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. Consequently, clinicians who provide primary care to persons with HIV infection should have knowledge and skills to recognize and manage common primary care conditions, and implement 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 demonstrate 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 (driven by CD4 count) 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 (PIs) 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 conferred 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.[19,20,21] 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 through 2014, the age-adjusted prevalence of hypertension among persons aged 20 years and older was 34%. The 2017 ACC/AHA 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). The 2017 ACC/AHA Hypertension Guideline also notes the importance of obtaining accurate blood pressure measurements; steps required before and during the measurement include:

- 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 their feet on the floor and support the patient's arm used to obtain 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. The 2017 ACC/AHA 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.

Current Guidelines for the Management of Hypertension

The 2017 ACC/AHA Hypertension Guideline addresses thresholds for treatment initiation and blood pressure goals (Table 1); in addition the guidelines provide recommendations regarding medication treatment approaches. 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 the 2017 ACC/AHA Hypertension Guideline 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 for stage 2 hypertension and an average blood pressure more than 20 mm Hg systolic or 10 mm Hg diastolic above 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 individuals with chronic kidney disease (stage 3 or higher, or stage 1 or 2 with albuminuria [≥300 mg/day, 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 and it increases the risk of acute myocardial infarction.[24,25,26,27,28] In persons with HIV, presence of hypertension is associated with traditional risk factors such as increasing age, obesity, African American race, diabetes, or hyperlipidemia.[25] 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.[29,30] 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.[24] 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.[31]

Management of Hypertension in Persons with HIV

Management of hypertension in persons with HIV is not specifically addressed by the 2017 ACC/AHA Hypertension Guideline referenced above or by the HIVMA Primary Care Guidelines.[23,32] 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 ACC/AHA Hypertension Guideline.[23] 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 recommended if a calcium channel blocker is used with either atazanavir or saquinavir.[33,34]
Hyperlipidemia

Overview

Combined data from the CDC and NHANES shows that approximately 12% of United States adults 20 years of age and older have elevated total cholesterol (defined as greater than or equal to 240 mg/dL). 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%. Elevated cholesterol can lead to atherosclerotic cardiovascular disease (ASCVD), the leading cause of preventable death in the United States.

Lipid-Lowering Agents

Multiple different classes of lipid-lowering agents are now available. The statins remain the primary initial drug class used to treat elevated low-density lipoprotein (LDL) cholesterol.

- **Statins (HMG-CoA Reductase Inhibitors):** The statin class of medication works by inhibiting cholesterol synthesis. Specifically, these medications inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme responsible for converting HMG-CoA to mevalonic acid—a key step in cholesterol synthesis. In addition, statins also increase the number of low-density lipoprotein (LDL) receptors. For treatment purposes, statins are categorized based on their impact on lowering LDL cholesterol (LDL-C): high-intensity lowers LDL cholesterol by at least 50%, moderate-intensity lowers LDL-C by 30 to 50%, and low-intensity lowers LDL-C by less than 30%. Note that some statins have more than one intensity classification based on dose-dependent potency. The statins have the potential to cause hepatotoxicity, myopathy, and new onset diabetes mellitus.

- **Cholesterol Absorption Inhibitors:** Ezetimibe is the only approved medication in this class and it targets the Niemann–Pick C1-like 1 (NPC1L1) protein and thereby selectively inhibits intestinal and biliary cholesterol absorption. The reduced cholesterol absorption causes decreased delivery of intestinal cholesterol to the liver and lower circulating levels of cholesterol. This medication also likely increases the number of cell LDL receptors. Ezetimibe is generally well tolerated and in combination with a statin it lowers LDL cholesterol by an additional 15 to 20%, but raises high-density lipoprotein (HDL) cholesterol minimally (about 1 to 2%). When used, it is typically given in combination with a statin and it is available as a combination pill, ezetimide-simvastatin.

- **Bile Acid Sequestrants:** These agents are large molecular weight polymers that bind to bile acids and bile salts in the intestines, forming an insoluble complex that is excreted in stool. Commonly used bile acid sequestrants include cholestyramine, colesevelam, and colestipol; these medications lower LDL-C by about 15 to 30%. Since these medications are not systemically absorbed, they are generally considered safe, but they may cause bloating and gastrointestinal discomfort. These medications should not be used in someone with biliary obstruction, severe constipation, or severe hypertriglyceridemia.

- **PCSK9 Inhibitors:** The PCSK9 inhibitors are injectable humanized monoclonal antibodies that bind to proprotein convertase subtilisin–kexin type 9 (PCSK9) and thereby decrease degradation of LDL receptors. At the surface of hepatocytes, the LDL receptors act as binding sites for circulating LDL cholesterol—a key step for processing and removal of the LDL. Within the hepatocytes, the LDL receptors have a recycling process, whereby they either return to the cell surface or they are shunted to the lysosome and degraded. The enzyme PCSK9 enhances movement of the LDL receptors to the lysosome. Accordingly, the PCSK9 inhibitors reduce the impact of PCSK9 on LDL receptor shunting to lysosomes, effectively creating more LDL receptors at the surface of the hepatocyte. This class of medications includes alirocumab and evolocumab; both of these agents are very potent, lowering LDL cholesterol by about 40 to 60%. These medications are safe, but require subcutaneous injection and are very expensive.
Fibrates (PPAR Agonists): The fibrates—derivatives of fibric acid—exert their action as an agonist of peroxisome proliferator activated receptor alpha (PPAR-α), a protein that increases gene transcription of proteins that regulate metabolism of triglycerides and HDL. Fibrates can lower triglycerides by approximately 40% and increase HDL by 15%, but they have minimal impact on LDL levels. Commonly used fibrates include bezafibrate, clofibrate, fenofibrate, and gemfibrozil.

Guidelines for the Management of Dyslipidemia

In the United States, the 2018 ACC/AHA Cholesterol Treatment Guidelines are the most important guidelines for the management of hyperlipidemia. These guidelines are extensive and focus on recommendations for primary and secondary prevention of ASCVD in the general population, including persons with diabetes mellitus. The 2018 ACC/AHA Cholesterol Treatment Guidelines discuss multiple factors to consider when deciding whether to initiate lipid-lowering treatment, including prior ASCVD event, age, LDL-C levels, high-risk conditions, and estimated 10-year risk for heart disease (using the American College of Cardiology ASCVD Risk Estimator). In contrast to earlier 2013 ACC/AHA guidelines, the 2018 guidelines recommend follow-up lipid monitoring after initiating statin therapy and modifying treatment, if necessary, until the person receiving treatment achieves target LDL goals.

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. In general, the initial goal of statin therapy for secondary prevention in persons with ASCVD is to achieve a 50% or greater reduction in LDL-C levels and an absolute LDL-C level less than 70 mg/dL. The following summarizes key recommendations in the guidelines for secondary prevention in persons with ASCVD; detailed recommendations are given in the guidelines.

Secondary Prevention in Persons with Clinical ASCVD

All persons with clinical ASCVD should receive counseling for optimizing a healthy lifestyle and all should receive secondary prevention with lipid-lowering therapy. The type and intensity of the lipid-lowering therapy depends on (1) the risk of developing future ASCVD events (not at very high risk versus very high risk) (Table 2), (2) age relative to 75 years of age, (3) tolerance of statin therapy, and (4) results with statin therapy. In general, the initial goal of statin therapy for secondary prevention in persons with ASCVD is to achieve a 50% or greater reduction in LDL-C levels and an absolute LDL-C level less than 70 mg/dL. The following summarizes key recommendations in the guidelines for secondary prevention in persons with ASCVD; detailed recommendations are given in the guidelines.

- **Age 75 Years and Younger (and Not at Very High Risk):** Initiate therapy with a high-intensity statin; if the high-intensity statin is not tolerated, then use a moderate-intensity statin. If while on statin therapy, the LDL-C remains at 70 mg/dL or greater, consider adding ezetimibe.
- **Age Older than 75 Years (and Not at Very High Risk):** Initiate therapy with a moderate- or high-intensity statin.
- **Very High Risk (Regardless of Age):** Individuals who meet criteria for a very high risk of having a future ASCVD event should initially receive a high-intensity or maximally-tolerated statin. If while on statin therapy, the LDL-C remains at 70 mg/dL or greater, adding ezetimibe is reasonable. If the LDL-C remains at 70 mg/dL or greater while on a high-intensity statin and ezetimibe, it is reasonable to add a PCSK9 inhibitor.
Primary Prevention in Adults

The following summarizes key recommendations from the 2018 ACC/AHA Cholesterol Treatment Guidelines regarding lipid management for primary prevention of ASCVD.[35] In general the target LDL-C goals for primary prevention are not as stringent as with secondary prevention.[35] Detailed explanations and recommendations are contained in the guidelines.[35] The following highlights key recommendations in these guidelines.

- **LDL-C of 190 mg/dL or Greater**: For individuals with an LDL-C of 190 mg/dL, no further risk assessment is needed and therapy can be initiated with a high-intensity statin. Further management of these individuals is based on age and response to therapy.

- **Diabetes Mellitus**: For persons with diabetes mellitus aged 40 to 75 years, perform further risk assessment. In general, initiate therapy with a moderate-intensity statin, but consider using a high-intensity statin if the individual has multiple ASCVD risk factors. Consider adding ezetimibe if the 10-year ASCVD risk is greater than 20%. For persons with diabetes who are older than 75 years of age, it is reasonable to continue statin therapy, but the decision to initiate statin therapy at this age should be based on a discussion between the medical provider and the patient.

- **LDL-C of 71 to 189 mg/dL and Age 40 to 75 Years, without Diabetes**: For this group of individuals, the most important first step is to estimate the 10-year ASCVD risk using the American College of Cardiology ASCVD Risk Estimator. In addition, it is important to evaluate for any ASCVD risk enhancers that exist (Table 3). These recommendations are based primarily on the following 10-year risk categories: low risk (less than 5%), borderline risk (5% up to 7.5%), intermediate risk (7.5% up to 20%), and high risk (20% or greater). For all of these categories, a “Risk Discussion” is recommended to decide whether statin therapy should be initiated. In general, the higher the 10-year ASCVD risk category and the greater number of concomitant ASCVD risk enhancers, the more likely that treatment with a statin should be recommended.

Management of Hypertriglyceridemia

Elevated triglycerides can also increase the risk of cardiovascular disease. The 2018 ACC/AHA Cholesterol Treatment Guidelines outlines two categorizes of elevated triglycerides: (1) moderate hypertriglyceridemia (fasting or nonfasting triglycerides 150 to 499 mg/dL) or severe hypertriglyceridemia (fasting triglycerides 500 mg/dL or greater).[35] The following summarizes key recommendations from the 2018 ACC/AHA Cholesterol Treatment Guidelines regarding lipid management for primary prevention of ASCVD.[35] Detailed explanations and recommendations are contained in the guidelines.[35]

- **Adults 20 Years of Age and Older and Fasting or Nonfasting Triglyceride Level 175 to 499 mg/dL**: For this population, clinicians should focus on addressing and modifying lifestyle factors, as needed and optimally managing secondary factors, such as diabetes mellitus, chronic liver or kidney disease, or hypothyroidism. In addition, patients should, if possible, stop taking any medication that may increase triglycerides.

- **Adults 40 to 75 years of age with Moderate or Severe Hypertriglyceridemia and ASCVD risk of 7.5% or Higher**: For this group, these guidelines suggest it is reasonable to reevaluate the ASCVD after the individual addresses lifestyle and secondary factors; if triglycerides are persistently elevated, and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy.

- **Adults 40 to 75 years of age with Severe Hypertriglyceridemia and ASCVD risk of 7.5% or Higher**: For this group with severe hypertriglyceridemia, a reasonable approach is to address any potential reversible causes of hypertriglyceridemia and initiate lipid-lowering therapy with a statin.

- **Adult with Severe Hypertriglyceridemia, especially Fasting Triglyceride Levels of 1,000 mg/dL or Greater**: The guidelines suggest it is reasonable to first address other
causes of hypertriglyceridemia; if triglyceride levels remain elevated or increase, then implement a very low-fat diet, avoid alcohol and refined carbohydrates, increase consumption of omega-3 fatty acids, and start fibrate therapy if necessary to prevent pancreatitis.

Special Considerations for Persons with HIV

Although the association between HIV and elevated ASCVD risk has been documented and is discussed and listed as an ASCVD risk enhancer in the 2018 ACC/AHA Cholesterol Treatment Guidelines, HIV has not been incorporated into formal risk assessment recommendations.[7] In addition, large studies evaluating clinical end points for cardioprotective therapy in people with HIV have not been published, and long-term data on cardiovascular disease incidence in the modern antiretroviral therapy era is lacking.[7] The AIDS Clinical Trials Group (ACTG) Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) trial is an ongoing randomized, double-blind, international trial of pitavastatin 4 mg versus placebo for primary cardiovascular disease prevention in more than 7,500 persons with HIV, with an aim to test whether statin therapy reduces the risk for major adverse cardiovascular events in persons with HIV.[45,46]

Mechanism of Lipid Disorders Associated with HIV

The pathophysiology of cardiovascular disease and dyslipidemia in HIV is multifactorial—it has been associated with traditional risk factors, such as hypertension, diabetes mellitus, dyslipidemia, family history, and tobacco use, as well as with HIV itself and antiretroviral therapy.[3,9] Possible mechanisms suggested include genetic factors, increased triglycerides, insulin resistance, increased activity of various hepatic enzymes, and abnormal HDL metabolism.[47,48] Patient lifestyle and environmental factors may also contribute, as increasing rates of obesity and metabolic syndromes have been observed in people with HIV, both related to antiretroviral therapy and independent of antiretroviral therapy.[3,13] Chronic HIV can lead to abnormalities in lipid levels, vascular stiffness, inflammation, and immune activation even with effective antiretroviral therapy and virologic suppression.[49] Compared to individuals without HIV, people with HIV have been shown to have a higher prevalence of atypical, high-risk, noncalcified coronary plaques.[3,49]

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 strand transfer inhibitors (INSTIs) exerting the least lipid effect; within classes, certain agents are recognized to cause more adverse lipid effects than others (Figure 5).[47,50] If an individual with HIV has abnormal lipid levels while taking antiretroviral therapy, a review of the antiretroviral regimen should be performed to identify medications that may be contributing to lipid abnormalities, particularly efavirenz, protease inhibitors, and boosting agents (ritonavir and cobicistat).[7] Modern preferred unboosted INSTI-based antiretroviral regimens generally do not adversely impact lipid parameters and switching to an INSTI-based regimen from a boosted-protease inhibitor can improve lipids.[51,52] Tenofovir DF, but not tenofovir alafenamide, typically lowers LDL and triglyceride levels.[53] Although switching the NRTI backbone to one that includes tenofovir DF may improve lipids, this benefit is usually outweighed by the potential adverse renal and bone effects caused by tenofovir DF. 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.[48,50]

General Approach to Management of Hyperlipidemia in Persons with HIV

For multiple reasons, including cardiovascular benefit, all persons with HIV should be receiving antiretroviral therapy.[7] Effective antiretroviral therapy does not completely nullify the adverse
cardiovascular impact from HIV, but it does significantly reduce it. Given that no previous risk assessment models or guidelines have focused on the management of hyperlipidemia in people with HIV, the 2019 AHA Statement on CVD and HIV offers a pragmatic approach to cardiovascular disease risk assessment and prevention in persons with HIV who are receiving fully suppressive antiretroviral therapy.[7]

**Lifestyle Optimization and Management of Other Risk Factors**

All persons with HIV should receive counseling on lifestyle optimization that includes smoking cessation, eating a cardiac-healthy diet, engaging in regular exercise, and limiting alcohol intake to less than 7 drinks per week.[7] In addition, management of other factors that influence ASCVD, including hypertension and diabetes mellitus, should be optimized.[7]

**Lipid-Lowering Therapy in Persons with HIV**

Recommendations from the 2018 ACC/AHA Cholesterol Treatment Guidelines for lipid-lowering agents should not be generalized to persons with HIV, as many statin medications have potential significant drug interactions with antiretroviral medications. When lipid-lowering therapy is indicated for persons with HIV, the 2019 AHA Statement on CVD and HIV recommends using one of following three statins:

- Atorvastatin: 10 to 80 mg orally once daily
- Rosuvastatin: 5 to 40 mg orally once daily
- Pitavastatin: 2 to 4 mg orally once daily

**Drug Interactions with Lipid-Lowering Therapies**

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. 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 an NNRTI.[54] Potentially dangerous drug interactions can occur between statin therapy and HIV antiretroviral medications, particularly with HIV PIs, NNRTIs, and the pharmacologic boosters ritonavir and cobicistat.[32, 33, 50, 55, 56, 57] 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.[57]

**Titrating Statin Doses and Monitoring for Adverse Effects**

If a statin is started, the recommendation is to “start low, go slow,” carefully titrating up the dose to minimize side effects and drug interactions while still obtaining response.[7] Particularly with atorvastatin and rosuvastatin, the recommendation is to exercise caution at the high end of the dose range to avoid potential adverse effects from a drug interaction.[7] Although the 2019 AHA Statement on CVD and HIV does not give a target goal for treatment response, the 2018 ACC/AHA Cholesterol Treatment Guidelines recommend using a goal of 50% or greater reduction in LDL-C levels. Once the statin is started, a lipid panel should be checked 4 to 12 weeks after initiation to assess for treatment response, with the goal to slowly titrate up the statin dose if needed to achieve the target LDL level. Following this, lipids should be checked every 6 months if abnormal and once yearly if stable. The statins have the potential to cause muscle and liver toxicity, especially when used at high doses. The dose of the statin should be decreased, or the medication discontinued if the person taking a statin experiences and of the following: severe muscle aches (or unexplained muscle weakness), an increase in serum creatine kinase to greater than 10 times the upper limit of normal,
Use of Nonstatin Therapies

The use of nonstatin therapies may be considered in persons with HIV in the following situations: (1) as adjunctive therapy in combination with a statin in persons who have high cardiovascular risk, (2) persons who are intolerant of statins (2), and (3) persons who fail to respond adequately to statins. In patients with familial hyperlipidemia, a high-dose statin, then ezetimibe, and last a PCSK9 inhibitor can be trialed, if LDL levels remain elevated despite maximal therapy. The use of ezetimibe or PCSK9 inhibitors is limited mainly to secondary prevention in persons at very high risk of an ASCVD event, or those who have not adequately responded to statin therapy.[35]

- **Cholesterol Absorption Inhibitor**: The use of oral ezetimibe, a cholesterol absorption inhibitor, has been studied in persons with HIV.[58, 59, 60] can be considered. There are, however, no specific guidelines for the use of ezetimibe in persons with HIV. It is reasonable to utilize ezetimibe in persons with HIV similar to the recommended use in persons without HIV, mainly as an adjunct to statin therapy in persons who do not adequately respond to or are intolerant to statin therapy.[35] The dose of ezetimibe is 10 mg once daily.

- **Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) Inhibitors**: In persons without HIV, the use of a PCSK9 inhibitor has been shown to dramatically lower LDL levels, even when used in the setting of a background statin.[39, 41] There are, however, sparse data on the safety and efficacy of PCSK9 inhibitors in persons with HIV. An ongoing trial—the Effect of PCSK9 Inhibition on Cardiovascular Risk in Treated HIV Infection [EPIC-HIV]—is evaluating the impact of PCSK9 inhibitors on lipid levels, subclinical ASCVD, and inflammatory markers in persons with HIV. Two PCSK9 inhibitors, both given by subcutaneous injection, are approved for use in the United States: alirocumab and evolocumab.[7] Although PCSK9 inhibitors are potent, safe, and dosed infrequently, they require subcutaneous injections and are very expensive.[39, 41]

Use of Statins to Decrease Chronic Inflammation in Persons with HIV

Although statins may confer additional benefits related to decreasing chronic inflammation in individuals 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, rosuvastatin slowed kidney function decline modestly after 24 weeks of therapy in participants with HIV (all of whom had stable LDL less than or equal to 130 mg/dL at baseline).[61] 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.[62, 63]

Treatment of Hypertriglyceridemia in Persons with HIV

Elevated triglyceride levels are common among persons with HIV. Unlike the 2018 ACC/AHA Cholesterol Treatment Guidelines that define persistently elevated, primary hypertriglyceridemia as 150 mg/dL or greater as an ASCVD risk enhancer, the 2019 AHA Statement on CVD and HIV does not include elevated triglycerides as an ASCVD risk enhancer.[7, 35] Studies in large cohorts have demonstrated that triglyceride levels, which are often labile and sensitive to antiretroviral changes in persons with HIV, either were not predictive of cardiovascular disease end points independently of other cardiovascular disease risk factors, or were associated with marginally elevated ASCVD risk in people with HIV.[7, 64, 65] Although hypertriglyceridemia may not play a large role in ASCVD risk in people with HIV, treatment of severe hypertriglyceridemia (fasting triglyceride levels above 500 mg/dL) is important to prevent acute pancreatitis. An evaluation should take place for secondary causes of hypertriglyceridemia, such as diabetes mellitus, chronic liver disease, kidney disease, nephrotic syndrome, hypothyroidism, and medications with a known impact of increasing triglyceride levels. If the antiretroviral regimen includes one or more medications that are likely elevating triglyceride levels, then consideration should be given to changing the regimen. Since there are no
guidelines for the management of hypertriglyceridemia in persons with HIV, we recommend following the general recommendations in the 2018 ACC/AHA Cholesterol Treatment Guidelines.[35]

- **Non-Pharmacologic Interventions to Lower Triglyceride Levels**: For persons with moderate (150 to 499 mg/dL) or severe (greater than 500 mg/dL) elevated triglyceride levels, non-pharmacologic interventions are indicated. First-line non-pharmacologic options for lowering high triglyceride levels include implementation of a low-fat diet, minimizing intake of refined carbohydrates, avoiding alcohol use, and increasing consumption of omega-3-fatty acids. Management should include addressing obesity and metabolic syndrome.

- **Pharmacologic Management of High Triglyceride Levels**: For individuals with severe hypertriglyceridemia (greater than 500 mg/dL) in whom dietary and non-pharmacologic interventions are insufficient to bring triglyceride levels to goal, pharmacologic intervention may be needed. If the individual with severe hypertriglyceridemia has an ASCVD risk of 7.5% or greater, it is reasonable to initiate therapy with a statin, particularly if the triglyceride levels are less than 1,000 mg/dL. It is also reasonable to start a triglyceride lowering drug (fibrate), especially if the triglyceride levels are greater than 1,000 mg/dL.
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.[22] 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.[66,67,68,69,70,71,72,73,74,75,76] In the most recent version of these guidelines, Standards of Medical Care in Diabetes—2019, key points 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 (Table 4).[72] 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 (USPSTF) 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.[77]

- **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.[72]

- **Definition of Prediabetes**: Individuals are defined as having prediabetes if screening tests reveal any one 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%.[72] 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.[72] 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.[67] 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.[67] Some individuals with diabetes will require additional oral hypoglycemic agents, insulin, or glucagon-like peptide-1 (GLP-1) agonists.[67] 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.[67]

- **Monitoring and Goal for HbA1c**: Ongoing monitoring of HbA1c is recommended every 6 months if at treatment goal or every 3 months if not at goal.[70] 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%.[70] A goal HbA1c of less than 7.0% is considered...
as a reasonable goal for many nonpregnant adults.\[70\] A less stringent goal (HbA1c less than 8.0%) is considered appropriate for some individuals with diabetes, especially if they have experienced severe hyperglycemia, or other factors are present, such as a short life expectancy or existing major complications from long-standing diabetes.\[70\] For some individuals with diabetes, an HbA1c goal of less than 6.5% is recommended, if it can be achieved without significant hypoglycemia.\[70\] Targeting stringent control is controversial given the finding from a large randomized control trial (ADVANCE) that found no evidence that maintaining an HbA1c less than 6.5% provided long-term benefit with respect to mortality or macrovascular events.\[78\]

- **Screening for Complications**: Persons should undergo annual screening for complications of type 2 diabetes, including nephropathy, retinopathy, and neuropathy.\[66\] 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.\[66\] Comprehensive and dilated eye examinations and determination for follow-up should be conducted by an ophthalmologist or an optometrist.\[66\] Persons with type 2 diabetes should 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.\[66\]

- **Lifestyle Management**: Persons with diabetes should receive individualized counseling for nutritional therapy, psychosocial support, smoking cessation (if indicated), and self-management support.\[75\] Exercise guidelines recommend, in general, at least 150 minutes per week of moderate-intensity aerobic activity and at least twice-weekly resistance training.\[75\]

- **Use of Aspirin in Persons with Diabetes**: Those with diabetes and a history of ASCVD should receive a daily low-dose aspirin (75 to 162 mg) as secondary prevention strategy.\[69\] Daily low-dose aspirin may be considered for use as a primary cardiovascular disease prevention strategy for individuals with diabetes who have increased cardiovascular risk, but this should be a shared decision-making process weighing the benefits versus the risk of bleeding.\[69\]

- **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%.\[69\] For persons with diabetes who have ASCVD (or a 10-year ASCVD risk of greater than 15%), the target blood pressure goal is less than 130/80 mm Hg.\[69\]

- **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.\[69\]

- **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.\[69\] 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 initiating or changing therapy, and yearly thereafter.\[69\] Increased LDL should be managed aggressively with statin therapy and in accordance with the 2018 ACC/AHA Cholesterol Treatment Guidelines.\[44,69\]

### 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 without 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.\[79\] 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 HbA1c 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. The HIVMA Primary Care Guidelines make the following recommendations related to diabetes for persons with HIV:[32]

- 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 an 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.[81]
- 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 antiretroviral medication can indirectly contribute to elevated 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.
- Use of metformin with certain antiretroviral medications should also be carefully monitored. For example, concurrent use of metformin with dolutegravir or bictegravir can increase the concentrations of metformin.[56]
Chronic Kidney Disease

Overview

Based on NHANES data collected from 2011 through 2014, the prevalence of chronic kidney disease among adults in the United States older than 20 years was approximately 15%. The 2012 National Kidney Foundation Practice Guideline defines chronic kidney disease 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 6), but the 2012 National Kidney Foundation Practice Guideline recommends classifying chronic kidney disease by cause, glomerular filtration rate 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, end-stage renal disease, and all-cause mortality (Figure 7).

Renal Guidelines

In 2013, the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) published 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 to help health professionals interpret the NKF-KDOQI guidelines, particularly regarding the definition and classification of chronic kidney disease.

Special Considerations for Persons with HIV

As in the general population, chronic kidney disease has significant implications for outcomes including end-stage renal disease, cardiovascular disease, and all-cause mortality. The risk of developing chronic kidney disease is higher in patients with CD4 counts less than 200 cells/mm³, elevated HIV RNA levels, black race, older age, female sex, injection drug use, or comorbidities such as diabetes, hypertension, and hepatitis C. As the HIV epidemic has shifted in the United States, so has the epidemiology of HIV-related chronic kidney disease. Earlier in the epidemic, HIV-related kidney disease predominantly resulted from sequela of HIV infection, such as with HIV-associated nephropathy (HIVAN) or immune complex disease; these disorders most often occurred in persons with untreated HIV, high HIV RNA levels, and low CD4 cell counts. In the current era, since most people with HIV achieve virologic suppression on antiretroviral therapy and have a near normal expected lifespan, the cause of renal disease has shifted from HIV itself to chronic comorbid conditions, such as hypertension, diabetes, and chronic hepatitis C virus infection. In addition, certain antiretroviral agents have played and continue to play a role in causing chronic kidney disease in persons with HIV.

Guidelines and Recommendations for Persons with HIV

The HIV Medical Association (HIVMA) has provided a comprehensive HIVMA CKD Clinical Practice Guideline that addresses 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 KDIGO definitions outlined above. The following summarizes key recommendations regarding the evaluation, management, and prevention of renal disease in persons with HIV, with an emphasis on recommendations in the HIVMA CKD Clinical Practice Guideline.

Baseline Evaluation and Routine Monitoring for Renal Disease

- Persons with HIV should have a creatinine-based estimated glomerular filtration rate (eGFR) at time of HIV diagnosis, when antiretroviral therapy is initiated or changed, and at least
twice a year. [81]

- 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 a year. [81] 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 obtaining a urinalysis every 6 months in persons taking a regimen that includes tenofovir DF or tenofovir alafenamide. [86]

- 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. Persons with HIV diagnosed with chronic kidney disease should have serum phosphate monitoring every 6 months if they are taking a regimen that includes tenofovir alafenamide or tenofovir DF. [86]

**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/1.73 m² that fails to resolve with removal of any potential nephrotoxic drugs. [81] 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/1.73 m².

- Individuals with HIV and end-stage renal disease should undergo evaluation for their potential candidacy for renal transplantation.

**HIV-Associated Nephropathy (HIVAN)**

All individuals with HIV-associated nephropathy (HIVAN) should receive treatment with effective antiretroviral therapy at diagnosis. [81, 84] Antiretroviral therapy should not be withheld due to severity of renal dysfunction or due to status of CD4 cell count. For refractory HIVAN, treatment may include ACE inhibitor or ARB, and possibly also corticosteroids. [81, 84]

**Antiretroviral Therapy and Chronic Kidney Disease**

Certain antiretroviral agents can cause nephrotoxicity, usually through tubular injury with tenofovir DF or crystal nephropathy from atazanavir or indinavir. [85, 87, 88, 89] Antiretroviral therapy-related nephrotoxicity from tenofovir DF most frequently involves a proximal tubular nephropathy, which can progress to Fanconi syndrome. [84] 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 a PI, particularly ritonavir-boosted protease inhibitors. [81, 90] With antiretroviral-associated nephrotoxicity, full renal recovery does not always occur after withdrawal of the offending drug. Tenofovir DF (and any coformulations that include tenofovir DF) should, if feasible, be avoided in persons with a baseline GFR less than 60 mL/min/1.73 m². [81] If tenofovir DF is used in a person with a creatinine clearance less than 50 mL/min, a dose reduction is required. Tenofovir alafenamide, a prodrug of tenofovir, achieves higher intracellular but lower plasma levels of tenofovir than tenofovir DF. In addition, tenofovir alafenamide is not transmitted into the proximal tubular cells via the organic anion transporters 1 and 3. [84, 89] For these reasons, tenofovir alafenamide causes significantly less nephrotoxicity than tenofovir DF. Although tenofovir alafenamide is less nephrotoxic than tenofovir DF, rare cases of nephrotoxicity associated with tenofovir alafenamide have been reported. [91, 92, 93] Tenofovir alafenamide is not recommended for persons with a creatinine clearance less than 30 mL/min.

**Evaluating Tenofovir DF-Associated Nephrotoxicity**
For individuals who develop renal dysfunction in the setting of tenofovir DF use, it can be challenging determining 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 8).[81]

- 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.[81] 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.[81]

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 cause (e.g. evidence of proximal tubular dysfunction or new-onset or worsening proteinuria).[81]

Renal Dosing of Antiretroviral Medications

The CKD-Epidemiology collaboration (CKD-EPI) or Cockcroft-Gault equation should be used 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 website.

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 without altering actual renal function.[32,81] In these settings, a 10 to 20% elevation (or 0.1 to 0.2 mg/dL increase) in serum creatinine may be expected.[94] Elevations in serum creatinine typically occur in the first few weeks of therapy and then plateau.[95] The additive effect of these medications on serum creatinine is unclear (e.g. dolutegravir combined with rilpivirine or dolutegravir combined with cobicistat). After initiation of these medications, a repeat serum creatinine should be obtained within one month to establish a new baseline. If the creatinine is elevated beyond the expected elevation on the first check, repeat the serum creatinine to get a better marker for true renal function.[84,96,97,98]

ASCVD Prevention in Persons with HIV and Renal Disease

- **Aspirin:** Persons with HIV and chronic kidney disease may be considered candidates for low-dose aspirin (75 to 100 mg/day), though risk of bleeding and benefits of primary cardiovascular disease prevention should be weighed in the decision process.[81] Note the 2019 ACC/AHA Primary CVD Prevention Guideline recommends against the use of aspirin for
primary prevention of ASCVD in adults at any age who are at increased risk of bleeding, including those with chronic kidney disease. [99]

- **Lipid-Lowering Therapy:** In accordance with the 2018 ACC/AHA Cholesterol Treatment Guidelines, chronic kidney disease is considered among the ASCVD risk enhancers. [35, 100] Accordingly, many persons with HIV and kidney disease will receive statin therapy. Although there are no studies of statin therapy in patients with both HIV and chronic kidney disease, the HIVMA CKD Clinical Practice Guideline cites evidence of statin benefit in persons without HIV who have chronic kidney disease. [32] There is also accumulating evidence that statin therapy slows kidney function decline in persons with HIV on antiretroviral therapy. [61] 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).
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. The USPSTF reported that by 2020 an estimated 12.3 million persons living in the United States who are older than 50 years of age will have osteoporosis. Risk factors for osteoporosis and associated fractures include increasing age, female sex, postmenopause, hypogonadism, 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. 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, often referred to as the FRAX Calculation 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. If previous DXA results are not available, the calculator can still be used. 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 2018 USPSTF Osteoporosis Screening Guidelines provide recommendations for three groups of adults: (1) women 65 years of age and older, postmenopausal women younger than 65 years of age, and (3) men. Women 65 Years of Age and Older: Screening for osteoporosis should be performed in all women aged 65 years of age and older. A central DXA scan is most commonly used for screening. Postmenopausal Women Younger than 65 Years of Age: Screening for osteoporosis is recommended for postmenopausal women younger than 65 years of age who are at increased risk of osteoporosis, as determined by a clinical risk assessment tool, such as the FRAX Calculation Tool. More specifically, these guidelines recommend using the risk assessment tool for postmenopausal women younger than 65 who have at least one of the following risk factors for developing osteoporosis: parental history of hip fracture, smoking, excessive alcohol consumption, or low body weight. Men: There is no recommendation for or against screening for osteoporosis in men due to insufficient data. Note that 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.
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 bisphosphonates (including alendronate, risedronate, or zoledronic acid) or denosumab therapy, and avoiding use of hormonal therapy or selective estrogen receptor modulators. 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. 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 (e.g. 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.

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. Specific osteoporosis risk factors that are unique to persons with HIV include increased inflammation, altered bone metabolism, and toxicities related to antiretroviral medications. 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. In contrast, tenofovir alafenamide does not cause significant loss of bone mineral density. 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. 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. The following summarizes recommendations from the HIVMA Primary Care Guidelines and the Recommendations for Evaluation and Management of Bone Disease in HIV.

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) specific to their country and the patient’s race/ethnicity. 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 adjust the estimate considering the increased risk of osteoporosis conferred by
HIV. A DXA scan should be performed if the FRAX tool determines the 10-year risk of major osteoporotic fracture to be greater than 10%.

- 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).
- Routine measurement of serum or urine markers of bone turnover or inflammation for screening or treatment monitoring is not recommended for persons with HIV.

**Management Recommendations for Persons with HIV**

- Persons 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 to ensure 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 of age 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 the major known 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.

**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 follow established guidelines for the general population without HIV; several exceptions exist as outlined below.[111]
- 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.[102] 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 the United States).[103]

- 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.[102]
- Treatment duration should be individualized, though the 2017 ACP guideline recommends discontinuing treatment after 5 years in the general population.[102]
- 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.[115,116]
- Some experts would repeat DXA scan after 3 to 5 years of pharmacotherapy, and in individuals with worsening bone mineral density, 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 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.
Tobacco Use and Smoking Cessation

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 use tobacco products, one in four adults are exposed to second-hand smoke, and approximately 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).[117,118,119] 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.

Guidelines for tobacco Cessation

In 2008, the USPSTF released a clinical practice guideline for treating tobacco use and dependence.[120] In 2015, USPSTF released recommendations for Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women.[121] In 2018, the American College of Cardiology (ACC) published a decision pathway, incorporating new evidence, for tobacco cessation treatment in adults.[122] Key points from these guidelines include:

- 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.[122]
- Telephonic tobacco Quitlines may be able to provide intensive tobacco cessation counseling (1-800-QUITNOW). Intensive counseling has been proven more effective than brief intervention.[122]
- 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 5).[122] Certain combination therapies have also been found to be effective, and the combination of counseling and medication is more effective than either alone (Figure 9).[120]
- Within 2 to 4 weeks of a quit attempt, follow-up contact with the individual attempting to quit is recommended, either in person or via telephone or electronic health record portal. This follow-up contact is important for monitoring tobacco cessation treatment, especially since the risk of smoking relapse is high in the immediate period after a quit attempt.[122]
- Evidence regarding the use of electronic nicotine delivery systems (e-cigarettes, vaping) for tobacco cessation is insufficient to make recommendations.[122] Since the release of the 2018 guidelines, multiple reports have generated alarming concerns for the safety of vaping.[123,124,125]
- Evidence is also insufficient to assess the risks versus benefits of pharmacotherapy interventions for tobacco cessation in pregnant women.[122]

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.[126] 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. The conclusions in the Cochrane review are congruent with the major tobacco cessation guidelines.[120,121,122,126]

Most experts recommend using either combination nicotine replacement products or varenicline monotherapy as preferred therapy for smoking cessation treatment, and sustained release bupropion (with or without nicotine replacement) as alternative therapy. Data regarding the combination of nicotine replacement therapy with varenicline are mixed and this combination is not
recommended in the 2018 ACC Tobacco Cessation Guideline, though it is felt to be well tolerated and can be considered an option for those who do not succeed with either combination nicotine replacement therapy or varenicline alone.\cite{122,127,128} 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.\cite{129} 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; later that year, the Federal Drug Administration removed the varenicline black box warning.\cite{122,130}

**Special Considerations for Persons with HIV**

Individuals with HIV smoke at approximately twice the rate of those without HIV.\cite{131} Among persons with HIV, one study in the United States found no difference in the prevalence of smoking in women versus men.\cite{132} This finding contrasts with the overall United States population, where tobacco use is substantially higher among men than women, suggesting that HIV may be associated with a relative increase in smoking among women.\cite{133,134} 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.\cite{135} Smoking is linked to multiple medical problems among individuals with HIV, including major cardiovascular disease, non-AIDS-defining cancers, and bacterial pneumonia.\cite{136} 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.\cite{137} 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.\cite{9}

The major tobacco cessation guidelines do not address smoking cessation in persons with HIV, and the HIVMA Primary Care Guidelines do not provide recommendations for specific interventions related to smoking cessation.\cite{32,120,121,122} In a randomized, double-blind, placebo-controlled trial in France that involved 248 adults with HIV, investigators compared a 3-month course of varenicline in combination with smoking cessation counseling versus placebo with counseling.\cite{138} At 48 weeks following the randomized intervention, a higher proportion of participants in the combination varenicline plus smoking cessation counseling arm had abstained from smoking as compared with the placebo-counseling arm.\cite{138} There are no significant drug interactions between varenicline and antiretroviral therapy, though interactions can occur between bupropion and antiretroviral medications that may result in lower bupropion levels.\cite{34}
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.[139] 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.[140,141] 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, influenza and pneumococcal immunization, 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.[142] Compared with the prevalence of obstructive lung disease in the general population, which ranges from 5.9 to 20.2%,[143,144] studies have shown a prevalence of greater than 16% among individuals with HIV.[142,145] Investigators have proposed a mechanism whereby HIV enhances the risk of developing obstructive lung disease, but this has not been fully elucidated.[142] Certainly, smoking contributes to this increased risk since individuals with HIV infection are twice as likely to smoke as those without HIV. Other factors that may predispose persons with HIV to lung disease include increased CDB 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, including oral candidiasis, bacterial pneumonia, and tuberculosis. In addition, the metabolism of corticosteroids, especially fluticasone (inhaled) and budesonide (inhaled), is inhibited by protease inhibitors, ritonavir, and cobicistat, and concomitant use of these agents this can cause dangerous systemic levels of corticosteroids and induce serious side effects (Cushing’s syndrome and osteoporosis).[34,142] 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.[34]
Cancer Screening

Overview

Persons with HIV have an overall increased risk of cancer (and younger age of onset) compared with the general population.\[146,147,148\] 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.\[149,150\] 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.\[150,151,152,153\] 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 CDC and the ongoing HIV/AIDS Cancer Match Study (which links 15 United States population-based HIV and cancer registries) showed a sharp increase in non-AIDS-defining cancers among persons with HIV during the 15-year period from 1991 through 2005.\[152,154\] Data from projected cancer incidence rates and burden of incident cancer cases in adults with HIV in the United States suggest the trend of increasing non-AIDS-defining cancers will continue, and that by 2030, prostate and lung cancer will be the most common types of cancer in people with HIV.\[148\] Kaposi’s 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.\[148,155\] 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’s 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.\[156\] In this same study, there was no excess of colon, breast, or prostate cancer among persons with HIV compared with the general population.\[156\] Other studies have shown rates of prostate and colorectal cancer similar to, or slightly lower than in the general population.\[152,157\] There are no data to suggest antiretroviral medications cause an increased risk of malignancy.\[150,158\]

Cancer Surveillance

The shifting spectrum of cancer in persons with HIV underscores the importance of incorporating standardized cancer surveillance practices in the care of persons with HIV, including those with relatively preserved immune function. The USPSTF has developed a useful database tool to retrieve individualized screening recommendations, including 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 to individuals with HIV have also been issued.

Cancer Screening Recommendations Not Impacted by HIV

Breast Cancer Screening

In the United States, breast cancer is the most common cancer in women, regardless of race or ethnicity.\[159\] 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.\[160\] The HIVMA Primary Care Guidelines recommend that women with HIV follow the same breast cancer screening guidelines as for women without HIV.\[32\] 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.
• **USPSTF Recommendations for Breast Cancer Screening**: The USPSTF recommends biennial screening mammography for all women aged 50 to 74 years.[161] 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.[161] These guidelines state there is insufficient evidence to recommend for or against breast cancer screening in women 75 years of age and older.[161]

• **American Cancer Society**: For women who have an average risk of breast cancer, the American Cancer Society (ACS) recommends annual mammography screening beginning at age 45 years.[162,163] Women age 40 to 44 years should have the opportunity to begin annual screening.[162] At 55 years of age, women should transition to biannual mammography screening or have the opportunity to begin annual mammography screening.[162] 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.[162]

**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.[164] 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.

• **American Cancer Society**: In 2018, the American Cancer Society issued a guideline update, which recommends screening adults with an average risk of colorectal cancer starting at age 45 years.[165] This is a qualified recommendation (one in which there is clear evidence of benefit but less certainty about the balance of benefits and harms), whereas their recommendation to screen adults aged 50 years and older is a strong recommendation.[165]

• **USPSTF Recommendations for Colorectal Cancer Screening**: The USPSTF recommends screening for colorectal cancer in adults between the ages of 50 and 75 years.[166,167] Decisions regarding colorectal cancer screening for persons aged 76 to 85 years should be individualized.[166] The USPSTF does not recommend performing routine screening in adults older than 85 years of age.[166] The USPSTF guidelines provide the following screening options, with the ultimate goal to improve screening rates: (1) stool-based tests (e.g. fecal occult blood testing [FOBT]), (2) fecal immunochemical testing (FIT), and FIT-DNA testing, and (3) direct visualization tests (e.g. flexible sigmoidoscopy with or without FIT, colonoscopy, and computed tomographic colonography).[166] The screening interval depends on the screening modality and the results of the screening tests.

• **U.S. Multi-Society Task Force (USMSTF)**: In 2017, the USMSTF on Colorectal Cancer issued recommendations for colorectal cancer screening in the general population.[168] 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 6).[168] The USMSTF guideline ranks the existing screening tools (Table 7).[168] In 2012, the USMSTF published updated recommendations for colonoscopy surveillance based on the most advanced findings from the baseline colonoscopy (Table 8).[169,170]

**Lung Cancer Screening**

In the United States, lung cancer is the third most common cancer and the leading cause of cancer deaths among men and women.[159,171] Increasing age and cumulative exposure to tobacco smoke are cited as the two most important risk factors for lung cancer.[171] In people with HIV, lung cancer is the leading cause of mortality from cancer.[171] Compared to the general population, persons with HIV have higher rates of lung cancer and may have poorer outcomes.[172] Proposed
mechanisms that may place individuals with HIV at greater risk for lung cancer include higher rates of smoking, chronic HIV-related inflammation, inflammation in response to lung infections, and overall immunosuppression as measured by CD4 cell count.\[173,174]\ The National Lung Screening Trial is a large, multi-center, randomized controlled trial that randomized participants aged 55 to 74 years at high risk for lung cancer to three annual screenings with either low-dose computed tomography or single-view posteroanterior chest radiography.\[175]\ Screening with computed tomography offered a relative reduction in mortality from lung cancer of 20% compared to only 6.4% with chest radiography.\[175]\ At this time, recommendations for lung cancer screening for people with HIV are the same as in the general population and are summarized in the following guidelines.

- **American Cancer Society**: The American Cancer Society recommends annual low-dose computed tomography for those aged 55 to 74 years in “fairly good” health with a greater than 30 pack-year smoking history and who either currently smoke or have quit within the past 15 years.\[171]\  
- **USPSTF Recommendations for Lung Cancer Screening**: The USPSTF recommends annual screening with low-dose computed tomography in patients aged 55 to 80 years who have a greater than or equal to 30 pack-year smoking history either with current tobacco use or in those who have quit within the past 15 years.\[171]\ Yearly screening should be discontinued once a person has not smoked for 15 years or develops problems in their health that may limit life expectancy or the ability or willingness to take part in curative strategies. The USPSTF has recommended screening up to 80 years based on modeling studies.\[171]\ 

**Prostate Cancer Screening**

Men with and without HIV have a similar risk of prostate cancer.\[146,155,157,176]\ 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 overdiagnosis and unnecessary treatment is high.

- **USPSTF Recommendations for Prostate Cancer Screening**: The USPSTF recommends prostate cancer screening should be an individualized decision for men 55 to 69 years of age.\[177]\ The guidelines note that the three most important risk factors for prostate cancer are: older age, African American race, and family history.\[177]\ The recommended screening test, if performed, is a measurement of the level of prostate-specific antigen (PSA) in the blood.\[177]\ For men 70 years of age and older, the USPSTF guidelines do not recommend routinely screening for prostate cancer.\[177]\ 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.\[177]\ 

**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.\[178]\ 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
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 (regardless of mode of HIV transmission), 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 annual 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).[179,180]

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 vaccination.

Anal Cancer Screening

Among individuals with HIV, the incidence of anal cancer is increased in relative incidence compared to the general population.[146] 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.[155] 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:[32]

Indications for Anal Pap Testing: Anal Pap smears should be performed in (1) men who have sex with men, (2) women with a history of receptive anal intercourse or abnormal cervical Pap test results, and (3) all individuals with HIV who have genital warts.[32] 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.[32,178]

- **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.[178] 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 persons with HIV, and cardiovascular risk reduction should be a priority.
- Calcium channel blockers should be avoided in persons 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 on suppressive antiretroviral therapy who would benefit from statin therapy, three are preferred: atorvastatin, rosuvastatin, and pitavastatin. Simvastatin and lovastatin should be avoided due to drug interactions with certain antiretroviral medications.
- Persons with HIV should undergo regular screening for the development of diabetes mellitus.
- Persons with HIV 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/mm³, elevated HIV RNA levels, black race, female sex, older age, diabetes, and hypertension.
- Tenofovir DF carries a risk of nephrotoxicity in persons with HIV that is increased in persons with lower body weight, a lower creatinine clearance at tenofovir DF initiation, or receipt of a PI, especially PIs boosted with ritonavir.
- All postmenopausal women and all men 50 years of age and older should receive DXA scans.
- Persons with HIV 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, Kaposi’s sarcoma, non-Hodgkin’s 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.

- Colon cancer, breast cancer, and prostate cancer screening recommendations are the same for persons with HIV as for the general population. Due to disproportionate risks of developing cervical and anal cancer among individuals with HIV, these cancers warrant different screening protocols.
**Citations**


47. Dubé MP, Stein JH, Aberg JA, et al. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral

[PubMed Abstract]


[PubMed Abstract]


[PubMed Abstract]


[AIDSinfo]


[PubMed Abstract]


[PubMed Abstract]


[PubMed Abstract]


[PubMed Abstract]


[PubMed Abstract]


[AIDSinfo]


83. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney


86. 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. December 18, 2019. [AIDSinfo]


95. Lindeman TA, Duggan JM, Sahloff EG. Evaluation of Serum Creatinine Changes With Integrase


[PubMed Abstract]

[PubMed Abstract]


178. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of


References


**Figures**

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


![Kaiser Observational Study Graph](image-url)
Figure 2 Veterans Aging Cohort: Rates of Acute Myocardial Infarction by HIV Status and Age Group


Veterans Aging Cohort Study, 2003-2009
### 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>Hypertension: Stage 1</td>
<td>130 – 139 mm Hg</td>
<td>80 – 89 mm Hg</td>
</tr>
<tr>
<td>Hypertension: 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: Intensity of Statins


<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 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td>Fluvastatin 40 mg bid</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg</td>
<td>Pitavastatin 1-4 mg</td>
</tr>
</tbody>
</table>
Figure 5 Impact of Antiretroviral Medications on Lipid Levels


<table>
<thead>
<tr>
<th>Class</th>
<th>Impact on Lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>• Stavudine &gt; Zidovudine &gt; Abacavir: ↑TG and ↑LDL</td>
</tr>
<tr>
<td></td>
<td>• Tenofovir alafenamide: ↑TG, ↑LDL, ↑HDL (no change in TC:HDL ratio)</td>
</tr>
<tr>
<td></td>
<td>• Tenofovir DF has been associated with lower lipid levels than abacavir or tenofovir alafenamide</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>• Efavirenz: ↑TG, ↑LDL, ↑HDL</td>
</tr>
<tr>
<td>PIs</td>
<td>• All ritonavir- or cobicistat-boosted PIs: ↑TG, ↑LDL, ↑HDL</td>
</tr>
<tr>
<td></td>
<td>• Lopinavir-ritonavir and Fosamprenavir &gt; Darunavir + Ritonavir and Atazanavir + Ritonavir: ↑TG</td>
</tr>
<tr>
<td>INSTIs</td>
<td>• Elvitegravir-Cobicistat: ↑TG, ↑LDL, ↑HDL</td>
</tr>
<tr>
<td>Els</td>
<td>• N/A</td>
</tr>
</tbody>
</table>

Abbreviations: NRTIs = nucleoside reverse transcriptase inhibitors; NNRTIs = nonnucleoside reverse transcriptase inhibitors; PIs = protease inhibitors; INSTIs = integrase strand transfer inhibitors; Els = entry inhibitors
**Figure 6 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>
Figure 7 Prognosis of Chronic Kidney Disease by GFR and Albuminuria Categories: KIDGO 2012

Abbreviations: GFR = glomerular filtration rate


Prognosis of CKD by GFR and Albuminuria Categories KIDGO 2012

<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>&lt; 30 mg/g</td>
</tr>
<tr>
<td>G3a Mildly to moderately decreased</td>
<td>45-59</td>
</tr>
<tr>
<td>G3b Moderately to severely decreased</td>
<td>30-44</td>
</tr>
<tr>
<td>G4 Severe decreased</td>
<td>15-29</td>
</tr>
<tr>
<td>G5 Kidney Failure</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

Green=low risk. Yellow=moderately increased risk. Orange=high risk. Red=severely high risk.
**Figure 8 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-</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td>Lower than reference value (normal, 2.8–4.4 mg/dL)</td>
</tr>
<tr>
<td>for GFR</td>
<td></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,</td>
</tr>
<tr>
<td></td>
<td>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 9 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>

*A Abstinence rate 6 months post quit*
<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</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</td>
<td>&lt;80 mm/Hg</td>
<td>Recommend healthy lifestyle changes and reassess in 3 to 6 months</td>
</tr>
<tr>
<td>Hypertension: Stage 1</td>
<td>130-139 mm/Hg</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 to 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.
<table>
<thead>
<tr>
<th>BP Category</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Treatment or Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1 medication); reassess in 1 month for effectiveness of medication therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ If goal is met after 1 month, reassess in 3 to 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ If goal is not met after 1 month, consider different medication or titration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>○ Continue monthly follow-up until control is achieved</td>
</tr>
<tr>
<td>BP Category</td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Treatment or Follow-Up</td>
</tr>
<tr>
<td>--------------</td>
<td>----------</td>
<td>-----------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Hypertension: Stage 2</td>
<td>≥140 mm/Hg or</td>
<td>≥90 mm/Hg</td>
<td>Recommend healthy lifestyle changes and BP-lowering medication (initiate with 2 medications of different classes); reassess in 1 month for effectiveness. If goal is not met after 1 month, consider different medications or titration. Continue monthly follow-up until control is achieved.</td>
</tr>
</tbody>
</table>

Source:

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

### Very High-Risk* of Future Atherosclerotic Cardiovascular Disease Events

<table>
<thead>
<tr>
<th>Major Atherosclerotic Cardiovascular Disease (ASCVD) Events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recent acute coronary syndrome (within the past 12 months)</td>
<td></td>
</tr>
<tr>
<td>• History of myocardial infarction (other than recent acute coronary syndrome event listed above)</td>
<td></td>
</tr>
<tr>
<td>• History of ischemic stroke</td>
<td></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>
<td></td>
</tr>
</tbody>
</table>

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

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

Source:

### Table 3. **2018 American College of Cardiology/American Heart Association Guideline on the Management of Blood Cholesterol**

#### Atherosclerotic Cardiovascular Disease (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 (\geq 160 \text{ mg/dL} (\geq 4.1 \text{ 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 (\geq 175 \text{ mg/dL}, [\geq 2.0 \text{ mmol/L}])</td>
</tr>
</tbody>
</table>

#### Heterozygous familial hypercholesterolemia

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• hs-CRP (\geq 2.0 \text{ mg/dL})</td>
</tr>
<tr>
<td>• Lipoprotein (a) levels (&gt;50 \text{ mg/dL} (or &gt;125 \text{ nmol/L}))</td>
</tr>
<tr>
<td>• apoB (\geq 130 \text{ mg/dL})</td>
</tr>
<tr>
<td>• Current smoking</td>
</tr>
<tr>
<td>• Ankle-brachial index (ABI) (&lt; 0.9)</td>
</tr>
</tbody>
</table>

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

**Source:**

Grundy SM, Stone NJ, Bailey AL, et al. 2018
Table 4. **American Diabetes Association**

**2019 Classification and Diagnosis of Diabetes**

<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 ( \geq 25 \text{ kg/m}^2 ) or ( \geq 23 \text{ kg/m}^2 ) in Asian Americans) adults who have one or more of the following risk factors:</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>• History of cardiovascular disease</td>
</tr>
<tr>
<td>• Hypertension (( \geq 140/90 \text{ 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>
<tr>
<td>2. Patients with prediabetes (HbA1c ( \geq 5.7% ) [39 mmol/mol], impaired glucose tolerance, or impaired fasting glucose) should be tested yearly.</td>
</tr>
<tr>
<td>3. Women who were diagnosed with gestational diabetes mellitus should have lifelong testing at least every 3 years.</td>
</tr>
<tr>
<td>4. For all other patients, testing should begin at age 45 years.</td>
</tr>
<tr>
<td>5. 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 and risk status.</td>
</tr>
</tbody>
</table>

Source:

Table 5. 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment.

<table>
<thead>
<tr>
<th>Drug (doses)</th>
<th>How Sold (U.S.)</th>
<th>Dosing Instructions</th>
<th>Administration</th>
<th>Common Side Effects</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine patch</td>
<td>OTC or Rx</td>
<td>Starting dose: 21 mg for ≥10 cigarettes per day.</td>
<td>Apply a new patch each morning to dry skin.</td>
<td>Skin irritation</td>
<td>The easiest nicotine product to use.</td>
<td>User cannot alter dose if cravings occur during the day.</td>
</tr>
<tr>
<td>21 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 mg</td>
<td></td>
<td></td>
<td>Rotate application site to avoid skin irritation.</td>
<td>Trouble sleeping</td>
<td>Provides a steady nicotine level.</td>
<td></td>
</tr>
<tr>
<td>7 mg</td>
<td></td>
<td></td>
<td>May start patch before or on quit date.</td>
<td>Vivid dreams</td>
<td>Combination NRT therapy: as needed, can add gum, lozenge, inhaler, or nasal spray to patch to cover situational cravings.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use ≥3 months.</td>
<td>Keep using even if a slip occurs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 6 weeks, option to taper to lower doses for 2-6 weeks.</td>
<td>If insomnia or disturbing dreams, remove patch at bedtime.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use ≥3 months.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 6 weeks, continue original dose or taper to lower doses (either option acceptable).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine lozenge</td>
<td>OTC or Rx</td>
<td>If first cigarette is ≤30 minutes of waking: 4 mg.</td>
<td>Place between gum and cheek, let it melt slowly. Use 1 piece every 1-2 hours (Max: 20/day).</td>
<td>Mouth irritation, Hiccups, Heartburn, Nausea</td>
<td>User controls nicotine dose. Oral substitute for cigarettes. May be added to patch to cover situational cravings. Easier to use than gum for those with dental work.</td>
<td>No food or drink 15 minutes prior to use and during use.</td>
</tr>
<tr>
<td>4 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (doses)</td>
<td>How Sold (U.S.)</td>
<td>Dosing Instructions</td>
<td>Administration</td>
<td>Common Side Effects</td>
<td>Advantages</td>
<td>Disadvantages</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------</td>
<td>---------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>------------</td>
<td>---------------</td>
</tr>
</tbody>
</table>
| Nicotine gum      | OTC or Rx       | If first cigarette is ≤30 minutes of waking: 4 mg.  
If first cigarette is >30 minutes of waking: 2 mg.  
Use ≥3 months. | Chew briefly until mouth tingles, then ‘park’ gum inside cheek until tingle fades. Repeat chew-and-park each time tingle fades. Discard gum after 30 minutes of use.  
Use ~ 1 piece per hour (Max: 24/day). | Mouth irritation, jaw soreness, Heartburn, Hiccups, Nausea | User controls nicotine dose. Oral substitute for cigarettes. May be added to patch to cover situational cravings. | Not chewed in same way as regular gum; requires careful instruction. Can damage dental work and be difficult to use with dentures. No food or drink 15 minutes prior to use and during use. |
| Nicotine inhaler  | Rx only         | 10 mg/cartridge.  
Each cartridge has ~80 puffs.  
Use ≥3 months. | Puff into mouth/throat until cravings subside. Do not inhale into lungs.  
Change cartridge when nicotine taste disappears.  
Use 1 cartridge every 1-2 hours (Max: 16/day). | Mouth and throat irritation, Coughing if inhaled too deeply | User controls nicotine dose. Mimics hand-to-mouth ritual of smoking cigarettes. May be added to patch to cover situational cravings. | Frequent puffing required. |
| Nicotine nasal spray | Rx only    | 10 mg/mL.  
0.5 mg per spray.  
Each bottle has ~200 sprays.  
Use ≥3 months. | Use 1 spray to each nostril.  
Use spray every 1-2 hours (Max: 80/day). | Nasal and throat irritation, Rhinitis, Sneezing, Coughing, Tearing | User controls nicotine dose. Most rapid delivery of nicotine among all NRT products. May be added to | Has the most side effects of all NRT products. Some users cannot tolerate local irritation to nasal mucosa. |
<table>
<thead>
<tr>
<th>Drug (doses)</th>
<th>How Sold (U.S.)</th>
<th>Dosing Instructions</th>
<th>Administration</th>
<th>Common Side Effects</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline (tablet)</td>
<td>Rx only</td>
<td>Days 1-3: 0.5 mg/day. Days 4-7: 0.5 mg twice a day. Day 8+: 1 mg twice a day. Use 3-6 months.</td>
<td>Start 1-4 weeks before quit date. Take with food and a tall glass of water to minimize nausea.</td>
<td>Nausea Insomnia Vivid dreams Headache</td>
<td>Quit date can be flexible, from 1 week to 3 months after starting drug. Dual action: relieves nicotine withdrawal and blocks reward of smoking. Oral agent (pill).</td>
<td>Because of previous FDA warning (now removed), many patients fear psychiatric adverse events, even though they are no more common than with other cessation medications.</td>
</tr>
<tr>
<td>0.5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion sustained release (SR) (tablet)</td>
<td>Rx only</td>
<td>150 mg/day for 3 days, then 150 mg twice a day. Use 3-6 months.</td>
<td>Start 1-2 weeks before quit date.</td>
<td>Insomnia Agitation Dry mouth Headache</td>
<td>May lessen post-cessation weight gain while drug is being taken. Oral agent (pill).</td>
<td>Increases seizure risk: not for use if seizure disorder or binge drinking.</td>
</tr>
<tr>
<td>150 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* All are FDA-approved as smoking cessation aids and listed as a first-line medication by U.S. Clinical Practice Guidelines (Fiore, 2008)

+ Recommended duration of use for medications is at least 3 months but extending dose to 6 months is frequently done to prevent relapse to tobacco use. Patching dosing differs slightly from FDA labeling.

Abbreviations: FDA = U.S. Food and Drug Administration; NRT = nicotine replacement therapy; OTC = over the counter (no prescription required); Rx = prescription required.

Source:
<table>
<thead>
<tr>
<th>Group</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average-risk persons</td>
<td>Initiate screening at age 50</td>
</tr>
<tr>
<td>African Americans</td>
<td>Initiate screening at age 45</td>
</tr>
<tr>
<td>Family Colon Cancer Syndrome X</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 7. 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>
</tr>
</thead>
<tbody>
<tr>
<td>• Colonoscopy every 10 years</td>
</tr>
<tr>
<td>• Annual fecal immunochemical test (FIT)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tier 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CT colonography every 5 years</td>
</tr>
<tr>
<td>• FIT-fecal DNA every 3 years</td>
</tr>
<tr>
<td>• Flexible sigmoidoscopy every 10 years (or every 5 years)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tier 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Capsule colonoscopy every 5 years</td>
</tr>
</tbody>
</table>

#### Available Tests Not Currently Recommended

- Septin 9

Source:

Table 8. **U.S. Multi-Society Task Force on Colorectal Cancer**

### Guidelines for Colonoscopy Surveillance After Screening and Polypectomy

<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 polyps</td>
<td>10 years</td>
<td>Moderate</td>
</tr>
<tr>
<td>Small (&lt;10 mm) hyperplastic polyps 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 Sessile serrated polyp with dysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR 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:
