultaneous administration of an angiotensin-converting-enzyme inhibitor and an angiotensin-receptor blocker.

Special Considerations for Persons with HIV

Hypertension in Persons with HIV

Hypertension is common in persons with HIV.[23, 24, 25, 26, 27] Hypertension increases the risk of acute myocardial infarction independent of, and in addition to, that contributed by HIV.[26] In persons with HIV, hypertension is associated with traditional risk factors such as increasing age, obesity, African American race, diabetes, or hyperlipidemia.[24] Data are conflicting regarding the association of HIV, antiretroviral therapy, and hypertension. Some early studies linked hypertension to antiretroviral therapy, in particular protease inhibitors, but this has not been supported in more recent investigations.[28, 29] For instance, in a cross-sectional study at two Navy medical centers, hypertension was most strongly associated with age over 40 years and duration of HIV infection of greater than 10 years; diabetes, African American race, and elevated body mass index (BMI) also contributed to increased odds of developing hypertension.[23] Among women with HIV, these same factors of increasing age, African American race, and elevated BMI contributed to the development of hypertension; notably, however, in both the Navy study and the Women’s Interagency Study, there was no association between hypertension and antiretroviral therapy. In the D:A:D study, a large international prospective cohort study, neither the type of antiretroviral therapy at baseline nor the cumulative exposure to protease inhibitors or nucleoside reverse transcriptase inhibitors (NRTIs) predicted hypertension, though exposure to non-nucleoside reverse transcriptase inhibitors (NNRTIs) was associated with decreased risk of hypertension.[30]

Management of Hypertension in Persons with HIV

Management of hypertension in persons with HIV infection is not specifically addressed by the 2017 Hypertension Guideline referenced above or by the HIVMA Primary Care Guidelines.[22, 31] Nevertheless, given that both hypertension and HIV are cardiovascular risk factors, both should be managed aggressively, and it is reasonable to follow the recommendations in the 2017 Hypertension Guideline.[22] In addition, clinicians should consider the risk of drug interactions when adding any anti-hypertensive medication to a background of antiretroviral therapy. In particular, clinicians should use caution when administering calcium channel blockers, such as amlodipine, diltiazem, felodipine, nifedipine, and verapamil, in patients taking protease inhibitors or cobicistat, since these medications can raise levels of calcium channel blocker drugs; electrocardiographic monitoring is recommend if a calcium channel blocker is used with either atazanavir or saquinavir.[32, 33]
Hyperlipidemia

Overview

Combined data from the CDC and NHANES shows that approximately 12% of United States adults age 20 and older have elevated total cholesterol (defined as greater than or equal to 240 mg/dL).[0] Although screening rates have improved to approximately 70% of adults, this still falls short of the Healthy People 2020 target for cholesterol screening of at least 82%.[0] Elevated cholesterol can lead to atherosclerotic cardiovascular disease (ASCVD), the leading cause of preventable death in the United States.

Guidelines for the Management of Dyslipidemia

In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) released the Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, which is markedly different from the prior cholesterol guidelines published in 2002 and updated in 2004.[41] The new guideline primarily focuses on targeting four groups of individuals with evidence of clear benefit from pharmacologic therapy, and it no longer recommends monitoring of cholesterol levels and treating to specific goals once statin therapy is initiated. Whether a patient should be treated with statin therapy and at what dose is based on the individual’s clinical conditions, baseline LDL-cholesterol (LDL-C), and estimated 10-year ASCVD risk (Figure 4).[0,41] The key points from the 2013 ACC/AHA Cholesterol Guideline are outlined below:

Identifying Candidates for Statin Therapy

The four groups of persons 21 years of age or older in which the benefits of statins clearly outweigh the adverse events include:

1. Individuals with clinical ASCVD, defined as acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin
2. Individuals with LDL-C of 190 mg/dL or greater
3. Individuals with diabetes mellitus, age 40-75 years, and LDL-C 70-189 mg/dL
4. Individuals 40-75 years of age, no diabetes, no clinical ASCVD, and with LDL-C 70-189 mg/dL and estimated 10-year ASCVD risk of 7.5% or greater, as determined by the new Pooled Cohort Equations to estimate 10-year ASCVD risk in both white and black men and women who do not have ASCVD. See the ASCVD Risk Estimator.

Baseline Evaluation and Initiation of Therapy

Evaluation for secondary causes of hyperlipidemia should be considered, particularly in persons with severe elevations of LDL-C (greater than or equal to 190 mg/dL) or triglycerides (greater than or equal to 500 mg/dL). Major secondary causes that are encountered in clinical practice include diet, medications (diuretics, cyclosporine, glucocorticoids, and amiodarone), medical diseases (biliary obstruction or nephrotic syndrome), and disorders of altered metabolism (hypothyroidism, obesity, pregnancy, and diabetes). For patients meeting criteria for benefit from statin therapy, the guideline specifies whether high-, moderate-, or low-intensity statin should be initiated, depending on age, calculated ASCVD risk, LDL-C level, and other clinical factors (Figure 5).[41]

Monitoring and Treatment Goals

- A lipid panel should be performed at baseline and 4 to 12 weeks after initiation of statin therapy to determine adherence to the medication. Thereafter, lipid panels can be measured
every 3 to 12 months.

- The current guideline no longer recommends treating to a specific target LDL-C level. Instead, monitoring is recommended to evaluate for an anticipated therapeutic response and to confirm adherence. High-intensity statin therapy is anticipated to reduce LDL-C by approximately 50% or more from the untreated baseline, and moderate-intensity therapy is expected to reduce LDL-C approximately 30% to 50% from the untreated baseline. Adjustments to the management of hyperlipidemia are recommended based on failure to achieve these LDL-C reductions, rather than failure to meet a specific LDL-C measurement.
- There are no data to support that routinely adding a nonstatin drug to high-intensity statin therapy provides any incremental cardiovascular risk reduction with an acceptable margin of safety. Use of nonstatin therapy may be considered in high-risk patients (ASCVD, diabetes, or LDL 190 mg/dL or greater) who are intolerant to statins or fail to respond adequately to statins.
- At all visits, providers should assess and reinforce the importance of adherence to medication and lifestyle modifications.

**GUIDELINES FOR THE MANAGEMENT OF Hypertriglyceridemia**

Elevated triglycerides can also increase the risk of cardiovascular disease. The 2011 AHA Scientific Statement on Triglycerides and Cardiovascular Disease classifies triglyceride levels into four categories: normal, borderline-high, high, and very high (Figure 6). Patients with very high triglyceride levels (500 mg/dL or greater) should undergo evaluation for secondary causes of hyperlipidemia, such as diet, medications, or metabolic disorders.

**Management of Hypertriglyceridemia**

Hypertriglyceridemia can often be managed with intensive lifestyle change including weight loss, restriction in dietary fats, elimination of alcohol intake, and increased exercise. The 2013 ACC/AHA Cholesterol Guideline refers to the 2011 AHA Scientific Statement on Triglycerides and Cardiovascular Disease for management of elevated triglyceride levels. Per this statement, triglyceride levels of 500 mg/dL or greater should be managed with medications; fibrates, immediate-release niacin, and omega-3 methyl esters cause the greatest percentage of triglyceride reduction, though clinical trial data are lacking.

Note: since the publication of the cholesterol and triglyceride guidelines, new information has become available regarding the appropriate use of niacin in the treatment of lipid disorders. Among participants with ASCVD in a large, randomized controlled trial, the addition of extended-release niacin-laropiprant to statin-based LDL cholesterol-lowering therapy did not significantly reduce the risk of major vascular events but did increase the risk of serious adverse events, including serious infections and bleeding events. Laropiprant is a compound that reduces flushing caused by niacin, but it is no longer manufactured. Niacin may still be an acceptable medication for certain individuals, but the benefits must be considered carefully in light of these newly identified hazards.

**Special Considerations for Persons with HIV Infection**

**Lipid Disorders Associated with HIV Infection**

Dyslipidemia has been associated with traditional risk factors as well as with HIV itself and antiretroviral therapy. Chronic HIV infection causes a rise in triglyceride levels (possibly due to increased levels of serum interferon-alfa, slowing of triglyceride metabolism, and impaired hepatic synthesis of fatty acids) and a decrease in total cholesterol, HDL, and LDL that is consistent with a chronic inflammatory state. The mechanisms for these latter changes are likely multifactorial, due to a combination of genetic factors, patient lifestyle, increased triglycerides, insulin resistance, increased activity of various hepatic enzymes, and abnormal HDL metabolism. Compared to individuals without HIV infection, those with HIV infection have also been shown to have a higher
prevalence of atypical, high-risk coronary plaques.[3,13]

**Lipid Changes After Initiation of Antiretroviral Therapy**

After starting antiretroviral therapy, a patient’s lipid levels typically return to baseline and then rise above pre-treatment levels, except for HDL, which remains persistently low. The magnitude of lipid changes following the introduction of antiretroviral therapy depends on a patient’s gender, race/ethnicity, underlying genetic polymorphisms, and the lipid profile of the specific antiretroviral regimen.[45]

**Effect of Antiretroviral Therapy on Lipids**

Each class of antiretroviral therapy has a distinct effect on baseline lipid levels, with protease inhibitors generally causing the greatest increases in lipid levels (especially LDL and triglycerides) and integrase inhibitors exerting the least lipid effect; within classes, certain agents are recognized to cause more adverse lipid effects than others (Figure 7).[44,46]

**Strategies for Antiretroviral Therapy Modification for Patients with Dyslipidemia**

If a patient’s lipid levels are found to be abnormal while on antiretroviral therapy, a review of the individual’s antiretroviral regimen should be performed to identify medications that may be contributing to lipid abnormalities, including efavirenz, protease inhibitors, and boosting agents such as ritonavir and cobicistat. Providers should engage these patients in a discussion of the risks and benefits of modifying the antiretroviral regimen, adding a lipid-lowering medication, adopting lifestyle modifications, or a combination of these strategies. If a decision is made to change a patient’s existing antiretroviral therapy regimen to a more “lipid-friendly” antiretroviral regimen, the goal of maintaining viral suppression is paramount, and current and archived resistance mutations must be taken into consideration when deciding on the new regimen.[45,46] Several randomized, controlled trials have been performed to study the effect of switching antiretroviral regimens (sometimes referred to as “switch studies”). In SWITCHMRK 1 and 2, a switch from lopinavir-ritonavir to raltegravir resulted in improved lipid parameters but also a higher rate of virologic failure in the raltegravir group.[47] In the ATAZIP study, patients switching from lopinavir-ritonavir to atazanavir plus ritonavir also experienced an improvement in lipids, without sacrificing virologic efficacy (subjects in the atazanavir group had fewer virologic or overall treatment failures compared with the lopinavir-ritonavir group).[48] Similarly, in the SWAN study, patients on a variety of protease inhibitor-based regimens were switched to atazanavir-containing regimens (with or without ritonavir), and this resulted in an overall improvement in both lipid parameters and virologic efficacy.[49] An alternative strategy for antiretroviral therapy modification is to add an antiretroviral agent with benign lipid effects to an optimized background regimen; this approach was studied in ACTG 5206, where tenofovir was added as an intensification agent to a stable antiretroviral background and was shown to improve lipid parameters.

**Treatment of Dyslipidemia in Persons with HIV Infection**

The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults comments that individuals with HIV infection have an increased risk of developing ASCVD, but does not make any specific treatment recommendations for this population. A subsequent systematic review of the safety and efficacy of statin therapy in persons with HIV infection concludes that medical providers are in a relatively data-free zone when considering statin therapy, despite the increased cardiovascular risk in persons living with HIV.[41,50] This has contributed to undertreatment of lipid disorders in persons with HIV infection: the prevalence of dyslipidemia among persons with HIV infection is as high as 80%, yet as few as 5% of persons with HIV infection who are on antiretroviral therapy are also taking a statin medication.[50] In addition, studies have shown that the 2013 ACC/AHA Guideline and the adjunctive 10-year ASCVD risk calculator likely underestimate cardiovascular risk in persons with HIV infection even as they expand.
the overall statin-eligible population. Many experts encourage more aggressive management of dyslipidemia and other cardiac risk factors (obesity, smoking, hypertension, diabetes mellitus, etc.) in the persons with HIV infection. The Infectious Disease Society of America (IDSA) issued Guidelines for the Management of Dyslipidemia in HIV-Infected Adults Receiving Antiretroviral Therapy in 2003, which provided a solid review of the pathophysiology of lipid disorders in HIV infection as well as a review of the evidence and suggested stepwise approach to managing lipid disorders in persons with HIV infection; however, this document is now more than 10 years old and has not been updated or replaced. The Primary Care Guidelines for the Management of Persons Infected with HIV, published in 2013, issued the following recommendations regarding HIV-specific lipid management:

- All individuals with HIV infection should have fasting lipid screening at entry to care, prior to and within 1 to 3 months of initiating antiretroviral therapy, and then every 6 to 12 months while on antiretroviral therapy. Individuals who are not on antiretroviral therapy should have annual fasting lipid measurements.
- Patients with abnormal lipid levels should be managed according to the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) published in 2001. These guidelines were subsequently replaced in 2013 by the ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, almost simultaneously with the release of the Primary Care Guidelines for the Management of Persons Infected with HIV. Thus, many experts would recommend using the 2013 ACC/AHA guideline to identify individuals with HIV infection who would benefit from pharmacotherapy for dyslipidemia, acknowledging that neither the NCEP nor the ACC/AHA guidelines are based on any studies in which persons living with HIV are represented.
- If medical therapy is indicated, initial treatment should consist of the lowest possible dose of a statin titrated to tolerability and response. Careful review of the patient’s antiretroviral therapy regimen for possible drug interactions should guide the decision of which statin to start in persons with HIV infection. This guidance differs from the 2013 ACC/AHA recommendation to select a particular statin and dose depending on ASCVD risk stratification.
- Potentially dangerous drug interactions can occur between statin therapy and HIV antiretroviral medications, particularly with HIV protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and the pharmacologic boosters ritonavir and cobicistat. For example, ritonavir and cobicistat can dramatically increase serum levels of simvastatin and lovastatin, thus increasing the risk of statin-related hepatotoxicity, myopathy, and rhabdomyolysis. For this reason, simvastatin and lovastatin are contraindicated in combination with ritonavir- or cobicistat-containing regimens. Conversely, the NNRTI efavirenz induces statin metabolism and thus may decrease the efficacy of some statins.
- In general, pravastatin, low-dose atorvastatin, pitavastatin, and rosuvastatin are less likely to cause drug interactions with antiretroviral medications and are the preferred agents for patients on antiretroviral therapy, particularly regimens containing a PI or NNRTI.
- As in the general population, there are no data to support that routinely adding a nonstatin drug to high-intensity statin therapy provides any incremental cardiovascular risk reduction with an acceptable margin of safety. Use of nonstatin therapy may be considered in high-risk patients (ASCVD, diabetes, or LDL 190 mg/dL or greater) who are intolerant to statins or fail to respond adequately to statins. Combination statin-fibrate therapy has been shown to be safe and effective to treat refractory lipid disorders, though a risk of myopathy persists. No studies have been conducted in persons with HIV infection to address safety or efficacy of statin-niacin combination therapy, but given the risks exposed when this combination was studied in persons without HIV infection, this combination should be used with caution in persons with HIV infection.
- Although statins may confer additional benefits related to decreasing chronic inflammation in
individuals living with HIV, there is currently no indication to use statins except for lipid-lowering therapy and ASCVD prevention in this population. In the SATURN-HIV Trial, rosvuavstatin slowed kidney function decline modestly after 24 weeks of therapy in participants with HIV infection (all of whom had stable LDL less than or equal to 130 mg/dL at baseline).[3,54] Interim analyses of this study population also demonstrated small but statistically significant increases in bone mineral density; however, this benefit was not seen at the end of the study period.[55,56] Ongoing studies, including the ACTG REPRIEVE trial, a randomized double-blind trial of pitavastatin 4 mg versus placebo for primary cardiovascular disease prevention in 6,500 persons with HIV infection, aim to provide further guidance as to optimal use of statin therapy in persons living with HIV.

- Medical providers should address other factors that influence ASCVD, including tobacco use, hypertension, diabetes mellitus, diet, and exercise at all visits.

### Treatment of Hypertriglyceridemia in Persons with HIV Infection

Elevated triglyceride levels are common among persons with HIV infection and deserve special attention. Although the 2011 AHA Scientific Statement on Triglycerides and Cardiovascular Disease defines a normal triglyceride level as less than 150 mg/dL, the 2003 IDSA Guidelines for the Management of Dyslipidemia in HIV-Infected Adults Receiving Antiretroviral Therapy use a triglyceride target of less than 200 mg/dL, and this higher cut-off has been used as the outcome measure in various clinical trials involving persons with HIV infection as well.[53]

- **Non-Pharmacologic Interventions to Lower Triglyceride Levels:** Dietary modification is considered first-line therapy for high triglycerides in the 2011 AHA Scientific Statement on Triglycerides and Cardiovascular Disease and the 2003 IDSA Guidelines for the Management of Dyslipidemia in HIV-Infected Adults Receiving Antiretroviral Therapy, with data from a meta-analysis confirming that a stringent diet can improve triglyceride levels in persons with HIV infection; however, there have been mixed results when diet has been compared to statin or other therapy for the reduction of triglycerides, and there has been scant detail about the triglyceride diets used in the studies.[44,45,57] Exercise, smoking cessation, and aggressive control of hyperglycemia (in the setting of comorbid diabetes) are all additional lifestyle factors that play a role in reducing triglyceride levels.

- **Pharmacologic Management of High Triglyceride Levels:** For individuals in whom dietary modification is insufficient to bring triglyceride levels to goal, fibrates are considered first-line pharmacologic therapy, and fenofibrate is preferred over gemfibrozil due to fewer drug interactions. Second-line therapies include fish oil and niacin. In ACTG 5186, a randomized controlled trial that evaluated fenofibrate (160 mg/day) and fish oil (3 g/day) for the treatment of high triglyceride levels, the mean reductions in triglyceride levels from baseline were 46% in the fish oil group, 58% in the fenofibrate group, and 65% in the combined group; overall, combination therapy was safe and effective, with 22% of study participants achieving a triglyceride level below 200 mg/dL.[58] Monotherapy with niacin alone was proven effective at lowering triglycerides, inducing a median decrease of 153 mg/dL from baseline.[8] Another randomized controlled trial evaluated the effects of fibrate and statin therapy, alone and in combination, on lipid levels.[53] This study confirmed that fibrates are the more effective triglyceride-lowering agent; the statin-fibrate combination did not significantly lower triglycerides compared to fibrate therapy alone and furthermore, combination therapy did not decrease inflammatory markers, such as high-sensitivity C-reactive protein (often used as a biomarker of increased cardiac risk).[59] There is no clinically proven benefit to vitamin E. In general, the management of hypertriglyceridemia in persons with HIV should follow the approach as outlined above for management of hypertriglyceridemia in the general population. The specific management of triglycerides in persons with HIV infection is not addressed in the HIV primary care guidelines but according to the HIV lipid guideline from 2003, initial approach to elevated triglycerides should be as follows:

  - **Triglyceride level 200 to 500 mg/dL and elevated LDL:** Initiate therapy with
statin alone.

- **Triglyceride level greater than 500 mg/dL**: Initiate therapy with fibrates, or alternatively, with fish oil or niacin.

- **Triglycerides Refractory to Fibrate Therapy**: Consider adding fish oil or niacin to fibrate therapy. The addition of statin therapy is unlikely to have significant clinical benefit and increases the risk of myopathy. Another option to treat refractory triglyceride levels is to switch the antiretroviral regimen (balancing the risks and benefits of making such a change, as was addressed in the switch studies above).
Diabetes Mellitus

Overview

Diabetes mellitus affects approximately 12% of the United States population aged 20 years and older and contributes to significant morbidity, decreased quality of life, rising health care costs, and mortality. [21] Patients with diabetes mellitus require frequent monitoring of laboratory values and for the development of microvascular complications, including kidney disease, retinopathy, neuropathy, and atherosclerotic cardiovascular disease.

Current Guidelines

The American Diabetic Association (ADA) maintains updated guidelines pertaining to the screening, diagnosis and management of diabetes, with the most recent version published in 2019. [60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70] Key points from these guidelines include:

- **Indications for Diabetes Screening**: Routine screening for type 2 diabetes mellitus and prediabetes should be considered in all adults who are overweight or obese (BMI 25 kg/m² or greater) and have at least one additional risk factor for diabetes, such as physical inactivity, first-degree relative with diabetes, or high-risk race/ethnicity (Figure 8). [66] In the absence of additional risk factors, overweight and obese adults should be screened starting at age 45 years. If tests are normal, screening should be repeated approximately every 3 years. The U.S. Preventive Services Task Force also recommends screening for type 2 diabetes as part of cardiovascular risk assessment in adults 40 to 70 years of age who are overweight or obese. [71]

- **Diabetes Diagnostic Criteria**: The diagnosis of diabetes mellitus can be made using several different criteria: (1) HbA1c greater than or equal to 6.5%, (2) fasting glucose (fasting defined as no caloric intake for 8 or more hours) greater than or equal to 126 mg/dL, (3) 2-hour plasma glucose greater than or equal to 200 mg/dL during an oral glucose tolerance test using a 75 gram glucose load, or (4) a random glucose greater than or equal to 200 mg/dL in the setting of classic symptoms of hyperglycemia. [66]

- **Definition of Prediabetes**: Individuals are defined as having prediabetes if screening tests reveal on of the following (1) fasting glucose of 100 to 125 mg/dL, (2) a 2-hour plasma glucose level of 140 to 199 mg/dL after an oral glucose tolerance test, or (3) HbA1c of 5.7 to 6.4%. [66] Individuals with prediabetes should be informed of their increased risk of developing type 2 diabetes and cardiovascular disease, and they should be encouraged to pursue lifestyle modifications including weight loss and increased physical activity to lower these risks. [66] Repeat screening should occur annually in this population.

- **Pharmacologic Therapy**: For persons who meet criteria for type 2 diabetes, pharmacologic therapy in addition to lifestyle modifications is warranted. [61] Metformin is the preferred initial pharmacologic agent in the treatment of type 2 diabetes mellitus, as long as it is not contraindicated and the patient can tolerate it. [61] Some individuals with diabetes will require additional oral hypoglycemic agents, insulin, or glucagon-like peptide-1 (GLP-1) agonists. [61] Since there is little data regarding addition of a second agent to metformin, treatment should be individualized and patient centered. The 2019 Guideline has a new approach to injectable therapy, stating that for persons with diabetes in whom atherosclerotic heart disease, heart failure, or chronic kidney disease predominates, the best choice for a second agent may be a GLP-1 receptor agonist or a sodium-glucose cotransporter 2 (SGLT2) inhibitor that has demonstrated cardiovascular risk reduction. [61]

- **Monitoring and Goal for HbA1c**: Ongoing monitoring of HbA1c should occur every 6 months if at treatment goal or every 3 months if not at goal is recommended. [64] The ideal HbA1c target is unclear but recommended targets range from the most stringent goal of less than 6.5 to the least stringent goal of less than 8.0%. [64] A goal HbA1c of less than 7.0% is considered as a reasonable goal for many nonpregnant adults. [64] Less stringent goals
(HbA1c less 8.0%) is considered appropriate for some individuals with diabetes, especially if they have experienced severe glycemia, or other factors are present, such as a short life expectancy or existing major complications from long-standing diabetes.[64] For some individualized persons with diabetes, a HbA1c goal of less than 6.5% is recommended if it can be achieved without significant hypoglycemia.[64] Targeting stringent control is controversial given the finding from a large randomized control trial (ADVANCE) that found no evidence that maintaining a HgbA1c less than 6.5% provided long-term benefit with respect to mortality or macrovascular events.[72]

- **Screening for Complications:** Persons should undergo annual screening for complications of type 2 diabetes, including nephropathy, retinopathy, and neuropathy.[60] Annual screening for chronic kidney disease should consist of urinary albumin (e.g. spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate in persons with type 1 diabetes with duration of 5 years or longer, those with type 2 diabetes, and in all who have comorbid hypertension.[60] Comprehensive and dilated eye examinations and determination for follow-up should be conducted by an ophthalmologist or an optometrist.[60] Persons with type 2 diabetes be assessed for diabetic peripheral neuropathy starting at diagnosis and those with type 1 should undergo assessment 5 years after the diagnosis; thereafter, screening for neuropathy should occur at least annually. Screening for neuropathy should also include screening for distal symmetric polyneuropathy and autonomic neuropathy.[60]

- **Lifestyle Management:** Persons with diabetes should receive individualized counseling for nutritional therapy, psychosocial support, smoking cessation (if indicated) and self-management support.[69] Exercise guidelines recommend, in general, at least 150 minutes per week of moderate-intensity aerobic activity and at least twice-weekly resistance training.[69]

- **Use of Aspirin in Persons with Diabetes:** Those with diabetes who have a history of cardiovascular risk should receive a daily low-dose aspirin (75 to 162 mg).[63] Daily low-dose aspirin may be considered for primary cardiovascular disease prevention strategy in those individuals with diabetes who have increased cardiovascular risk, but this should be a shared decision-making process.[63]

- **Target Blood Pressure in Persons with Diabetes:** The ADA recommends a target blood pressure of less than 140/90 mm Hg in persons with type 2 diabetes who have a 10-year ASCVD risk less than 15%.[63] For hypertensive diabetics who already have ASCVD or who have a 10-year ASCVD risk of greater than 15%, the target blood pressure goal is less than 130/80 mm Hg.[63]

- **Treating Hypertension in Persons with Diabetes:** For individuals with diabetes and hypertension, the ADA recommends therapy with either an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II blocker (ARB), thiazide-type diuretic, or calcium channel blocker; for those with microalbuminuria, an ACE or ARB should be the first-line choice.[63] A meta-analysis has concluded that ACE inhibitors reduce all-cause mortality, cardiovascular events, and heart failure whereas ARBs only reduce the incidence of heart failure.[73]

- **Lipid Screening and Management of Hyperlipidemia:** Lipid screening is advised in adults with type 2 diabetes at baseline and at least every 5 years thereafter.[63] For persons with diabetes who require treatment for lipid disorders, a lipid profile should be obtained at initiation of lipid-lowering therapy, within 4 to 12 weeks after initiation or changing therapy, and yearly thereafter.[63] Increased LDL should be managed aggressively with statin therapy and in accordance with the 2018 ACC/AHA Blood Cholesterol Guideline.[41,63]

**Special Considerations for Persons with HIV**

Persons with HIV have an increased risk of diabetes, which is further heightened by antiretroviral therapy. The Multicenter Cohort Study demonstrated a prevalence of 5% among men with HIV, 7% among men with HIV infection not taking antiretroviral therapy, and 14% among men with HIV taking antiretroviral therapy; after adjustment for body mass index (BMI) and age, this represented a 4-fold increase in the incidence of diabetes in men with HIV taking antiretroviral therapy compared to men without HIV.[74] Traditional metabolic risk factors (elevated triglycerides or LDL, high blood
pressure, high waist to hip ratio) and lifestyle risk factors such as smoking and inactivity can augment the role that HIV and antiretroviral medications play in increasing insulin resistance in persons with HIV. Thus, medical providers should be vigilant in monitoring for glucose abnormalities and be aware of the comorbidities associated with HIV that may make the diagnosis and management of diabetes more challenging. For example, persons with HIV have higher rates of anemia, which can falsely lower HgbA1c levels due to decreased red blood cell survival, as well as higher rates of abnormal renal function and lactic acidosis, which can increase the risk of metformin toxicity. [75] The Primary Care Guidelines for the Management of Persons Infected with HIV make the following recommendations related to diabetes for persons with HIV:[31]

- For all persons with HIV, fasting glucose or HbA1c should be measured at entry into care, prior to starting medications, and repeated within 1 to 3 months after starting antiretroviral therapy.
- For persons with HIV who are taking antiretroviral therapy, using a lower HbA1c cutoff to diagnose diabetes mellitus (5.8% or greater versus the 6.5% or greater cutoff recommended for the general population) increases the sensitivity of the screening test; however, the 6.5% cutoff is still considered the standard for diagnosis in this population.
- Individuals with prediabetes should be managed aggressively with lifestyle modifications per ADA guidelines to prevent progression to frank diabetes.
- In most cases, persons with HIV and mild blood glucose abnormalities can be effectively managed with lifestyle changes that include weight loss, increased exercise, and dietary modification. If therapeutic intervention is warranted, selecting hypoglycemic medications with insulin-sensitizing mechanisms of action are preferred. In general, management should occur according to the ADA guidelines.
- Persons with HIV who have type 2 diabetes should undergo HbA1c level monitoring every 6 months, with a HbA1c goal of less than 7%, which is in accordance with the ADA guidelines.
- In addition to routine monitoring of kidney function (addressed in the section on chronic kidney disease), persons with HIV should have annual monitoring of urine albuminuria in accordance with the ADA guidelines.[76]
- There is no evidence that switching antiretroviral therapy is beneficial for impaired glucose tolerance; however, a careful evaluation for drug interactions should be conducted in these patients as some antiretrovirals can indirectly contribute to increased plasma glucose levels. For example, protease inhibitors and cobicistat can increase drug levels of quetiapine or certain corticosteroids (inhaled or oral) and thus cause hyperglycemia.
Chronic Kidney Disease

Overview

Based on NHANES data collected from 2011 to 2014, the prevalence of chronic kidney disease among adults in the United States older than 20 years was approximately 15%. The National Kidney Foundation defines chronic kidney disease (CKD) as abnormalities of kidney structure or function present for greater than 3 months, with implications for health. Historically, CKD has been classified by stages (stage 1 through stage 5) based on glomerular filtration rate (GFR) (Figure 9), but the most recent National Kidney Foundation guidelines recommend classifying CKD by cause, glomerular filtration rate (GFR) category, and albuminuria category in recognition of the fact that GFR and albuminuria are complementary and independent predictors of important clinical outcomes, including CKD progression, ESRD, and all-cause mortality (Figure 10).

Current Renal Guidelines

The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) has recently published updated guidelines for evaluation and management of chronic kidney disease. Full discussion of these guidelines is beyond the scope of this lesson, but the National Kidney Foundation work group has issued a useful commentary.

Special Considerations for Persons with HIV

As in the general population, chronic kidney disease has significant implications for outcomes including end-stage renal disease (ESRD), cardiovascular disease, and all-cause mortality. The risk of developing chronic kidney disease is higher in patients with CD4 less than 200 cells/mm$^3$, elevated HIV RNA levels, black race, older age, female sex, injection drug use, or comorbidities such as diabetes, hypertension, and hepatitis C.

Guidelines for Persons with HIV

The HIV Medical Association (HIVMA) has provided a comprehensive HIVMA CKD Clinical Practice Guideline that address renal disease among persons with HIV and it provides management recommendations. Staging for chronic kidney disease in the HIVMA CKD Clinical Practice Guideline follows the KGIDO definitions outlined earlier in this topic. Key points from the HIVMA document are included here.

Baseline Evaluation and Routine Monitoring for Persons with HIV

- All persons with HIV should have measurement of glomerular filtration rate (GFR) at time of HIV diagnosis, when antiretroviral therapy is initiated or changed, and at least twice annually in stable patients.
- All persons with HIV should have a urinalysis or a quantitative measure of albuminuria/proteinuria measurement at baseline, when antiretroviral therapy is initiated or changed, and at least once annually in stable patients. Proteinuria of 1+ or greater on urinalysis should be quantified with either albumin-to-creatinine ratio (often called a urine microalbumin test) or a protein-to-creatinine ratio. Both the albumin-to-creatinine ratio and protein-to-creatinine ratio can be obtained from a spot urine sample or from a 24-hour urine collection. Note the Adult and Adolescent ARV Guidelines recommend more frequent measurement of chemistry panels (every 3 to 6 months), and urinalysis (every 6 months), in persons taking tenofovir DF or tenofovir alafenamide.
- Workup for new-onset kidney disease in persons with HIV should include serum chemistry panel, urinalysis, quantitative measure of albuminuria, assessment of glucose and blood pressure control, markers of proximal tubular dysfunction, renal sonogram, and medication
review to determine any agents that may be nephrotoxic or require renal dosing.

**Referral for Persons with HIV and Renal Impairment**

- Persons with HIV should be referred to a nephrologist if GFR declines more than 25% from baseline (and to a level less than 60 mL/min/1.73m²) that fails to resolve with removal of any potential nephrotoxic drugs. Additional indications for referral include albuminuria greater than 300 mg/day, hematuria with either proteinuria or elevated blood pressure, and advanced kidney disease with GFR less than 30 mL/min/1.73m².
- Individuals with HIV and end-stage renal disease should undergo evaluation for their potential candidacy for renal transplantation.

**Pharmacologic Considerations for Persons with HIV**

- Avoid tenofovir DF (and any coformulations that include tenofovir DF) in persons with a baseline GFR less than 60 mL/min/1.73m².
- In persons with HIV who are taking tenofovir DF and experience a decline in GFR greater than 25% and to a level less than 60 mL/min/1.73m², substitute alternative antiretroviral drug(s) for tenofovir DF.
- Statin therapy should be given to all persons with HIV who have pre-ESRD, in accordance with the 2013 ACC/AHA Blood Cholesterol Guideline. The cholesterol guideline recommends statin therapy for any patient with a 10-year cardiovascular disease risk greater than 7.5%, a threshold that is generally met by having chronic kidney disease, according to a pooled analysis of population-based studies. Although there are no studies of statin therapy in patients with both HIV and chronic kidney disease, theHIVMA CKD Clinical Practice Guideline cite evidence of statin benefit in persons without HIV who have chronic kidney disease. There is also accumulating evidence that statin therapy slows kidney function decline in persons with HIV on antiretroviral therapy. Because studies of patients with ESRD on hemodialysis have not shown a reduction in cardiovascular events or mortality from statin therapy, statins are not recommended in this group (regardless of HIV status).
- Persons with HIV and chronic kidney disease should be considered candidates for low-dose aspirin (75 to 100 mg/day). Although the benefit of aspirin use to prevent CVD for persons with HIV has not been established, in the post-hoc analysis of the Hypertension Optimization Trial, in persons without HIV with GFR less than 60 mL/min/m², aspirin 75 mg daily was associated with significantly fewer CVD events and lower all-cause mortality, and the survival benefit increased in lower GFR categories.
- Use the CKD-Epidemiology collaboration (CKD-EPI) or Cockcroft-Gault equation to estimate creatinine clearance when dosing antiretroviral therapy or other drugs that may require renal dosing. See the Creatinine Clearance Calculator and the Glomerular Filtration Rate (GFR) Calculator in the Tools and Calculator section of this web site.

**HIV-Associated Nephropathy (HIVAN)**

All individuals with HIV-associated nephropathy (HIVAN) should receive treatment with effective antiretroviral therapy at diagnosis. Antiretroviral therapy should not be withheld due to severity of renal dysfunction or due to status of CD4 count. For refractory HIVAN, treatment may include ACE inhibitor or ARB, and possibly also corticosteroids.

**Antiretroviral Therapy and Chronic Kidney Disease**

Certain antiretroviral agents, particularly tenofovir DF, can lead to an increased risk of developing CKD. Nephrotoxicity from tenofovir DF most frequently causes a proximal tubular nephropathy, which rarely can progress to Fanconi syndrome. Several studies suggest that the risk for tenofovir DF-related kidney injury increases in the setting of older age, lower body weight, diabetes, hypertension, and with concomitant use of ritonavir-boosted protease inhibitors. A recent
study reported that Fanconi syndrome was only associated with concomitant use of lopinavir-ritonavir and a lower creatinine clearance at the time of initiation of tenofovir DF.[86] Two randomized trials and several observational studies reported greater GFR decline when tenofovir DF was combined with ritonavir-boosted protease inhibitors or unboosted atazanavir.[76] With antiretroviral-associated nephrotoxicity, full renal recovery does not always occur after withdrawal of the offending drug.

**Evaluating Tenofovir DF-Associated Nephrotoxicity**

As noted above, the HIVMA CKD Clinical Practice Guidelinerecommends avoiding tenofovir DF in persons with a GFR less than 60 mL/min/1.73m².[76] For individuals who develop renal dysfunction in the setting of tenofovir DF use, it can be challenging to determine whether tenofovir DF is the cause of the renal dysfunction. Measuring serum or urinary markers of proximal tubular dysfunction may be helpful in this scenario (Figure 11).[76]

- Two indicators in particular are highly specific markers of proximal tubular dysfunction: (1) glycosuria with normal serum glucose, and (2) urinary phosphorus wasting with low serum phosphorus. Additional markers that suggest proximal tubular dysfunction include serum parameters (hypokalemia and decreased serum bicarbonate) and urinary abnormalities (urine albumin-to-protein ratio less than 0.4).

- Phosphorus wasting can be determined by fractional excretion of phosphate. Normal fractional excretion of phosphate is generally defined as less than 10% and impaired fractional excretion of phosphate is defined as above 20%; thus, a fractional excretion of phosphate above 20% raises the likelihood of tenofovir toxicity whereas a result below 10% makes tenofovir toxicity unlikely.[76] See the [Fractional Excretion of Phosphate Calculator](#) in the Tools and Calculators section.

- Proteinuria is not specific for proximal tubular dysfunction but should also be included in the workup because data suggest that a lower albumin-to-protein ratio of less than 0.4 may be useful in distinguishing proteinuria due to proximal tubular dysfunction (secondary to tenofovir toxicity) from proteinuria due to glomerular disease.[76]

**Criteria for Discontinuing Tenofovir DF**

Regardless of the cause, the HIVMA CKD Clinical Practice Guideline states that tenofovir DF should be discontinued in persons with HIV who experience a decline in GFR greater than 25% and to a level less than 60 mL/min/1.73m², but this is particularly important when there is evidence that tenofovir DF is the culprit (e.g. evidence of proximal tubular dysfunction or new-onset or worsening proteinuria).[76]

**Medications Used in HIV Care that May Cause Benign Elevations in Serum Creatinine**

In contrast to tenofovir DF-induced changes in renal function that generally signify kidney damage, the medications bictegravir, cobicistat, dolutegravir, rilpivirine, and trimethoprim may decrease tubular creatinine secretion and raise serum creatinine (0.1 to 0.2 mg/dL) without altering actual renal function.[31,76]
Osteoporosis

Overview

An estimated 53 million men and women in the United States have osteoporosis or low bone density, and up to 50% of postmenopausal white women and 20% of men suffer an osteoporosis-related fracture during their lifetime.\[87\,88\,89\,90\] The U.S. Preventive Services Task Force reported that in 2012 an estimated 12 million Americans were living with osteoporosis of the hip.\[89\] Risk factors for osteoporosis and associated fractures include increasing age, female sex, postmenopause, hypogonadism or premature ovarian failure, low body weight, personal or family history of osteoporotic fracture, tobacco or alcohol use, rheumatoid arthritis, vitamin D deficiency, low calcium intake, falling, immobilization, as well as prolonged exposure to certain medications (such as glucocorticoids, anticoagulants, anticonvulsants, aromatase inhibitors, cancer chemotherapeutic drugs, and gonadotropin-releasing hormone agonists). Risk of osteoporosis differs depending on ethnic background with higher rates seen in white Americans compared to black Americans.\[90\] Osteoporosis is associated with chronic pain, disability, decreased quality of life, and increased mortality.

Screening for Osteoporosis

There is convincing evidence that screening for osteoporosis has predictive value for osteoporotic fractures in both women and men, and therapies are available to reduce fracture risk. Most commonly, screening is performed with measurement of bone mineral density by dual-energy x-ray absorptiometry (DXA) of the hip and lumbar spine. In addition, the University of Sheffield, UK developed the Fracture Risk Assessment (FRAX) tool to estimate 10-year osteoporotic fracture risk based on age, race, body mass index (BMI), secondary causes of osteoporosis, personal and parental fracture history, tobacco and alcohol use, and previous DXA results if available. The FRAX tool has been studied throughout the world and provides country-specific risk assessment, which can be used to select appropriate candidates for osteoporosis screening and treatment.

Current Guidelines

Screening Recommendations

In the general population, the USPSTF guidelines from 2011 recommend screening for osteoporosis in all women aged 65 years and older and in women aged 50 to 64 years whose fracture risk is equal or greater than that of a 65-year-old white woman without additional risk factors (specifically greater than or equal to a 9.3% 10-year risk for any osteoporotic fracture accessing the FRAX Calculation Tool (then selecting the United States and the appropriate race).\[89\] The USPSTF states there is insufficient evidence to assess the benefit of routine screening of men for osteoporosis in the general population.\[89\] In contrast, guidelines issued by the National Osteoporosis Foundation recommend that all men age 70 years and older and men age 50 to 69 years with increased risk for osteoporosis should undergo bone mineral density screening with DXA scan.\[87\]

Management Recommendations

In 2017, the American College of Physicians (ACP) released an evidence-based clinical practice guideline titled Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women, which recommends treating women with osteoporosis with bisphosphonate (including alendronate, risedronate, or zoledronic acid) or denosumab therapy, and avoiding use of hormonal therapy or selective estrogen receptor modulators to prevent osteoporotic fractures.\[88\] Treatment should generally be discontinued after 5 years, and monitoring for progression of osteoporosis during treatment is not recommended. Continuing treatment after the initial five years is controversial, but may be beneficial for some patients, particularly those whose bone mineral density remains in the
osteoporotic range after five years of treatment.\cite{91,92} Men with osteoporosis should be treated with bisphosphonates, though data is limited in this population. The guideline also addresses the complexities of treating women with osteopenia, and it recommends engaging women 65 years of age or older who are at a high risk for fracture (i.e. T-score between -2.0 and -2.5) in a discussion of risks and benefits of treatment, taking into account individual patient preferences and fracture risk profile. The National Osteoporosis Foundation more specifically recommends initiating treatment in women and men with osteopenia age 50 years and older with a 10-year hip fracture risk greater than or equal to 3% or a 10-year major osteoporosis-related fracture risk greater than or equal to 20% based on the United States FRAX tool.\cite{87}

**Special Considerations for Persons with HIV**

Lower bone density is more prevalent among persons with HIV, which has been largely explained by lower body weight and increased smoking rates but also by HIV-related factors.\cite{10,93,94,95} Specific osteoporosis risk factors that are unique to persons with HIV infection include increased inflammation, altered bone metabolism, and antiretroviral-related toxicities.\cite{96} Initiation of antiretroviral therapy is associated with a 2 to 6% decrease in bone mineral density during the first 2 years of therapy, which varies with the specific antiretroviral regimen used: tenofovir DF and boosted protease inhibitors, in particular, have been linked to greater loss of bone density compared with other antiretroviral agents.\cite{97,98} In contrast, tenofovir alafenamide does not cause significant loss of bone mineral density.\cite{99,100} Emerging data suggest that statin therapy improves bone mineral density in the general population, and the SATURN-HIV trial concluded that use of statin therapy in individuals with HIV is associated with significant increases in bone mineral density, but it worsened insulin resistance.\cite{55,56} Larger and longer studies in persons with HIV are needed to determine whether statins prevent fractures. At this point, statins are not indicated for primary treatment of low bone mineral density, but may have a positive effect on bone health when used for its lipid-lowering effect.\cite{55,56} The following summarizes recommendations from the HIVMA Primary Care Guidelines and the Recommendations for Evaluation and Management of Bone Disease in HIV.\cite{31,97}

**Screening Recommendations for Persons with HIV**

- All postmenopausal women with HIV and men age 50 years and older with HIV should undergo bone mineral density screening with a DXA scan. Bone mineral density should also be assessed with a DXA scan in all adults with HIV who have a major risk factor for fragility fracture, including personal history of fragility fracture, chronic glucocorticoid treatment (greater than or equal to 5 mg of prednisone daily or equivalent for at least 3 months), or high risk of falls.
- In men with HIV 40 to 49 years of age and premenopausal women with HIV 40 years of age and older without a major risk factor for osteoporotic fracture, clinicians should assess fracture risk using the Fracture Risk Assessment Tool (FRAX Calculation Tool). Risk assessment should be performed every 2 to 3 years or when a new clinical risk factor develops. When using the FRAX tool, some experts recommend checking the “secondary osteoporosis” box to better estimate the increased risk of osteoporosis conferred by HIV. If the FRAX tool determines the 10-year risk of major osteoporotic fracture to be greater than 10% in this population, a DXA scan should be performed.
- When interpreting DXA results, use T-scores for postmenopausal women and men age 50 years and older, and use Z-scores for persons younger than age 50 years.
- Optimal screening intervals (for DXA or FRAX assessment) are not clear for persons with HIV. Consider repeat DXA scanning after 1 to 2 years for individuals who have advanced osteopenia (T-score -2.0 to -2.49) and after 5 years in those with mild-to-moderate osteopenia (T-score of -1.01 to -1.99). Some experts suggest rescreening persons with an initial normal DXA after 15 years based on data in the general population; consider repeating a DXA scan sooner in persons with a new fragility fracture or new risk factors for osteoporosis.
Measurement of serum or urine markers of bone turnover or inflammation for screening or treatment monitoring is not recommended routinely in persons with HIV.

Management Recommendations for Persons with HIV

- Patients with osteoporosis (or at risk of osteoporosis) should, if possible, avoid tenofovir DF or boosted protease inhibitors.
- Dietary management strategies for high-risk patients should be employed, which include ensuring adequate calcium intake (1000 mg daily for men 50 to 70 years of age, 1200 mg daily for men 71 years of age and older and women 51 years and older) and vitamin D supplementation for vitamin D insufficiency (serum 25-hydroxy vitamin D level less than 20 ng/mL) and for vitamin D deficiency (serum 25-hydroxy vitamin D level less than 10 ng/mL). Of note, vitamin D screening is recommended in all individuals with low bone mineral density or history of a fragility fracture, but may be considered in persons who have any of major risk factors for low vitamin D levels (e.g. dark skin, dietary deficiency, avoidance of sun exposure, malabsorption, obesity, chronic kidney disease, or treatment with regimens containing efavirenz).
- Vitamin D supplementation should be titrated to a target serum 25-hydroxy vitamin D level of approximately 30 ng/mL.
- Lifestyle modifications for persons with osteopenia or osteoporosis include regular weight-bearing and muscle strengthening exercise, avoidance of falls, smoking cessation, and reduction in alcohol consumption.
- When interpreting DXA results, use T-scores for postmenopausal women and men age 50 years and older, and use Z-scores for persons less than 50 years of age.

Additional Evaluation for Persons with HIV

- For persons with HIV who have osteopenia or osteoporosis, possible treatable secondary causes for decreased bone mineral density should be identified and addressed; these secondary causes include smoking, alcohol use, sedentary lifestyle, low BMI, exposure to medications associated with bone loss (glucocorticoids, phenytoin, proton pump inhibitors, thiazolidinediones), vitamin D deficiency, renal disease, hyperparathyroidism, thyroid disease, and hypogonadism.
- It is important to rule out osteomalacia (softening of the bones due to demineralization, which can be caused by tenofovir DF-induced renal phosphate wasting and/or vitamin D deficiency) before treating with bisphosphonates; low vitamin D and calcium supplementation can also blunt the response to bisphosphonates and ideally should precede initiation of bisphosphonate therapy.

Pharmacotherapy Recommendations

- In general, the management of osteopenia or osteoporosis in persons with HIV should be should follow established guidelines for the general population without HIV; several exceptions exist as outlined below.[97]
- In 2017, the American College of Physicians (ACP) released an evidence-based clinical practice guideline titled Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women, which recommends initiating pharmacotherapy in women and men with osteoporosis.[88] The guideline also addresses the complexities of treating women with osteopenia, and it recommends engaging women 65 years of age or older who are at a high risk for fracture (i.e. T-score between -2.0 and -2.5) in a discussion of risks and benefits of treatment, taking into account individual patient preferences and fracture risk profile. The National Osteoporosis Foundation more specifically recommends initiating treatment in women and men with osteopenia 50 years of age and older who have an estimated 10-year hip fracture risk greater than or equal to 3% or a 10-year major osteoporosis-related fracture risk greater than or equal to 20% (based on the FRAX Calculation Tool for persons living in
When therapy is indicated for persons with HIV at risk for osteoporotic fractures, use alendronate or zoledronic acid, since other therapies have not been adequately studied in persons with HIV. This differs from the 2017 ACP guideline, which also includes risedronate and denosumab as possible initial drugs of choice in the general population.[87] Treatment duration should be individualized, though the 2017 ACP guideline recommends discontinuing treatment after five years in the general population.[88]

Bisphosphonates have been associated with adverse effects including esophagitis, osteonecrosis of the jaw, and atypical femoral fractures; patients on these medications should be monitored clinically for these outcomes.[101, 102]

Some experts would repeat DXA scan after 3 to 5 years of pharmacotherapy, and in individuals with worsening BMD, a new fracture, greater than 1 cm of height loss, or poor adherence to oral bisphosphonate therapy, alternate treatment including intravenous zoledronic acid or teriparatide could be considered, though data are limited with teriparatide and other osteoporosis pharmacotherapies in persons living with HIV.

Individuals receiving bisphosphonates with evidence of worsening bone mineral density, new fractures, suspected osteomalacia, or intolerance of treatment may benefit from referral to a bone health specialist.

Drug Interactions

Drug interactions are not expected with concurrent bisphosphonate and antiretroviral therapy, but caution should be used if calcium supplementation is administered in the form of an antacid such as calcium carbonate, as polyvalent cations can interfere with absorption of atazanavir, bictegravir, dolutegravir, elvitegravir, and rilpivirine. Calcium-containing antacids must be separated from antiretroviral therapy in these situations, and prescribing information for the specific antiretroviral medication should be consulted.
Smoking

Overview

Tobacco use is a worldwide epidemic and is the leading preventable cause of death, disease, and disability in the United States. Data from the Centers for Disease Control and Prevention indicate that about 1 in 5 adults smoke, 21% of adults are exposed to second-hand smoke, and 40% of children 3 to 11 years of age are exposed to second-hand smoke (this number is nearly 70% for non-Hispanic black children in the same age group).[103,104] Tobacco use is a chronic disease and often requires behavioral support, pharmacologic therapy, and multiple attempts to quit. Tobacco use treatments are available and effective, and clinicians should be aware of best practices for counseling and treatment.

Current Guideline

The U.S. Public Health Service released a Clinical Practice guideline for Treating Tobacco Use and Dependence in 2008.[105]. The key points summarized in this guideline are as follows:

- The 5A’s: ask about tobacco use at every visit, advise all tobacco users to quit, assess willingness to quit, assist the individual in quitting (medications, counseling), and arrange follow-up contact.
- Telephonic tobacco quitlines may be able to provide more intensive tobacco cessation counseling (1-800-QUITNOW). Intensive counseling has been proven more effective than brief intervention.
- Seven first-line medications reliably increase long-term smoking abstinence rates: sustained-release bupropion, nicotine replacement products (gum, inhaler, lozenge, nasal spray, patch) and varenicline (Table 3).[105] Certain combination therapies have also been found to be effective, and the combination of counseling and medication is more effective than either alone (Figure 12).[105]

Since the publication of the U.S. Public Health Service guideline in 2008, a Cochrane review found that nicotine replacement therapy, bupropion, and varenicline all improve the chances of successful smoking cessation, and none have an incidence of adverse effects that should mitigate their use.[106] In addition, combination nicotine-replacement therapy (long-acting plus short-acting) and varenicline are equally effective; nortriptyline also increases the chances of quitting, but the FDA has not approved nortriptyline for smoking cessation. These results from the Cochrane review support the current U.S. Public Health Service guideline. Therefore, most experts recommend using either combination nicotine replacement products or varenicline monotherapy as first-line therapy and using sustained release bupropion (with or without nicotine replacement) as an alternative therapy. One randomized, blinded, placebo-controlled clinical trial has demonstrated that varenicline in combination with nicotine replacement is more effective than varenicline alone at achieving tobacco cessation at 12 weeks (end of treatment) and at 6 months, but further studies are needed to assess long-term efficacy and safety.[107] In contrast, another randomized, blinded, placebo-controlled clinical trial found that combining varenicline with sustained release bupropion does not appear to improve long-term smoking abstinence outcomes.[108] Despite early data that raised concerns about the cardiovascular safety of varenicline (and a warning on the package insert about this risk, especially in patients with known cardiovascular disease), a systematic review and meta-analysis concluded in 2016 that these concerns were unfounded.[109]

Special Considerations for Persons with HIV

Individuals with HIV smoke at approximately twice the rate of those without HIV.[110] The excess mortality of smokers is tripled and the population-attributable risk of death associated with smoking is doubled among persons with HIV compared with the population of persons without HIV.[111]
Smoking is linked to multiple medical problems among individuals with HIV, including major cardiovascular disease, non-AIDS-defining cancers, and bacterial pneumonia. A study of women with HIV starting antiretroviral therapy found that smokers had poorer virologic and immunologic responses to antiretroviral therapy, higher risk of death, and higher rates of progression to AIDS. In the HIV Outpatient Study, a prospective observational cohort study of persons with HIV receiving care since 1993, the attributable risk of incident cardiovascular disease events for tobacco smoking was 26.7%, which was similar to the attributable risk associated with baseline CD4 count less than 500 cells/mm$^3$ and perhaps surprisingly, greater than the attributable risks associated with male sex or diabetes. Unfortunately, there is a lack of randomized controlled trial data evaluating the efficacy of interventions for smoking cessation in this population, and the HIVMA Primary Care Guidelines do not address specific interventions related to smoking cessation. There are no significant drug interactions between varenicline and antiretroviral therapy, though interactions can occur between bupropion and antiretrovirals that may result in lower bupropion levels.
Obstructive Lung Disease

Overview

Obstructive lung disease, including both asthma and chronic obstructive pulmonary disease (COPD), is responsible for substantial morbidity and mortality worldwide, and is a leading reason that patients seek medical care in both office and hospital settings. The burden of chronic lung disease affects patients, their families, and society as a whole through lost work and school, lessened quality of life, avoidable emergency room visits, costly hospitalizations, and death.[114] Risk factors for the development of obstructive lung disease include tobacco use, second-hand exposure to smoke, low socioeconomic status, older age, and certain genetics factors.

Current Guidelines

Professional guidelines are available for the management of both asthma and COPD.[114,115] The asthma guidelines emphasize the importance of developing an asthma action plan, identifying environmental triggers and barriers to treatment adherence, and using a stepwise approach to controlling asthma through a combination of medications for both long-term control and quick relief. Guidelines for COPD recommend establishing a diagnosis by spirometry and highlight management strategies, including smoking cessation, inhaled therapies (bronchodilators, anticholinergics, long-acting β-agonists, corticosteroids), pulmonary rehabilitation programs, and supplemental long-term oxygen in select patients.

Special Considerations for Persons with HIV

Relationship between HIV and Chronic Obstructive Lung Disease

Evidence suggests a possible association between HIV and obstructive lung disease, independent of smoking history; poor HIV control (higher plasma HIV RNA levels) and advanced immunosuppression (low CD4 cell count) may contribute to this increased risk.[116] Compared with the prevalence of obstructive lung disease of 6.8% in the general adult population (as estimated by National Health and Nutrition Examination Survey data), studies have shown a prevalence of over 16% among individuals with HIV.[116,117] Investigators have proposed a mechanism whereby HIV enhances the risk of developing obstructive lung disease, but this has not been fully elucidated.[116] Certainly, smoking contributes to this increased risk since individuals with HIV infection are twice as likely to smoke as those without HIV infection. Other factors that may predispose persons with HIV to lung disease include increased CD8 T-cell activation, increased levels of inflammatory cytokines, decreased antioxidant defenses, and more frequent episodes of pneumonia. At the current time, no HIV-specific guidelines exist for the management of obstructive lung disease in this population. In the absence of guidelines, it is reasonable to follow existing asthma and COPD guidelines that pertain to the general population. Smoking cessation should be strongly encouraged in smokers with HIV.

Complications with Inhaled Corticosteroids

Respiratory medications commonly recommended for obstructive lung disease, particularly inhaled corticosteroids, may pose increased risk of complications in persons with HIV. Inhaled corticosteroids are associated with oral candidiasis, bacterial pneumonia, and tuberculosis among individuals without HIV, and this risk could be augmented by HIV. In addition, the metabolism of corticosteroids, especially fluticasone (inhaled) and budesonide (inhaled), is inhibited by protease inhibitors and potentially by cobicistat-containing antiretroviral regimens, and this can cause dangerous systemic levels of corticosteroids and induce serious side effects (Cushing’s syndrome and osteoporosis).[33,116] Salmeterol levels may also increase significantly when used concomitantly with protease inhibitors (particularly ritonavir) or cobicistat, so caution should be used when
considering this long-acting β-agonist due to concerns about increased risk of salmeterol-associated cardiovascular events.[33]
Cancer Screening

Overview

Persons with HIV have an overall increased risk of cancer (and younger age of onset) compared with the general population.\cite{118,119} Research suggests a correlation between HIV-related immunodeficiency and malignancy, possibly through a mechanism of immune dysregulation and decreased immune surveillance; it is now well recognized that a low CD4 cell count increases the risk of malignancy.\cite{120} As persons with HIV are living longer in the current era of effective antiretroviral therapy, a shift has occurred from predominantly AIDS-defining malignancies to non-AIDS-defining malignancies.\cite{121,122,123} Since 2003, the number of non-AIDS-defining malignancies has exceeded the number of AIDS-defining malignancies and consequently, clinicians must be vigilant in surveillance for all forms of malignancy, AIDS-associated or not.

Changing Cancer Epidemiology in Persons with HIV

Data from the ongoing HIV/AIDS Cancer Match Study (which links 15 United States population-based HIV and cancer registries) and the Centers for Disease Control and Prevention showed a sharp increase in non-AIDS-defining cancers among persons with HIV during the 15-year period from 1991 and 2005.\cite{122,124} Kaposi sarcoma and non-Hodgkin's lymphoma (both AIDS-defining malignancies) along with lung cancer (linked to excess tobacco exposure) are currently the most common cancers in persons with HIV.\cite{125} In a recent study examining excess cancers among individuals with HIV in the United States, half of all excess deaths were due to AIDS-defining cancers (Kaposi's sarcoma, non-Hodgkin lymphoma, cervical cancer) and half were due to non-AIDS-defining cancers (lung, anal, liver, oral/pharyngeal cancers); most of these cancers are mediated by viral coinfections; in this same study, there was no excess of colon, breast, or prostate cancer among persons with HIV compared with the general population.\cite{126} Other studies have shown rates of prostate and colorectal cancer are similar to, or slightly lower, than that those in the general population.\cite{122,127} There are no data to suggest that antiretroviral medications are associated with an increased rate of malignancy.\cite{128} Indeed, intermittent antiretroviral therapy (compared with continuous therapy) is associated with an increase in the rate of non-AIDS-defining cancers.\cite{123}

Cancer Surveillance

The shifting spectrum of cancer in persons with HIV underscores the importance of incorporating standardized cancer surveillance practices in the care of the persons with HIV, including those with relatively preserved immune function. The U.S. Preventive Services Database has developed a useful tool to retrieve individualized screening recommendations, including recommendations for cancer screening (Published Recommendations). Note these cancer screening recommendations are for the general population and not specifically for persons with HIV. Recommendations regarding screening for malignancies specific for individuals with HIV have also been issued.

Cancer Screening Recommendations Not Impacted by HIV

Colon Cancer Screening

In the general United States population, colon cancer is the third most common non-skin cancer among men and women, accounting for 50,000 deaths per year.\cite{129} Although persons with HIV may have a slightly higher risk for developing colon cancer, screening for colon cancer in persons with HIV should not be based on HIV RNA levels or CD4 cell count.

- **U.S. Preventive Services Task Force (USPSTF):** The USPSTF recommends screening for colorectal cancer in adults between the ages of 50 and 75 years.\cite{130,131} Decisions regarding colorectal cancer screening for persons aged 76 to 85 years should be
individualized.[130] The USPSTF does not recommend performing routine screening in adults older than 85 years of age.[130] The guidelines provide the following screening options, with the ultimate goal to improve screening rates: stool-based tests (e.g. fecal occult blood testing [FOBT], fecal immunochemical testing [FIT], and FIT-DNA testing); direct visualization tests (e.g. flexible sigmoidoscopy with or without FIT; colonoscopy, and computed tomographic colonography); and serology tests (e.g. circulating methylated SEPT9 DNA).[130] The screening interval depends on the screening modality and the results of the screening tests.

- **U.S. Multi-Society Task Force (MSTF):** In 2017, the U.S. MSTF on Colorectal Cancer issued recommendations for colorectal cancer screening in the general population.[132] These guidelines recommend initiating screening at 50 years of age in average-risk persons; earlier age of onset for screening is recommended in certain high-risk groups, including African Americans, persons with hereditary risk for colon cancer, and those with first-degree family members previously diagnosed with cancer or advanced adenoma (Table 4).[132] The MSTF guidelines rank the existing screening tools (Table 5).[132]

- **Surveillance and Screening Intervals:** In 2012, the U.S. MSTF published updated recommendation for colonoscopy surveillance based on most advanced findings from the baseline colonoscopy (Table 6).[133,134]

### Prostate Cancer Screening

Men with and without HIV have a similar risk of prostate cancer.[118,125,127,135] The reduction in prostate cancer mortality achieved with prostate-specific antigen (PSA)-based screening is small, whereas the potential for patients to experience adverse effects from over-diagnosis and unnecessary treatment is high.

- **U.S. Preventive Services Task Force (USPSTF):** The USPSTF recommends prostate cancer screening should be an individualized decision for men 55 to 69 years of age.[136] The guidelines note that the three most important risk factors for prostate cancer are: older age, African American race, and family history.[136] The recommended screening test, if performed, is a measurement of the level of prostate-specific antigen (PSA) in the blood.[136] For men 70 years of age and older, the USPSTF guidelines do not recommend routinely screening for prostate cancer.[136] The USPSTF recommends that prostate cancer screening in transgender persons should be based on the presence or absence of a prostate, not on the person's identified gender or sexual preference.[136]

### Breast Cancer Screening

In the United States, breast cancer is the most common cancer in women, regardless of race or ethnicity, and is the leading cause of cancer death in Hispanic women; breast cancer is the second leading cause of cancer death among white, black, and Asian women, and the third leading cause of cancer death among American Indian/Alaskan Native women.[137] Although unusual clinical presentations and more rapid progression of breast cancer have been reported among women with HIV, breast cancer prevalence does not appear to be increased in women with HIV.[138] The HIVMA Primary Care Guidelines recommend that women with HIV follow the same breast cancer screening guidelines as for women without HIV.[31] Nevertheless, there are some differences among professional organizations as to the optimal age of initiation and the frequency of breast cancer screening in women with and without HIV.

- **U.S. Preventive Services Task Force (USPSTF):** The U.S. Preventive Services Task Force recommends biennial screening mammography for all women aged 50 to 74 years.[139] The decision to start earlier biennial screening (for women 40 to 49 years of age) should be an individual one, with the option to begin screening in women who place a higher value on the potential benefit than the potential harm of breast cancer screening.[139] These guidelines state there is insufficient evidence to recommend for or against breast cancer screening in women 75 years of age and older.[139]
• **American Cancer Society (ACS):** For women who have an average risk of breast cancer, the American Cancer Society (ACS) recommends annual mammography screening beginning at age 45 years.\[140,141\] Women age 40 to 44 years should have the opportunity to begin annual screening.\[140\] At 55 years of age, women should transition to biannual mammography screening or have the opportunity to begin annual mammography screening.\[140\] The ACS guidelines recommend that screening mammography should continue in women who have overall good health and a life expectancy of at least 10 years.\[140\]

**Cancer Screening Recommendations Specific to HIV**

**Cervical Cancer Screening**

Abnormal cervical cytology is nearly 11 times more common among women with HIV compared with the general female population and is associated with the presence of human papilloma virus (HPV) infection and immune dysfunction. Cervical cancer screening recommendations for women with HIV differ from those in women without HIV, as outlined in the Adult and Adolescent Opportunistic Infection Guidelines.\[142\] Note the guidelines do not fully address screening in transgender persons; for screening purposes, cervical cancer screening should be based on the presence of a cervix rather than on a person’s identified gender or sexual preference.

• **Cervical Cancer Screening at Entry to HIV Care:** Sexually active women with HIV should undergo cervical cancer screening at initial entry to HIV care and again 12 months later; some experts repeat cervical cancer screening after 6 months, consistent with previous guidelines. The screening test used should be determined by the woman’s age, as reviewed below.

• **Age of Onset for Screening:** Although initiation of cervical cancer screening is recommended at age 21 years in the general population, medical providers should screen for cervical cancer in adolescents and young women with HIV within 1 year of onset of sexual activity, and by age 21 at the latest, due to concerns about more rapid progression of cervical abnormalities in women with HIV.

• **Duration of Cervical Cancer Screening:** Cervical cancer screening should continue throughout the life of a woman with HIV, as opposed to the recommendation to stop after age 65 in the general population.

• **Screening in Women Younger than 30 Years of Age:** Annual Pap testing is recommended in women with HIV, but if 3 consecutive screens are normal, Pap tests can be performed every 3 years. Cotesting with HPV is not recommended for routine screening in this age group due to high HPV prevalence, but HPV testing can be done reflexively on abnormal Pap results to direct further evaluation.

• **Screening in Women 30 Years of Age or Older:** Cotesting with Pap and HPV is recommended, and if both tests are negative, the recommended screening interval is every 3 years. If HPV testing is not available, screening recommendations are the same as those in women younger than 30 years of age.

• **Management of Normal Pap Test and Positive HPV Test Results:** If HPV genotype testing is performed and is positive for HPV 16 or 18, colposcopy is recommended. If genotype testing is not performed or is negative for HPV 16 and 18, repeat co-testing in 1 year is acceptable. If either of the repeat Pap or HPV test results is abnormal, colposcopy should be performed.

• **Management of Abnormal Pap Smear Results:** For any Pap test result of low-grade squamous intraepithelial lesion (LSIL) or worse, colposcopy is recommended, regardless of HPV status. If the Pap test demonstrates atypical squamous cells of undetermined significance (ASC-US), HPV testing should be performed in women of all ages with HIV. If the HPV test is positive, the woman should be referred for colposcopy. Women with ASC-US in whom HPV testing is negative or not done may be rescreened with Pap smear and reflex HPV test in 6 to 12 months. If the subsequent result is ASC-US or worse, or if the HPV test is
positive, referral to colposcopy is indicated. For further management of abnormal screening tests, additional guidelines and algorithms are available through the American Society for Colposcopy and Cervical Pathology (ASCCP).[143,144]

- **Screening for Women who have Received HPV Vaccine:** Cervical cancer screening recommendations for women with HIV are not altered if they have received prior HPV vaccine.

**Anal Cancer Screening**

Among individuals with HIV, the incidence of anal cancer is increased in relative incidence compared to the general population.[118] The risk of anal cancer in persons with HIV is particularly high among men who have sex with men, with one study estimating 83% excess cases of anal cancer in this group.[125] HPV has been implicated in the pathogenesis of most anal malignancies. Screening for anal cancer and its precursors remains controversial, with recommendations varying between experts. The Primary Care Guidelines for the Management of Persons Infected with HIV recommend:[31]

- **Indications for Anal Pap Testing:** Anal Pap smears should be performed in men who have sex with men, women with a history of receptive anal intercourse OR abnormal cervical Pap test results, AND all individuals with HIV who have genital warts.[31] Note that this is characterized as a “weak recommendation” and the Adult and Adolescent Opportunistic Infection Guidelines do not recommend either for or against anal cancer screening.

- **Other Modalities for Anal Cancer Screening:** HPV testing is not recommended as part of screening at this time, although an annual digital rectal examination may detect masses associated with anal neoplasm or dysplasia, anal warts, other STDs, and prostate abnormalities and should be considered as part of anal health screening.[31,142]

- **Management of Abnormal Anal Pap Test Result:** Abnormal anal Pap testing (ASC-US or worse) requires follow-up with high-resolution anoscopy and possible biopsy and treatment.[142] When implementing anal Pap testing in clinical settings, it is critical to establish a follow-up plan and ensure access to providers who can deliver these services.
Summary Points

- Cardiovascular diseases are an area of special concern to patients infected with HIV, and cardiovascular risk reduction should be a priority.
- There is increasing overlap in the epidemiology of HIV and cardiovascular disease, with both epidemics disproportionately affecting Hispanics and non-Hispanic blacks.
- Calcium channel blockers should be avoided in patients taking protease inhibitors or cobicistat due to risk of drug interactions.
- There is limited trial data to inform clinical decision-making regarding lipid management in persons with HIV infection, and this has likely led to undertreatment of lipid disorders in this population that is already at higher risk for cardiovascular events.
- For persons with HIV infection on antiretroviral therapy who would benefit from statin therapy, rosuvastatin offers the best combination of safety and efficacy. Low-dose atorvastatin, pitavastatin, and pravastatin are other alternatives. Simvastatin and lovastatin should be avoided due to drug interactions with certain antiretroviral medications.
- Persons with HIV infection should be screened regularly for the development of diabetes mellitus. There is no role for switching antiretroviral regimens in patients with impaired glucose tolerance.
- Persons with HIV infection should have routine laboratory monitoring of renal function. The risk of developing renal disease is higher in those patients with CD4 less than 200 cells/mm$^3$, elevated HIV RNA levels, black race, female sex, older age, or comorbidities such as diabetes, hypertension, and hepatitis C.
- Tenofovir DF carries a risk of nephrotoxicity that is increased in patients taking lopinavir/ritonavir and in patients with lower body weight and lower creatinine clearance at tenofovir DF initiation. Other predictors of tenofovir DF-related renal toxicity are still being studied.
- All postmenopausal women and all men 50 years of age and older should receive DXA scans.
- Assessment of morning testosterone levels is recommended in adult men with HIV who present with decreased bone mass, a low trauma fracture, decreased libido, erectile dysfunction, hot flashes, or sweats, and should be considered for nonspecific symptoms such as depression and fatigue.
- Persons with HIV infection smoke at twice the rate of those without HIV, and smokers with HIV infection who have access to antiretroviral therapy lose more years of life to smoking than to HIV.
- Among persons with HIV infection, Kaposi’s sarcoma and non-Hodgkin lymphoma, and lung cancer are the most common cancers. Since 2003, the number of non-AIDS-defining cancers has exceeded the number of AIDS-defining cancers. The total cancer burden in people with AIDS has increased since 1998.
- Colon cancer, breast cancer, and prostate cancer screening recommendations are the same for persons with HIV infection as for the general population. Due to disproportionate risks of developing cervical and anal cancer among individuals with HIV infection, these cancers warrant different screening protocols.
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47. Eron JJ, Young B, Cooper DA, et al. Switch to a raltegravir-based regimen versus continuation


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[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

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[PubMed Abstract]

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[PubMed Abstract]

[PubMed Abstract]

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[PubMed Abstract]

[PubMed Abstract]


79. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Laboratory testing: laboratory testing for initial assessment and monitoring of patients with HIV receiving antiretroviral therapy. October 25, 2018. [AIDSinfo] -


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[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -


Figures

Figure 1 Kaiser Observational Study (1996-2001): Coronary Heart Disease Hospitalization and Myocardial Infarction

Figure 2 Veterans Aging Cohort: Rates of Acute Myocardial Infarction by HIV Status and Age Group

Figure 3 2017 Hypertension Guidelines: Categories of Blood Pressure for Adults


<table>
<thead>
<tr>
<th>Blood Pressure Category</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120 mm Hg</td>
<td>&lt;80 mm Hg</td>
</tr>
<tr>
<td>Elevated</td>
<td>120 – 129 mm Hg</td>
<td>&lt;80 mm Hg</td>
</tr>
<tr>
<td><strong>Hypertension:</strong> Stage 1</td>
<td>130 – 139 mm Hg</td>
<td>80 – 89 mm Hg</td>
</tr>
<tr>
<td><strong>Hypertension:</strong> Stage 2</td>
<td>≥140 mm Hg</td>
<td>≥90 mm Hg</td>
</tr>
</tbody>
</table>

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
Figure 4 American College of Cardiology-American Heart Association Cholesterol Guidelines for Use of Statin Therapy

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; LCL-C = low density lipoprotein cholesterol. Diabetes mellitus includes type 1 or type 2. Clinical atherosclerotic CVD includes acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.

Figure 5 American College of Cardiology-American Heart Association Cholesterol Guidelines: Intensity of Statins

Source: Grundy SM, Stone NJ, Bailey AL, et al. 2018

<table>
<thead>
<tr>
<th>High-Intensity</th>
<th>Moderate-Intensity</th>
<th>Low-Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowers LDL–C by ≥50%</td>
<td>Lowers LDL–C by 30-49%</td>
<td>Lowers LDL–C by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
<td>Fluvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40-80 mg</td>
<td>Fluvastatin XL 80 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg bid</td>
<td>Fluvastatin 40 mg bid</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 1-4 mg</td>
<td></td>
</tr>
</tbody>
</table>
Figure 6 Classification of Triglyceride Levels


<table>
<thead>
<tr>
<th>Level</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 150 mg/dL</td>
<td>Normal</td>
</tr>
<tr>
<td>150-199 mg/dL</td>
<td>Borderline-high</td>
</tr>
<tr>
<td>200-499 mg/dL</td>
<td>High</td>
</tr>
<tr>
<td>≥ 500 mg/dL</td>
<td>Very high</td>
</tr>
</tbody>
</table>
**Figure 7 Impact of Antiretroviral Medications on Lipid Levels**


<table>
<thead>
<tr>
<th>Class</th>
<th>Impact on Lipids</th>
</tr>
</thead>
</table>
| NRTIs | - Stavudine > Zidovudine > Abacavir: ↑TG and ↑LDL  
- Tenofovir alafenamide > Tenofovir DF: ↓TG, ↑LDL, ↓HDL (no change in TC:HDL ratio) |
| NNRTIs | - Efavirenz: ↑TG, ↑LDL, ↑HDL |
| PIs | - All ritonavir- or cobicistat-boosted PIs: ↑TG, ↑LDL, ↑HDL  
- Lopinavir-ritonavir = Fosamprenavir + Ritonavir: ↑TG  
- Lopinavir-ritonavir > Darunavir + Ritonavir: ↑TG  
- Atazanavir + Ritonavir: ↑TG |
| INSTIs | - Elvitegravir-Cobicistat: ↑TG, ↑LDL, ↑HDL |
| Els | - NA |

Abbreviations: NRTIs = nucleoside reverse transcriptase inhibitors; NNRTIs = nonnucleoside reverse transcriptase inhibitors; PIs = protease inhibitors; INSTIs = integrase strand transfer inhibitors; Els = entry inhibitors
**Figure 8 American Diabetes Association: Criteria for Testing for Diabetes or Prediabetes in Asymptomatic Adults**


<table>
<thead>
<tr>
<th>Criteria for Testing for Diabetes or Prediabetes in Asymptomatic Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing should be considered in overweight or obese (BMI ≥25 kg/m² or ≥23 kg/m² in Asian Americans) adults who have one or more of the following risk factors:</td>
</tr>
<tr>
<td>• A1c ≥5.7% (39 mmol/mol), IGT, or IFG on previous testing</td>
</tr>
<tr>
<td>• First-degree relative with diabetes</td>
</tr>
<tr>
<td>• High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)</td>
</tr>
<tr>
<td>• Women who were diagnosed with gestational diabetes mellitus</td>
</tr>
<tr>
<td>• History of CVD</td>
</tr>
<tr>
<td>• Hypertension (≥140/90 mmHg or on therapy for hypertension)</td>
</tr>
<tr>
<td>• HDL cholesterol level &lt;35 mg/dL (0.90 mmol/L) and/or a triglyceride level &gt;250 mg/dL (2.82 mmol/L)</td>
</tr>
<tr>
<td>• Women with polycystic ovary syndrome</td>
</tr>
<tr>
<td>• Physical inactivity</td>
</tr>
<tr>
<td>• Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)</td>
</tr>
</tbody>
</table>

2. For all patients, testing should begin at age 45 years

3. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.
### Figure 9 GFR Categories in Chronic Kidney Disease


<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&gt;90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60-89</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>G3a</td>
<td>45-59</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>30-44</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15-29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt;15</td>
<td>Kidney Failure</td>
</tr>
</tbody>
</table>
**Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012**

Color key: Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk. Abbreviations: GFR = glomerular filtration rate


<table>
<thead>
<tr>
<th>GFR Categories (mL/min/1.73 m²)</th>
<th>Persistent Albuminuria Categories: Description and Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 Normal or high</td>
<td>A1 Normal/mildly increased</td>
</tr>
<tr>
<td>G2 Mildly decreased</td>
<td>A2 Moderately increased</td>
</tr>
<tr>
<td>G3a Mildly to moderately decreased</td>
<td>A3 Severely increased</td>
</tr>
<tr>
<td>G3b Moderately to severely decreased</td>
<td></td>
</tr>
<tr>
<td>G4 Severely decreased</td>
<td>&lt; 30 mg/g</td>
</tr>
<tr>
<td>G5 Kidney Failure</td>
<td>30-300 mg/g</td>
</tr>
<tr>
<td>G5 Kidney Failure</td>
<td>&gt; 300 mg/g</td>
</tr>
</tbody>
</table>

Green=low risk. Yellow=moderately increased risk. Orange=high risk. Red=severely high risk.
Figure 11 Common Laboratory Indicators of Proximal Tubular Dysfunction


<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Definition of Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum Abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Serum potassium concentration below laboratory reference range</td>
</tr>
<tr>
<td>Low serum bicarbonate</td>
<td>Serum bicarbonate concentration below laboratory reference range</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Serum phosphorous concentration below laboratory reference range</td>
</tr>
<tr>
<td><strong>Urine Abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Urine glucose on dipstick</td>
<td>Glycosuria in the absence of diabetes, or in diabetics with well-controlled blood glucose</td>
</tr>
<tr>
<td>Fractional excretion of phosphate</td>
<td>&lt;10% is normal and &gt;20% is abnormal</td>
</tr>
<tr>
<td>Tubular maximum for phosphate corrected for GFR</td>
<td>Lower than reference value (normal, 2.8–4.4 mg/dL)</td>
</tr>
<tr>
<td>Fractional excretion of uric acid</td>
<td>&lt;15% is normal and &gt;20% is abnormal</td>
</tr>
<tr>
<td>Urine albumin-to-protein ratio</td>
<td>uAPR &lt;0.4 suggests predominantly tubulointerstitial disease, whereas uAPR &gt;0.4 suggests predominantly glomerular disease</td>
</tr>
</tbody>
</table>

Abbreviations: GFR = glomerular filtration rate; uAPR, urine albumin-to-protein ratio;
Figure 12 Effectiveness and Abstinence Rates for Various Medications at 6-Months Post-Quit


<table>
<thead>
<tr>
<th>Medication</th>
<th>Estimated Abstinence Rate* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>13.8</td>
</tr>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Varenicline 2 mg/day</td>
<td>33.2</td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>24.2</td>
</tr>
<tr>
<td>Nicotine spray</td>
<td>26.7</td>
</tr>
<tr>
<td>Nicotine gum (&gt; 14 weeks)</td>
<td>26.1</td>
</tr>
<tr>
<td>Nicotine inhaler</td>
<td>25.4</td>
</tr>
<tr>
<td>Nicotine patch (&gt; 14 weeks)</td>
<td>23.7</td>
</tr>
<tr>
<td><strong>Combination Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Patch + nicotine gum or spray</td>
<td>36.5</td>
</tr>
<tr>
<td>Patch + bupropion SR</td>
<td>28.9</td>
</tr>
</tbody>
</table>

*Abstinence rate 6-months post quit
Table 1.

2017 Hypertension Guidelines: Blood Pressure Targets and Treatment Recommendations

<table>
<thead>
<tr>
<th>BP Category</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Treatment or Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120 mm/Hg and</td>
<td>&lt;80 mm/Hg</td>
<td>Evaluate yearly; encourage healthy lifestyle changes to maintain normal BP</td>
</tr>
<tr>
<td>Elevated</td>
<td>120-129 mm/Hg and</td>
<td>&lt;80 mm/Hg</td>
<td>Recommend healthy lifestyle changes and reassess in 3-6 months</td>
</tr>
<tr>
<td>Hypertension: Stage 1</td>
<td>130-139 mm/Hg or</td>
<td>80-89 mm/Hg</td>
<td>Assess the 10-year risk for heart disease and stroke using the atherosclerotic cardiovascular disease (ASCVD) risk calculator</td>
</tr>
</tbody>
</table>

- If risk is less than 10%, start with healthy lifestyle recommendations and reassess in 3-6 months
- If risk is greater than 10% or the patient has known clinical cardiovascular disease (CVD), diabetes mellitus, or chronic kidney disease, recommend lifestyle changes and BP-lowering medication (1 medication
<table>
<thead>
<tr>
<th>BP Category</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Treatment or Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension: Stage 2</td>
<td>≥140 mm/Hg or ≥90 mm/Hg</td>
<td></td>
<td>Recommend healthy lifestyle changes and BP-lowering medication (initiate with 2 medications of different classes if average BP more than 20/10 mm Hg above blood pressure target); reassess in 1 month for effectiveness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- If goal is met after 1 month, reassess in 3-6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- If goal is not met after 1 month, consider different medications or titration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Continue monthly follow-up until control is achieved</td>
</tr>
<tr>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- If goal is met after 1 month, reassess in 1 month for effectiveness of medication therapy

- If goal is met after 1 month, reassess in 3-6 months
- If goal is not met after 1 month, consider different medication or titration
- Continue monthly follow-up until control is achieved
<table>
<thead>
<tr>
<th>BP Category</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Treatment or Follow-Up</th>
</tr>
</thead>
</table>

Source:

Table 2. **2018 American College of Cardiology/American Heart Association Guideline on the Management of Blood Cholesterol**

**Very High-Risk* of Future ASCVD Events**

<table>
<thead>
<tr>
<th>Major ASCVD Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recent acute coronary syndrome (within the past 12 mo)</td>
</tr>
<tr>
<td>• History of myocardial infarction (other than recent acute coronary syndrome event listed above)</td>
</tr>
<tr>
<td>• History of ischemic stroke</td>
</tr>
<tr>
<td>• Symptomatic peripheral arterial disease (history of claudication with ankle brachial index (ABI) &lt;0.85, or previous revascularization or amputation</td>
</tr>
</tbody>
</table>

**High-Risk Conditions**

<table>
<thead>
<tr>
<th>High-Risk Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age 65 years and older</td>
</tr>
<tr>
<td>• Heterozygous familial hypercholesterolemia</td>
</tr>
<tr>
<td>• History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)</td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td>• Hypertension</td>
</tr>
<tr>
<td>• Chronic kidney disease (eGFR 15-59 mL/min/1.73 m²)</td>
</tr>
<tr>
<td>• Current smoking</td>
</tr>
<tr>
<td>• Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe</td>
</tr>
<tr>
<td>• History of congestive heart failure</td>
</tr>
</tbody>
</table>

*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions

Source:

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Precautions, contraindications</th>
<th>Adverse effects</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained release bupropion</td>
<td>History of seizure</td>
<td>Insomnia</td>
<td>150 mg every morning for 3 days, then 150 mg twice daily (begin treatment 1-2 weeks pre-quit)</td>
<td>7 - 12 weeks</td>
</tr>
<tr>
<td>hydrochloride</td>
<td>History of eating disorders</td>
<td>Dry Mouth, Seizures</td>
<td></td>
<td>Maintenance up to 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine gum</td>
<td>Mouth soreness, Dyspepsia</td>
<td></td>
<td>1-24 cigarettes/day: 2mg gum (up to 24 pieces/day ≥ 25 cigarettes/day: 4 mg gum (up to 24 pieces/day)</td>
<td>Up to 12 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine inhaler</td>
<td>Local irritation of mouth and</td>
<td>6-16 cartridges/day</td>
<td></td>
<td>Up to 6 months</td>
</tr>
<tr>
<td></td>
<td>throat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine lozenge</td>
<td>Nausea, Heartburn</td>
<td></td>
<td>First cigarette smoked ≥30 minutes after awakening: initiate with 2 mg lozenge First cigarette smoked &lt;30 min after awakening: initiate with 4 mg lozenge</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Weeks 1-6: 1 lozenge every 1-2 hours • Weeks 7-9: 1 lozenge every 2-4 hours • Weeks 10-12: 1 lozenge every 4-8 hours</td>
<td>Up to 12 weeks</td>
</tr>
<tr>
<td>Nicotine nasal spray</td>
<td>Nasal irritation</td>
<td>8-40 doses/day</td>
<td></td>
<td>3-6 months</td>
</tr>
<tr>
<td>Nicotine 24-hour patch</td>
<td>Local skin reaction</td>
<td></td>
<td>If smokes ≥10 cigarettes per day</td>
<td></td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>Precautions, contraindications</td>
<td>Adverse effects</td>
<td>Dosage</td>
<td>Duration</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------------</td>
<td>-----------------------</td>
<td>------------------------------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia</td>
<td>- Weeks 1-4: 21 mg/24 hours&lt;br&gt;- Weeks 5 and 6: 14 mg/24 hours&lt;br&gt;- Weeks 7 and 8: 7 mg/24 hours</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Nicotine 16-hour patch</td>
<td>If smokes &lt;10 cigarettes per day</td>
<td>Local skin reaction</td>
<td>- Weeks 1-6: 14 mg/24 hours&lt;br&gt;- Weeks 7 and 8: 7 mg/24 hours</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>If smokes ≥15 cigarettes per day</td>
<td></td>
<td>- Weeks 1-8: 25 mg/16 hours&lt;br&gt;- Weeks 9 and 10: 15 mg/16 hours&lt;br&gt;- Weeks 11 and 12: 10 mg/16 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Weeks 1 to 8: 15 mg/24 hours&lt;br&gt;- Weeks 9-12: 10 mg/16 hours</td>
<td></td>
</tr>
<tr>
<td>Varenicline</td>
<td>Significant kidney disease</td>
<td>Nausea, trouble sleeping</td>
<td>Begin treatment 1 week pre-quit</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>Precautions, contraindications</td>
<td>Adverse effects</td>
<td>Dosage</td>
<td>Duration</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------------------</td>
<td>----------------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>Patients on dialysis</td>
<td>Abnormal or vivid/ strange dreams</td>
<td>Depressed mood and other psychiatric symptoms</td>
<td>- 0.5 mg/day for 3 days, then - 0.5 mg twice/day for 4 days, then - 1 mg twice/day</td>
<td></td>
</tr>
</tbody>
</table>

* The information contained in this table is not comprehensive; see package inserts for additional safety information. Much of the content in this table is based on information in the 2008 U.S. Public Health Service Clinic Practice Guideline for Treating Tobacco Use and Dependence.

Source:

Table 4. **U.S. Multi-Society Task Force on Colorectal Cancer**

### U.S. Multi-Society Task Force Colorectal Cancer Screening Recommendations

<table>
<thead>
<tr>
<th>Group</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average-risk persons</strong></td>
<td>Initiate screening at age 50</td>
</tr>
<tr>
<td><strong>African Americans</strong></td>
<td>Initiate screening at age 45</td>
</tr>
<tr>
<td><strong>Family Colon Cancer Syndrome X</strong></td>
<td>Colonoscopy every 3-5 years beginning 10 years before the age at diagnosis of the youngest affected relative</td>
</tr>
<tr>
<td>Colorectal cancer or an advanced adenoma in two first-degree relatives diagnosed at any age OR colorectal cancer or an advanced adenoma in a single first-degree relative at age &lt;60 years;</td>
<td>Colonoscopy every 5 years beginning 10 years before the age at diagnosis of the youngest affected relative or age 40, whichever is earlier; for those with a single first-degree relative with colorectal cancer in whom no significant neoplasia appears by age 60 years, physicians can offer expanding the interval between colonoscopies</td>
</tr>
<tr>
<td>Colorectal cancer or an advanced adenoma in a single first-degree relative diagnosed at age ≥60 years</td>
<td>Begin screening at age 40 years; tests and intervals are as per the average-risk screening recommendations</td>
</tr>
</tbody>
</table>

**Source:**

Table 5. U.S. Multi-Society Task Force on Colorectal Cancer

Multi-Society Task Force Ranking of Current Colorectal Cancer Screening Tests

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Tier 2</th>
<th>Tier 3</th>
<th>Available Tests Not Currently Recommended</th>
</tr>
</thead>
</table>
| • Colonoscopy every 10 years
  • Annual fecal immunochemical test (FIT) | • CT colonography every 5 years
  • FIT-fecal DNA every 3 years
  • Flexible sigmoidoscopy every 10 years (or every 5 years) | • Capsule colonoscopy every 5 years |
|                     |                     |                                | • Septin 9 |

Source:

<table>
<thead>
<tr>
<th>Baseline Colonoscopy: Most Advanced Finding(s)</th>
<th>Recommended Surveillance Interval</th>
<th>Quality of Evidence to Support the Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No poly</td>
<td>10 years</td>
<td>Moderate</td>
</tr>
<tr>
<td>Small (&lt;10 mm) hyperplastic polys in rectum or sigmoid</td>
<td>10 years</td>
<td>Moderate</td>
</tr>
<tr>
<td>1–2 small (&lt;10 mm) tubular adenomas</td>
<td>5-10 years</td>
<td>Moderate</td>
</tr>
<tr>
<td>3–10 tubular adenomas</td>
<td>3 years</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt;10 adenomas</td>
<td>&lt;3 years</td>
<td>Moderate</td>
</tr>
<tr>
<td>One or more tubular adenomas ≥10 mm</td>
<td>3 years</td>
<td>High</td>
</tr>
<tr>
<td>One or more villous adenomas</td>
<td>3 years</td>
<td>Moderate</td>
</tr>
<tr>
<td>Adenoma with high-grade dysplasia</td>
<td>3 years</td>
<td>Moderate</td>
</tr>
<tr>
<td>Sessile serrated polyp(s) &lt;10 mm with no dysplasia</td>
<td>5 years</td>
<td>Low</td>
</tr>
<tr>
<td>Sessile serrated polyp(s) ≥10 mm</td>
<td>3 years</td>
<td>Low</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sessile serrated polyp with dysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traditional serrated adenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serrated polyposis syndrome*</td>
<td>1 year</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

NOTE: The recommendations assume that the baseline colonoscopy was complete and adequate and that all visible polyps were completely removed.

*Based on the World Health Organization definition of serrated polyposis syndrome, with one of the following criteria: (1) at least 5 serrated polyps proximal to sigmoid, with 2 or more ≥10 mm; (2) any serrated polyps proximal to sigmoid with family history of serrated polyposis syndrome; and (3) >20 serrated polyps of any size throughout the colon.

Source:

### ASCVD Risk Enhancers

<table>
<thead>
<tr>
<th>Clinical Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Family history of premature ASCVD</td>
</tr>
<tr>
<td>• Persistent elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)</td>
</tr>
<tr>
<td>• Chronic kidney disease</td>
</tr>
<tr>
<td>• Metabolic syndrome</td>
</tr>
<tr>
<td>• Conditions specific to women (e.g. preeclampsia, premature menopause)</td>
</tr>
<tr>
<td>• Inflammatory Diseases (especially rheumatoid arthritis, psoriasis, HIV)</td>
</tr>
<tr>
<td>• Ethnicity (e.g. South Asian ancestry)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lipid/Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Persistently elevated triglycerides (≥175 mg/dL, [≥2.0 mmol/L])</td>
</tr>
</tbody>
</table>

#### Heterozygous familial hypercholesterolemia

| • hs-CRP ≥2.0 mg/dL                      |
| • Lipoprotein (a) levels >50 mg/dL (or >125 nmol/L) |
| • apoB ≥130 mg/dL                        |
| • Current smoking                        |
| • Ankle-brachial index (ABI) <0.9        |

**Abbreviations:** ASCVD = atherosclerotic cardiovascular disease; LDL-C = low density lipoprotein cholesterol; hs-CRP = high sensitivity C-reactive protein