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A Review of Chronic Comorbidities in Adults Living with HIV: State of the Science

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Abstract

People living with HIV are living longer, high-quality lives; yet as they age, this population is at increased risk for developing chronic comorbidities, including cardiovascular disease, certain types of cancer (e.g., lung, anal, liver), and diabetes mellitus. The purpose of this state of the science review is to provide an evidence-based summary on common physical comorbidities experienced by people living and aging with HIV. We focus on those chronic conditions that are prevalent and growing, and share behavioral risk factors that are common in people living with HIV. We will discuss the current evidence on the epidemiology, physiology, prevention strategies, screening, and treatment options for people living with HIV across resource settings.

Keywords

Cancer; Cardiovascular Disease; Diabetes Mellitus; HIV; Multimorbidity

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Significant progress in the care and treatment of people living with HIV (PLWH) has transformed HIV into a chronic condition. As such, PLWH in every region of the world are currently living near normal lifespans if they are offered antiretroviral treatment and are adherent (Wandeler et al., 2016). While this progress should be celebrated, increased aging is also associated with increased risk for age-related chronic conditions, for which many PLWH are at higher risk (Friedman & Duffus, 2016).

The purpose of this review is to describe the current state of the science on common physical comorbidities experienced by people living and aging with HIV. We focus on those that are prevalent and growing, and share common risk factors, namely smoking, physical inactivity, poor dietary intake, and co-infections. We will discuss the current HIV-specific evidence on atherosclerotic cardiovascular disease, chronic obstructive pulmonary disease; lung, anal, and liver cancer; diabetes mellitus; and chronic kidney disease for PLWH across resource settings and will synthesize the clinical, research, and policy implications of these data.

Atherosclerotic Cardiovascular Disease

Atherosclerotic cardiovascular diseases (ASCVD; e.g., coronary artery disease, myocardial infarctions) have tripled in the past 20 years and are among the leading causes of hospitalizations, disability, and death among PLWH (Fleming et al., 2019; Hart et al., 2018; Shah et al., 2018). ASCVD are caused by a buildup of atherogenic plaque in the artery walls, resulting in coronary artery disease, angina, and myocardial infarctions. It is estimated that PLWH have a 1.5- to 2-fold increased risk of developing ASCVD (Feinstein et al., 2019). With improved treatment and care, the risk of myocardial infarction is decreasing (Klein et al., 2015), yet a recent analysis of a large U.S. dataset (i.e., MarketScan Commercial and Medicare datasets) found an approximately 1.3-fold increase in myocardial infarction, underscoring the need for primary prevention of ASCVD in PLWH (Alonso et al., 2019).

Factors Contributing to ASCVD Risk in PLWH

Increases in ASCVD in PLWH were first observed in the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study in the early 2000s. In this cohort, combination antiretroviral therapy (cART) was associated with an increased risk for myocardial infarction (Data Collection on Adverse Events of Anti-HIV Drugs [DAD] Study Group, 2003). Later, increased exposure to protease inhibitors (PIs) was implicated as a significant source of this excess risk (DAD Study Group, 2007; Nou et al., 2016) through metabolic side effects, such as dyslipidemia, lipodystrophy, and glucose intolerance. As cART has evolved to have fewer toxic cardiometabolic effects, many have investigated additional sources of increased ASCVD risk in PLWH and have increasingly focused on the role of inflammation.

Increased inflammation among PLWH persists, despite sustained HIV suppression, and is associated with accelerated development of atherosclerosis through vascular inflammation, endothelial dysfunction, hypercoagulability, and disrupted cholesterol transport and capacity (Hart et al., 2018; Nou et al., 2016). Biomarkers of systemic inflammation, including D-dimer, high sensitivity C-reactive protein (hsCRP), and interleukin 6 (IL-6), are among the most studied predictors of ASCVD in HIV and have consistently been associated with increased risk of clinical and subclinical ASCVD (Nou et al., 2016; Subramanya et al.,

2019). While HIV public health initiatives, such as test-and-treat and the 90-90-90 goals, have helped to increase the number of PLWH on effective HIV medications, they have also shortened the time between HIV infection and HIV viral suppression. The truncated time of uncontrolled HIV viremia has helped to moderate the cardiometabolic consequences of HIV infection and inflammation, and may help to partially explain the decreasing rates of myocardial infarction in recent years.

While substantial progress has been made in mitigating HIV-specific risk factors for ASCVD, less progress has been made in reducing the traditional risk factors related to the development of ASCVD. Hypertension, hyperlipidemia, obesity, tobacco and other substance use, sedentary lifestyles, and poor diet (high in sodium, high in fat, low in fiber) are elevated in PLWH and are significant contributors to their ASCVD risk. In high resource settings, approximately 42% of PLWH have hypertension and 36% have hyperlipidemia (Olaiya et al., 2018; Wong et al., 2017). Rates of obesity among PLWH range from 8% to 25%, with higher rates of obesity in women, racial and ethnic minorities, and with initiation of some HIV medications (e.g., integrase inhibitors; Bailin et al., 2020; Lake, 2017). Lifestyle factors, including tobacco and other substance use, sedentary behaviors, and diet, influence both traditional ASCVD risk factors and the pathways between inflammation and atherosclerosis. Approximately 37% to 50% of PLWH currently smoke tobacco (Mdodo et al., 2015; Weinberger et al., 2017), 48% of PLWH report a substance use disorder, and 20% report polysubstance use (Hartzler et al., 2017). While the estimated effect of tobacco and substance use on ASCVD varies (Raposeiras-Roubín et al., 2017), there is consensus that they are strongly associated with ASCVD in PLWH, and tailored interventions to mitigate their use are needed. Physical activity can reduce ASCVD by promoting a favorable cholesterol profile by increasing HDL level and function, reducing triglycerides and LDL levels, and reducing insulin sensitivity chronic inflammation (Nystoriak & Bhatnagar, 2018). Yet, on average, only half of PLWH engage in the recommended 150 to 300 minutes of moderate to vigorous physical activity or 75 minutes of vigorous physical activity and 2 days of resistance training per week in accordance with the U.S. Department of Health and Human Services Guidelines. A recent review found PLWH have the lowest levels of physical activity when compared to individuals with other chronic illnesses (Vancampfort et al., 2018). Diets high in fiber and low in salt and processed sugars are associated with improved cardiovascular health. While less is known about dietary intake in PLWH than the other traditional ASCVD risk factors, the limited existing evidence suggests that their diet quality is poor (e.g., high calorie, added sugar, low fiber) and lower than those without HIV (Webel et al., 2017; Weiss et al., 2019).

Preventing CVD in PLWH

The most important CVD prevention strategy is to help PLWH start and adhere to an effective ART regimen as early in their HIV diagnosis as possible (Feinstein et al., 2019). This will minimize inflammation-induced damage to the myocardium and vasculature that may lead to ASCVD. Additionally, strong evidence suggests reducing hypertension (Casey et al., 2019), hypercholesterolemia (Grundy et al., 2019), hyperglycemia (Fox et al., 2015), and stopping all tobacco use (Barua et al., 2018) through non-pharmacological or pharmacological approaches are likely to lead to immediate improvements in ASCVD risk

in PLWH (Arnett et al., 2019b); however, because of the potential for drug-drug interactions due to ART (e.g., between some protease inhibitors and lovastatin and simvastatin), non-pharmacological preventative strategies should be prioritized when possible. Additionally, engaging in physical activity, consuming a nutritious diet, and maintaining a healthy weight throughout the lifespan can also reduce the risk of ASCVD. While PLWH may not routinely engage with health care providers until later in their life, it is important to discuss, assess, and emphasize the importance of healthy lifestyle behaviors at each patient encounter. The physical activity recommendations for PLWH are similar to those without HIV infection - 150 to 300 minutes of moderate to vigorous physical activity or 75 minutes of vigorous physical activity per week and 2 days of strength training exercises (Montoya et al., 2019). Recent evidence demonstrated that PLWH mostly fail to meet these guidelines and that low physical activity is associated with increased CVD risk (Vancampfort et al., 2018; Willig et al., 2020). The Academy of Nutrition and Dietetics recently published HIV-specific guidelines for nutrition-related comorbidities (Willig, 2018). To mitigate ASCVD risk, they recommend eating foods rich in fiber, monounsaturated fats, vitamin D, calcium consisting mostly of vegetables, fruits and dairy products, and reducing the consumption of refined sugar, carbohydrates, and sodium (Willig et al., 2018). While dietary intake in PLWH has been less studied, limited data suggest that PLWH in the United States conform to approximately half the daily diet recommendations and consume diets high in refined sugars and carbohydrates (Webel et al., 2017; Weiss et al., 2019).

Clinical Tools to Screen for ASCVD in PLWH

Caring for PLWH with multimorbidity can be challenging. To reduce the overall burden on HIV and primary care providers, there are a number of screening tools that can be implemented in diverse clinical settings. Here we describe two free ASCVD tools that have a strong evidence base and are feasible to conduct during a patient encounter. Additional clinical tools can be found in Table 1.

Assisting patients to understand their risks is a key, but challenging, principle of shared decision making (Garcia-Retamero & Galesic, 2010; Webel et al., 2020). To simplify risk communication and the resultant decision-making, the American Heart Association and the American College of Cardiology have developed and calibrated their ASCVD risk estimator (Journal of the American College of Cardiology, 2020; Lloyd-Jones et al., 2017). For adults between the ages of 20 and 79 years, this tool can be used to help estimate the 10-year risk of an ASCVD event (e.g., myocardial infarction or stroke), forecast the potential impact of different interventions on that patient's ASCVD risk, and facilitate shared clinician-patient decision making about ASCVD interventions. Focusing on the most salient and clinically available risk factors (e.g., age, sex, race, blood pressure, smoking status, and cholesterol), this calculator has been studied in PLWH with mixed findings. A large national study found that the ASCVD risk was underestimated in women living with HIV, and suggested the development and calibration of an HIV-specific function to improve estimates (Triant, 2020). Similarly, the Mayo Clinic Statin Choice Decision Aid™ can assist clinicians to help visualize their patient's risk of ASCVD events and the change in risk due to a cholesterol-lowering intervention (Mayo Clinic, 2020). Unfortunately, this accessible tool does not yet account for blood-pressure-lowering medications or smoking cessation interventions.

The American Heart Association developed a second, more comprehensive tool, My Life Check™, to account for additional lifestyle factors influencing ASCVD (American Heart Association [AHA], 2020). In addition to age, sex, race, blood pressure, smoking status, and cholesterol, this tool assesses weight, diet, blood sugar, physical activity, and zip code. After completing the assessment, participants receive suggested interventions tailored to their unique risk, along with a number of tools to start improving those factors. While the individual components of My Life Check™ are derived from high-level evidence and embedded in clinical guidelines (Arnett et al., 2019a), there is less research on the use of the tool itself to effectively reduce cardiovascular risk in any population.

Treating ASCVD in PLWH

Treatment for ASCVD in PLWH resembles national guidelines for those without HIV with several notable exceptions. First, the most important factor in preventing and treating ASCVD in the context of HIV infection is helping the patient to achieve and maintain viral suppression as soon as possible after HIV infection (Feinstein et al., 2019). After that, an annual assessment of ASCVD and lifestyle optimization with routine follow-up (Figure 1) should be considered for all adults living with HIV, in every setting. While the lifestyle goals are the same for all PLWH throughout their lifespan (smoking cessation; maintaining a healthy weight; regular moderate-to-vigorous physical activity; and consuming a low salt, low sugar, low carbohydrate, high fiber diet), the strategies to achieve these goals must be tailored to the individual and their unique context. These strategies will need to be meaningful and available to the participant, creative, empathetic to their barriers, and dynamic to ensure continual growth and progress toward the individual's goals. While some participants may respond to mHealth interventions, others may be more comfortable with cognitive behavioral theory-based interventions or social support interventions (Montoya et al., 2019). Nonetheless, given the strong relationships PLWH experience with their health care team (Dawson-Rose et al., 2016), routine assessment, follow-up, and supportive feedback by their health care providers are likely to underscore the importance of lifestyle optimization.

The second unique consideration for PLWH is the increased risk for their HIV antiretroviral medication to interact with common cardiovascular medications. While modern ART has a lower potential for drug-drug interactions compared with earlier generation medications, cardiovascular medications are common sources of these interactions (Courlet et al., 2019). To prevent adverse effects, each patient's unique medical and medication history will need to be considered in the context of their health goals; however, there are some general guidelines that should be considered when prescribing cardiovascular medications. The lipid-lowering medication class, statins, are highly effective at reducing ASCVD, yet several of these medications are contraindicated with some ART, including simvastatin (when taking DRV/r, DRV/c, EVG/c, EFV) and lovastatin (when taking DRV/r, DRV/c, EVG/C, EFV). Atorvastatin, rosuvastatin, pravastatin, and pitavastatin can induce pharmacokinetic effects when taken with ART but have a lower risk for interactions. Using the lowest dose statin to reduce lipid levels is recommended (Devanathan et al., 2019). Additionally, calcium channel blockers (e.g., amlodipine, verapamil) can interact with DRV/r, DRV/c, EVG/c, EFV, and ETR, and may require dose adjustment (Devanathan et al., 2019). Additionally

emerging evidence suggests that antiplatelet medications (e.g., clopidogrel, prasugrel) may interact with RTV and COBI (Bravo et al., 2018). Given the increasing complexity of ASCVD treatment in PLWH, working closely with a pharmacist and utilizing the University of Liverpool HIV Drug Interaction Checker can help minimize the risk of drug-drug interactions or adverse events (Liverpool, 2020).

As PLWH continue to age, they will not only be diagnosed with ASCVD but also with heart failure, stroke, and peripheral arterial disease. While these conditions share prevention and screening similarities with ASCVD, they have unique HIV-specific screening, prevention, and treatment considerations. These cardiovascular conditions were excluded from this review for the sake of parsimony, not to minimize their importance. To learn more about the incidence, prevention, and management of these conditions, we refer the reader to these recent reviews (Beckman et al., 2018; Nguyen et al., 2020; Sinha & Feinstein, 2020).

Chronic Obstructive Pulmonary Disease and HIV

Chronic obstructive pulmonary disease (COPD) has emerged as a major cause of morbidity in PLWH. COPD is characterized by progressive airflow limitation and persistent respiratory symptoms, including shortness of breath, cough, and sputum production (Vogelmeier et al., 2017). Although population-based estimates of the prevalence of COPD in the United States are lacking, it has been demonstrated that COPD is more prevalent in PLWH compared to those without HIV (OR 1.14, 95%CI, 1.05–1.25; Antoniou et al., 2020), with as much as 25% of PLWH estimated to have COPD (Lalloo et al., 2016); however, this may underestimate the true prevalence, as many PLWH remain undiagnosed due to the lack of adequate screening, especially among women.

Physiologically, COPD is characterized by small airway obstruction (e.g., obstructive bronchiolitis) and parenchymal destruction (e.g., emphysema). Although smoking is the major risk factor for the development of COPD, nearly 25% of patients with COPD report having never smoked (Labaki & Rosenberg, 2020). Other risk factors may include exposure to environmental pollutants and lung irritants (including secondhand smoke), and $\alpha-1$ antitrypsin deficiency. Recently, HIV was identified as an independent risk factor for COPD, and this risk may be due to changes in immune function, direct effects of HIV, increased susceptibility to infection, and inflammatory factors (MacDonald et al., 2018).

Screening for COPD

Screening for COPD is recommended for anyone older than age 40 who has risk factors (e.g., smoking, respiratory symptoms). A diagnosis of COPD is made by conducting pulmonary function testing. Initially, forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are measured, followed by calculation of the ratio of FEV1/FVC (Labaki & Rosenberg, 2020). In patients with COPD, the FEV1/FVC ratio is low (less than 0.70), demonstrating limited expiratory airflow. COPD may be classified based on the FEV1 percent predicted value, with FEV1 >80% predicted, FEV1 of 50–79% predicted, and FEV1 30–49% predicted, or FEV1 < 30% predicted, corresponding to mild, moderate, severe, or very severe, respectively. While a certain level of reduction in FEV1 is normal due to aging, people with COPD show a rapid decline (defined using a common cutoff of >40 mL/year),

which is associated with respiratory disease and all-cause mortality (Makinson et al., 2018; Ronit et al., 2018).

While there are few clinical trials examining respiratory decline in PLWH, the Strategic Timing of ART Treatment (START) study, a large randomized clinical trial with patients from 20 countries, conducted a substudy that examined the effect of smoking on lung function and health status among PLWH (MacDonald et al., 2018). The START Pulmonary Substudy examined annual rate of FEV1 decline in more than 1,000 participants living with HIV over nearly 4 years (MacDonald et al., 2018). As expected, smokers had a significantly faster rate of FEV1 decline compared to nonsmokers. Importantly, there was no significant difference between continuous (daily) smokers and intermittent smokers, emphasizing the importance of smoking cessation for all PLWH regardless of their level of smoking.

Treating and Preventing COPD in HIV

Pharmacotherapy, in the form of respiratory inhalers, smoking cessation, pulmonary rehabilitation, administration of influenza and pneumococcal vaccines, and oxygen therapy (when needed) are the mainstays of treatment for patients with COPD, regardless of HIV status. Pharmacotherapy for COPD may include inhaled bronchodilators and corticosteroids.

Cigarette smoking is the most common and significant risk factor for COPD. Therefore, efforts to reduce smoking prevalence and improve smoking cessation among PLWH are critical. Please refer to an upcoming section on lung cancer prevention for a discussion of smoking cessation among PLWH.

Cancer among PLWH

Epidemiology in the United States and Around the Globe

As HIV has transitioned to a chronic illness, cancer has emerged as a leading cause of morbidity and mortality in PLWH (Ehren et al., 2014; Shiels et al., 2011). From 2011–2015, one in six deaths among PLWH in the United States was attributed to cancer (Horner et al., 2020), which exceeded cancer-related deaths in the general population for all age groups. Cancers in PLWH are typically divided into AIDS-defining cancers, such as Kaposi’s sarcoma, non-Hodgkin lymphoma, and cervical cancer, which may be associated with advanced immunosuppression, or non-AIDS–defining cancers (NADCs), such as lung, liver, and anal cancers, which may be associated with inflammation and certain risk behaviors (Engels, 2017). While combined data from national surveys demonstrated a decrease in the proportion of deaths attributed to AIDS-defining cancers between 2000 and 2010, the proportion of deaths attributed to NADCs increased significantly over the same period of time (Vandenhende et al., 2015). In the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study, nearly 10% of deaths in PLWH were due to cancer (Engels, 2017).

Lung Cancer in PLWH

Factors contributing to increased lung cancer risk in PLWH.—Lung cancer has emerged as a leading cause of morbidity and mortality in the United States (Ehren et al.,

2014; Shiels et al., 2011). Although lung cancer in PLWH may be related to the effects of chronic inflammation and immunomodulation (Sigel et al., 2016), the increased risk of lung cancer in PLWH is primarily due to the high prevalence of tobacco use. Smoking prevalence (~40%) is substantially higher in PLWH (Ledgerwood & Yskes, 2016) compared with the general population (15%; CDC, 2018) and is associated with increased rates of lung cancers (Clifford et al., 2012; Sigel et al., 2016; Sigel et al., 2012), and other malignancies (Antiretroviral Therapy Cohort, 2010; Niaura et al., 2000). In the era of cART, PLWH lose more years due to smoking than to HIV infection itself (Helleberg et al., 2015; Mamary et al., 2002; Reddy et al., 2016). One study found that the incidence rate of smoking-related cancers among PLWH smokers was more than five times higher compared with general population smokers (Helleberg et al., 2014). It has been estimated that at least 90% of lung cancers and 20% of all other cancers in PLWH could be prevented by eliminating smoking (Altekruse et al., 2018).

Smoking cessation and lung cancer prevention among PLWH.—Smoking cessation studies in PLWH have demonstrated disappointing outcomes, with low quit rates, poor adherence to therapy, and a lack of sustained abstinence (Cioe, 2013; Cui et al., 2012; Gritz et al., 2013; Ingersoll et al., 2009; Lloyd-Richardson et al., 2009; Matthews et al., 2013; Pacek & Cioe, 2015; Vidrine et al., 2012). Forty percent of smokers living with HIV express a willingness to quit (Benard et al., 2007) and two-thirds are interested in quitting when asked (Mamary et al., 2002). Pacek, Latkin, et al. (2014) found that among 267 PLWH who smoked, 74% were interested in quitting, 59% had used smoking cessation pharmacotherapy in the past, and 32% of those who hadn't used smoking pharmacotherapy previously were willing to try pharmacotherapy if it were prescribed (Pacek, Latkin, et al., 2014). Although they desire to quit and are motivated to quit, PLWH are less likely to quit compared to smokers in the general population, and few are able to achieve long-term abstinence (Mdodo et al., 2015; Pacek, Harrell, et al., 2014; Pacek, Latkin, et al., 2014; Tami-Maury et al., 2013). On average, PWLH smoke heavily (15–19 cigarettes/day), are moderately or highly nicotine dependent (67%), and use multiple forms of tobacco, including cigars, pipes, and chewing tobacco (Shuter et al., 2012; Tami-Maury et al., 2013); all factors that reduce the success of smoking cessation attempts.

To date, tobacco cessation clinical trials in PLWH have included the use of a transdermal nicotine patch (Cropsey et al., 2013; Ingersoll et al., 2009; Lloyd-Richardson et al., 2009; Manuel et al., 2013; Moadel et al., 2012); varenicline, a prescription drug to treat nicotine addiction (Chew et al., 2014; Cropsey et al., 2015; Cui et al., 2012; Ferketich et al., 2013); cognitive behavioral therapy (Matthews et al., 2013); in-person or computer-based counseling; web-based interventions; and brief advice to quit. Quit rates and sustained abstinence were generally low (8% to 20%), and differences between intervention and control groups were often non-significant (Humfleet et al., 2013; Lloyd-Richardson et al., 2009; Moadel et al., 2012; Stanton et al., 2015; Vidrine et al., 2012). When examining factors associated with successful quitting, however, Stanton (2015) and Vidrine et al. (2015) found that self-efficacy for smoking cessation mediated the effect of the smoking cessation intervention; while Browning and colleagues (2016) concluded that adherence to treatment was positively associated with sustained abstinence (Browning et al., 2016;

Stanton et al., 2015; Vidrine et al., 2015). In addition, de Dios and colleagues (2016) found that social support for smoking cessation was positively associated with nicotine patch adherence and indirectly associated with 7-day point prevalence abstinence. In a systematic review, Cooperman (2016) suggested that further research was needed to develop tailored interventions for PLWH that target adherence to smoking cessation pharmacotherapy, self-efficacy for quitting, and social support for smoking cessation (Cooperman, 2016).

Screening and treatment for lung cancer in PLWH.—Screening for lung cancer in PLWH does not differ from that of the general population (Sigel et al., 2017). The U.S. Preventive Services Task Force recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults, ages 55 to 80 years, who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. The American Cancer Society has similar recommendations (Smith et al., 2019). Two clinical trials for lung cancer screening have been conducted with PLWH. In the first trial, adherence to study protocol was low and only one lung cancer was detected (Hulbert et al., 2014). In the second trial, adherence was better and lung cancer was detected in participants younger than 55 years of age (the recommended age for initial screening in smokers; Makinson et al., 2016).

Surgery is the standard of care for early stage lung cancer. The effect of HIV on lung cancer treatment tolerability, toxicity, and effectiveness is not well described; however, the prognosis for PLWH who develop lung cancer has been shown to be worse than uninfected persons (Sigel et al., 2017). It is not known if the poorer outcomes are related to lung cancer treatment disparities, decreased tolerance to treatment, increased risk of treatment toxicity, or competing risk from HIV-associated morbidities (Sigel et al., 2012). While few well-controlled studies exist, one study that compared PLWH to those without HIV found more surgical complications and poorer survival following surgery in those with HIV (Marcus et al., 2015). Clearly, a focus is needed on prevention, early detection, and adequate treatment of primary lung cancers in PLWH to improve overall outcomes.

Preventing Lung Cancer in PLWH.—Smoking cessation is the key focus of lung cancer preventive efforts for PLWH, due to their high prevalence of cigarette smoking. Nurses have an important role in prevention by implementing the recommended 5As in clinical settings (Fiore et al., 2008). The 5As describe an effective and brief intervention that is feasible in HIV clinical settings. It consists of (a) *Ask* every patient about smoking, (b) *Advise* each smoker to quit, (c) *Assess* readiness to quit, (d) *Assist* by offering medication and providing or referring for counseling, and (e) *Arrange* for follow-up to prevent relapse and promote success. There are seven first-line FDA-approved medications (5 forms of nicotine-replacement therapy [patch, lozenge, gum, inhaler, nasal spray] and 2 non-nicotine [varenicline, bupropion]) for smoking cessation that have demonstrated safety and efficacy for all smokers, including PLWH. A comprehensive approach to smoking cessation, including some form of pharmacotherapy with behavioral counseling, has been shown to produce the best outcomes (Fiore et al., 2008).

Liver Cancer in PLWH

Epidemiology in the United States and around the globe.—Liver cancer is the fourth most common NADC in the United States (Robbins et al. 2015; Horner et al., 2020). Hepatocellular carcinoma (HCC) is the most common histologic form of liver cancer accounting for approximately 75% of all diagnoses (Petrick et al., 2020). Incident HCC occurs more frequently in PLWH as compared to the general population andeceiving an AIDS diagnosis in particular is associated with a 4-fold increased risk of incident HCC (Sahasrabuddhe et al., 2012). The increased risk of HCC in PLWH is primarily due to their disproportionate prevalence of conditions that are associated with chronic liver disease (Sahasrabuddhe et al., 2012).. In the NA-ACCORD study, liver cancer accounted for 0.9% of deaths in PLWH between 1995–2009, second only to lung cancer as a proportion of NADC-related deaths (Engels, 2017).

Globally, liver cancer is the fourth leading cause of cancer mortality worldwide (Bray et al., 2018). It is estimated that 85% of HCC diagnoses occur in low-resource or middle-resource countries (Yang et al., 2019). Regional variations in liver cancer incidence and mortality are attributed to multiple factors, including differences in the incidence of conditions leading to chronic liver disease, availability of liver cancer screening programs, and access to treatment.

Factors Contributing to Liver Cancer Risk in PLWH.—HCC usually occurs against a background of oxidative stress and inflammation due to chronic liver disease. Regardless of the agent triggering chronic liver disease, liver cirrhosis is the most important predisposing risk factor for HCC. Pre-existing cirrhosis is present in 80% of individuals with an HCC diagnosis (Marrero et al., 2018).

The role of HIV mono-infection in the etiology of HCC remains unclear. Findings from the Veterans Aging Cohort Study provide the strongest evidence to date implicating HIV viremia as an independent contributing factor to HCC risk (Torgersen et al., 2020). In contrast, prior studies failed to establish relationships between HIV viremia and HCC (Kowalkowski et al., 2014; Kramer et al., 2015; Park et al., 2018). Mixed evidence on the associations between low absolute CD4+ T-cell counts and HCC comes primarily from studies on HIV and HCV or HBV co-infection (Bruyand et al., 2011; Gjærde et al., 2016).

In the United States, the most common causes of HCC are HCV infection, followed by alcohol-associated liver disease, non-alcoholic fatty liver disease (NAFLD), and HBV (Younossi et al., 2015). Less-prevalent conditions, such as hereditary hemochromatosis, primary biliary cholangitis, and Wilson’s disease have also been associated with HCC development. HCC incidence (Marrero et al., 2018) and clinical features (Piscaglia et al., 2016) differ according to the underlying condition. For the most common causes of HCC, we summarize information on prevalence and disease progression in the general population and, as available, in PLWH.

Chronic HCV infection is the most important cause of HCC in high-income countries including the United States. It is associated with a 10- to 20-fold increased risk for HCC (McGlynn et al., 2020). HIV/HCV coinfection is associated with increases in overall

cirrhosis risk (~2-fold increased risk) and with accelerated HCV disease progression as compared to HCV mono-infection (Graham et al., 2001; Thein et al., 2008). The annual incidence of HCC in people with HCV-related cirrhosis ranges from 1% to 8% (El-Serag & Kanwal, 2014). In the United States, the prevalence of HCV infection (past or present) is estimated at 1.7% for the general population (Hofmeister et al., 2019) and between 6% and 25% in PLWH (Bosh et al., 2018; Crowell et al., 2015; Kim et al., 2013; Prussing et al., 2015; Weber et al., 2010).

Alcohol-associated liver disease is a general term used to refer to a spectrum of alcohol-related liver injuries including fatty liver, alcoholic hepatitis, and cirrhosis. In the United States, one “drink” is defined as a beverage containing about 14 g of alcohol. A daily alcohol intake of 80 grams for ≥ 10 years increases HCC risk approximately 5-fold over that of nondrinkers (Morgan et al., 2004). The annual incidence of HCC in alcohol-associated cirrhosis ranges from 1–4% (Pocha & Xie, 2019). In the United States, the prevalence of alcohol-associated liver disease is estimated at 8% to 9% for the general population (Dang et al., 2020). There are limited data on disease prevalence in PLWH. In a cross-sectional analysis of PLWH who were Medicare beneficiaries between 2006 and 2016, the prevalence of alcohol associated liver disease was estimated at 2.3% (Dang et al., 2020); however, prevalence estimates of alcohol use disorder in PLWH (12% to 76%) appear to exceed that of the general population (Duko et al., 2019).

NAFLD, including its advanced form non-alcoholic steatohepatitis, has emerged as the leading cause of chronic liver disease globally (Younossi, 2019). The American Association for the Study of Liver Diseases (AASLD) defines NAFLD as the presence of ≥ 5% liver fat without evidence of hepatocellular injury in the form of hepatocyte ballooning in those without significant alcohol consumption (Chalasani et al., 2018). Non-alcoholic steatohepatitis is defined as the presence of ≥ 5% liver fat and inflammation with hepatocyte injury, with or without liver fibrosis in those without significant alcohol consumption (Chalasani et al., 2018). NAFLD is associated with diabetes mellitus, obesity, and metabolic syndrome, including in PLWH (Maurice et al., 2017). The role of HIV and ART in development of NAFLD continues to be investigated (Seth & Sherman, 2019). NAFLD is associated with a 2.6-fold increased risk of HCC (Younossi et al., 2015). The annual incidence of HCC in NAFLD cirrhosis is estimated to range between 1–3% (Marrero et al., 2018). Depending on the study, NAFLD prevalence in the United States ranges from 11% to 46% in the general population (Younossi et al., 2016) and between 23% and 73% in PLWH (Dang et al., 2020; Maurice et al., 2017).

Chronic hepatitis B infection (HBV) is the most important cause of HCC in Eastern Asian and most North African countries where HBV is endemic (Yang et al., 2019). Multiple case control studies have compared HCC risk in HBV infected and uninfected groups. Chronic HBV infection is associated with between a 5- and 103-fold increased risk of developing HCC (McGlynn et al., 2020). There is strong evidence indicating that hepatitis B viral load is directly correlated with liver disease progression and the risk of HCC (Iloeje et al., 2006). HIV/HBV coinfection is associated with higher hepatitis B viral loads and accelerated HBV disease progression. The annual incidence of HCC in HBV cirrhosis is estimated at 3% to 8% (Marrero et al., 2018). The most recent estimates of HBV infection in the United States

are 4.2% in the general population (Shing et al., 2020), and 5.3% in PLWH (Leumi et al., 2020).

Preventing Liver Cancer in PLWH.—Nurses have an essential role in HCC prevention, which is largely focused on preventing and treating HCV and HBV infections, alcohol-associated liver disease, and NAFLD. Individuals at risk for HCV infection should receive counseling on injection hygiene and safe-sex practices that can prevent transmission. For those with HIV/HCV coinfection, treatment with direct-acting antiviral agents in multiple clinical trials resulted in sustained virologic response rates of ≥ 95%, irrespective of genotype and cirrhosis status (Naggie et al., 2015; Rockstroh et al., 2015; Rockstroh et al., 2018; Wyles et al., 2017). Achieving a sustained virologic response significantly reduces the risk of developing HCC (Ioannou et al., 2018). Nursing care coordination and case management can facilitate linkage to HCV infection treatment (Starbird et al., 2020) and treatment completion (Sherbuk et al., 2019).

HIV nurses can also integrate screening, brief intervention, and referral to treatment (SBIRT) for hazardous alcohol use into their clinical routines (Finnell et al., 2014). AASLD recommends that all patients should be routinely screened for alcohol use using validated questionnaires (Lucey et al., 2020). The U.S. Preventive Services Task Force recommends use of 1- to 3-item instruments, including the Alcohol Use Disorders Identification Test-Concise (AUDIT-C) or the National Institute of Alcohol Abuse and Alcoholism recommended Single Alcohol Screening Question (SASQ) as preliminary screening tools. (U.S. Preventive Services Taskforce, 2018). Positive screenings should be followed by screening with an instrument with greater sensitivity and specificity (e.g., AUDIT) to confirm hazardous alcohol use. Pharmacotherapy and referral to treatment are indicated for all individuals engaged in hazardous drinking. In the context of ALD, alcohol abstinence continues to be the mainstay of treatment. The effectiveness of abstinence can be enhanced with behavioral interventions that can be delivered by nurses, social workers, and other members of the HIV care team (Addolorato et al., 2016; Scott-Sheldon et al., 2017; Singal et al., 2018).

The American Gastroenterological Association recommends that patients with NAFLD cirrhosis receive counseling on abstaining from alcohol and tobacco use (Loomba et al., 2020). Optimal management of diabetes, dyslipidemia, and obesity using pharmacologic approaches and lifestyle modification is indicated for those with NAFLD and advanced liver fibrosis (Loomba et al., 2020).

Finally, vaccination can effectively prevent HBV infection and is recommended for all PLWH without evidence of past or current HBV infection (Schillie et al., 2018). All individuals with HIV/HBV coinfection should receive an antiretroviral therapy (ART) regimen that includes 2 drugs with activity against HBV: tenofovir (TAF or TDF) plus lamivudine or emtricitabine (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2019; Terrault et al., 2018). If tenofovir (TAF or TDF) cannot be safely used, entecavir with a fully suppressive ART regimen may be used as an alternative. The goal of HBV treatment is to suppress hepatitis B viremia, thereby preventing progression of liver disease. Discontinuation of anti-HBV drugs should be avoided due to the risk of hepatitis flares

(Dore et al., 2010). Treatment is continued indefinitely with monitoring of virologic response (HBV DNA levels) as part of routine medical care.

Clinical tools to Screen for Liver Cancer in PLWH.—Screening for HCC in PLWH does not differ from that of the general population. The goal of screening is to reduce HCC-related mortality by diagnosing the malignancy earlier in the disease course. Decisions to initiate HCC surveillance are guided by cirrhosis status and underlying HCC risk factors. AASLD recommends HCC screening every 6 months for all adults with cirrhosis, and certain populations at higher risk of HCC (without evidence of cirrhosis), using ultrasonography with or without alpha-fetoprotein (AFP) laboratory tests (Marrero et al., 2018). Patients with a lesion ≥ 1 cm on ultrasound or AFP > 20 ng/mL should undergo diagnostic evaluation with a multiphasic CT or MRI. The American Gastroenterological Association recently published similar guidance, but additionally recommended screening for those with NAFLD and evidence of advanced fibrosis (Loomba et al., 2020).

Treating liver cancer in PLWH.—HCC treatment is categorized into curative and non-curative treatment options. Treatment selection is based on multiple factors including (but not limited to) tumor stage and cirrhosis status. Early-stage HCC is amenable to curative treatment. Curative treatment approaches include local ablation, surgical resection, or liver transplantation. Noncurative treatment approaches may be used to slow tumor progression and include transarterial chemoembolization, transarterial radioembolization, stereotactic body radiation therapy, and systemic chemotherapy. The effect of HIV on HCC treatment tolerability, toxicity, and effectiveness is not well described; however, in general, the prognosis for PLWH who develop HCC has been shown to be worse than for persons without HIV (Pinato et al., 2019; Torgersen et al., 2020). In the United States, 5-year HCC survival is estimated at 10% in the general population (Golabi et al., 2017). Early detection HCC is essential to maximize survival.

Anal Cancer and HIV

Epidemiology of anal cancer among PLWH in the United States and around the globe.—Anal cancer has emerged as a common malignancy in PLWH, ranking third in incidence among NADCs (Horner et al., 2020). It is relatively rare in the general population, accounting for 0.5% of all new cancer diagnoses, and fewer than 9,000 cases annually in the United States (National Cancer Institute, 2020). Although multiple epidemiological studies reported increases in U.S. anal cancer rates between 1997–2007 (Colón-López et al., 2018; Islami et al., 2017; Nelson et al., 2013), incidence rates have declined since 2008 (Shiels et al., 2018). PLWH have a 19-fold increased risk of incident anal cancer as compared to the general population (Colón-López et al., 2018). The highest incidence occurs in men who have sex with men (MSM) living with HIV, and in people with an AIDS diagnosis.

Globally, anal cancer trends differ by country income status, with increases in incidence reported through 2007 in Australia, Canada, Denmark, France, Italy, the Netherlands, and the United Kingdom (Islami et al., 2017). As in the United States, it is a relatively rare diagnosis, ranking thirtieth among all new cancer cases, and thirty-first in deaths (Bray et

al., 2018). Women are disproportionately affected, representing 58% of all new anal cancer diagnoses in 2018 (Bray et al., 2018).

Factors contributing to increased anal cancer risk in PLWH.—There is strong evidence implicating persistent human papilloma virus (HPV) infection as a cause of anal squamous cell carcinoma (ASCC) — the dominant histologic type of anal cancer (Islami et al., 2017). Although more than 100 HPV types have been identified (Tong et al., 2014), HPV types 16 and 18 have the greatest oncogenic potential. These high-risk HPV types are detected in anal tissues in approximately 90% of ASCC cases (Martel, 2017; Alemany et al., 2015; Saraiya et al., 2015). Behaviors that increase the risk of HPV acquisition (e.g., number of sexual partners, anal intercourse) are commonly associated with increased anal cancer risk (Wasserman et al., 2017).

Most adults acquire HPV at some point in their lives, but the virus is usually cleared spontaneously. Living with HIV effectively doubles the risk of HPV acquisition and halves the rate of HPV clearance as compared to not living with HIV (Looker et al., 2018). Suppressive ART appears to be important for reducing HIV persistence and, therefore, reducing anal cancer risk (Kelly et al., 2020). In a recent meta-analysis, those receiving ART had a 35% lower high-risk HPV prevalence than individuals who were ART naïve, and ART users with a sustained undetectable HIV viral load had a 44% reduced risk of anal cancer compared to those without (Kelly et al., 2020).

Other risk factors associated with HPV persistence and anal cancer include conditions associated with immunosuppression (e.g., with use of immunosuppressive therapies following organ transplantation; Larsen et al., 2020) and to a lesser extent smoking (Wasserman et al., 2017). The latter is of particular significance given the high prevalence of tobacco use that is observed in PLWH. (We refer the reader to the section on lung cancer above.)

Preventing anal cancer in PLWH.—Recommended strategies for primary anal cancer prevention include HPV vaccination, behavioral strategies to reduce HPV exposure (e.g., condom use), smoking cessation, and treatment of pre-cancerous squamous intraepithelial lesions (SIL). These lesions are classified as low-grade squamous intraepithelial lesions (LSIL) or high-grade squamous intraepithelial lesions (HSIL) based on their malignancy potential (Roberts et al., 2017). Nurses are well-positioned to counsel patients on these strategies and to administer appropriate vaccinations. The Advisory Committee on Immunization Practices now recommends catch-up vaccinations for all people through age 26 years, regardless of HIV status (Meites et al., 2019). The 9-valent HPV vaccine (Guardasil-9) is the only FDA-approved vaccine currently available in the United States. It provides protection against high-risk HPA types that are implicated in the development of anal cancer. The HPV vaccine is FDA-approved for prevention, but not therapeutic use.

The Centers for Disease Control and Prevention (CDC) strongly recommend use of male latex condoms for preventing transmission or acquisition of HPV infection in PLWH (Panel on Opportunistic Infections in Adults and Adolescents with HIV, 2019); however, patients should be counseled that HPV can still be transmitted by skin to skin contact with HPV-

infected areas of the body that are not covered by a condom. Smoking cessation is broadly recommended for PLWH. Those with or at high-risk for anal cancer should be counseled on its association with both primary anal cancer and recurrence.

Currently, topical imiquimod, fluorouracil, trichloroacetic acid and cidofovir, and ablative therapies are recommended options for the treatment of LSIL or HSIL (Stewart et al., 2018). Comparisons of the various treatment protocols are limited. One ongoing study, the Anal Cancer HSIL Outcomes Research (ANCHOR) trial (NCT02135419), aims to determine whether screening and treatment of HSIL is effective in reducing subsequent anal cancer in PLWH compared with active monitoring (including anal cytology combined with high resolution anoscopy [HRA] and biopsy of any concerning lesions).

Screening tools for the detection of anal cancer.—Data on the benefits of routine anal cancer screening are not yet definitive, and there are currently no national recommendations for routine anal cancer screening in PLWH.. In the United States, the New York State Department of Health AIDS Institute recommends routine anal cancer screening using digital rectal examination and anal cytology for MSM living with HIV, cisgender women, transgender women, and transgender men beginning at age 35 (New York State Department of Health AIDS Institute, 2020). The goal of anal dysplasia screening is to identify and treat HSIL before they progress to irreversible high-grade lesions or local invasive disease (New York State Department of Health AIDS Institute, 2020). The CDC acknowledge that some specialists recommend anal cytology for PLWH, but recommend that it only be considered if there is access to HRA services (Panel on Opportunistic Infections in Adults and Adolescents with HIV, 2019). This is because abnormal cytology results require follow-up with direct visualization of the anal canal using HRA and biopsy of suspicious lesions.

Pending definitive randomized trials, a recent observational study provides some evidence for the benefit of structured screening programs using anal cytology in PLWH. In a single-center retrospective analysis of 3,111 PLWH receiving outpatient HIV care, participation in an annual anal cancer screening program was associated with a significant reduction in invasive ASCC incidence (HR, 0.20; 95% CI, .04–.97; Revollo et al., 2020). The median length of follow-up was 4.6 years in the screening group and 4.8 years in the non-screening group (Revollo et al., 2020).

Treating anal cancer.—Treatment modalities for ASCC may include radiation therapy, chemotherapy, excision, or combined modalities. Survival rates at five years exceed 80% in early stage cancer, with worsening survival in later stages (Leeds, 2016). Recurrence is common and optimal surveillance regimens have yet to be established. Data are mixed on whether PLWH experience greater treatment toxicities than those living without HIV, although overall survival appears to be similar (Bryant et al., 2018).

Diabetes and Chronic Kidney Disease among People with HIV

Epidemiology of Diabetes Mellitus in the United States and Around the Globe

Globally, it is estimated that 8.8% of adults have diabetes mellitus, and that number is expected to increase to 10.4% by 2040 (Ogurtsova et al., 2017). Developing countries may experience an increase in diabetes as high as 20% over the next 10 years (Cho et al., 2018). The prevalence of diabetes in PLWH in the United States is approximately 12% (Kalra et al., 2011), compared to a prevalence of 10.5% in the general population (CDC, 2020), and a global prevalence of 8.5% (Emerging Risk Factors Collaboration, 2010). A similar pattern of slightly increased prevalence has been reported in other parts of the world, including Sub-Saharan Africa and Asia (Kagaruki et al., 2014). As the prevalence of diabetes continues to increase worldwide (Emerging Risk Factors Collaboration, 2010), it can be assumed that the prevalence in PLWH will also increase (Kalra et al., 2011).

Diabetes mellitus physiology and its impact on PLWH.—Diabetes is a group of metabolic disorders manifested in the body's ability to produce and/or use insulin at the cellular level. The causes and risk factors for diabetes type 2 in PLWH are similar to those without HIV: aging, obesity, genetic disposition, and inflammation (Sarkar & Brown, 2019). Obesity leads to increased levels of circulating insulin which, if prolonged, can lead to insufficient production of insulin (Van Greevenbroek et al., 2013). PLWH are at slightly higher risk for developing diabetes, which is associated with a longer time living with HIV, chronic low levels of inflammation, oxidative stress, and mitochondrial damage caused by HIV treatment (Blas-Garcia et al., 2011; Brown et al., 2010; Tingstedt et al., 2019). For PLWH, an additional diagnosis of diabetes decreases life expectancy (Park et al., 2019). Poorly controlled diabetes leads to end organ damage, including kidney damage, due to the deleterious effects of excess glucose on the vascular system (Gregg et al., 2016). In one study of PLWH (N = 10,043), the only participants with acute kidney disease were those also diagnosed with diabetes (Park et al., 2019).

As Black, indigenous populations, and people of color (BIPOC) are over-represented in PLWH, racism can negatively affect diabetes mellitus-related health outcomes in these populations by inducing chronic stress and inequities in health care systems (Harrell et al., 2011). Notably, higher rates of discrimination have been associated with higher levels of glucose (Wagner et al., 2015). Accordingly, BIPOC experience worse diabetes-related health outcomes, such as amputations, when compared to the White population (Osborn et al., 2013). As disparities continue, health care providers need to actively advocate for equitable diabetes screening and medical treatment.

Preventing and screening for diabetes in PLWH.—People at risk for developing diabetes should be encouraged to control their weight, eat a low carbohydrate diet, and exercise. Losing a small amount of weight (5%−7%) and increasing weekly exercise decreases the risk of diabetes by over 50% (Tabák et al., 2012; CDC, 2018). As time on HIV treatment is a non-modifiable variable associated with the development of diabetes, close monitoring and early treatment would be appropriate in this population.

Screening tools include laboratory tests of hemoglobin A1C (A1C) and fasting glucose. Diabetes is diagnosed with an A1C greater than or equal to 6.5% or an abnormal oral glucose tolerance test (OGTT), which, while more sensitive, is less commonly used in the clinical setting for adults (Olson et al., 2010). For PLWH, A1C may be artificially lower due to ART-induced hemolysis that decreases the lifespan of hemoglobin cells (Slama et al., 2014). In contrast, the sensitivity of the OGTT to detect diabetes is not affected by HIV medications (Gianotti et al., 2011).

Treating diabetes in PLWH.—The introduction of new oral diabetes medications have improved glycymic control in people with diabetes. Current diabetes treatment recommendations for PLWH include an initial oral anti-diabetes medication (such as metformin) with the addition of a second medication if treatment goals are not obtained (such as a sulfonylurea, a thiazolidinedione, a sodium-glucose cotransporter-2 [SGLT-2] inhibitor, or a dipeptidyl peptidase – 4 [DPP-4] inhibitor; Qaseem et al., 2017). In one study of PLWH with diabetes, participants who were using insulin to manage glucose were more likely to reach A1C goals than those on oral anti-diabetes medications (ZuÑiga et al., 2016); however, it is important to note that many patients prefer oral over injectable treatment (Qaseem et al., 2017).

Recommendations for glucose self-monitoring vary from a few times a day to continuous monitoring, depending upon use and intensity of insulin treatment (American Diabetes Association, 2017). Barriers to monitoring include reluctance to test in a work place, cost, and stigma (Ong et al., 2014). Among PLWH, stigma may be a greater barrier due to concerns of exposing co-workers who are aware of the HIV status to a blood-borne pathogen.

Diets need to be based on patients' personal preferences and cultural norms to promote sustained adherence (MacLeod et al., 2017). Interventions that include carbohydrate counting have shown efficacy for decreasing A1C (MacLeod et al., 2017). For PLWH with diabetes mellitus, a low carbohydrate diet can be compatible with the need to consume vitamin-rich foods to support the immune system (Botros et al., 2012).

Food insecurity can interfere with diabetes management. In non-HIV-infected populations, food insecurity has been associated with lower rates of glucose self-monitoring (Seligman et al., 2010), perhaps due to the price of testing strips and competing financial priorities (Gucciardi et al., 2014). Food insecurity may be alarmingly high among PLWH, with one study reporting a prevalence of 71% among adults living in a resource-rich setting (Anema et al., 2011). Food insecurity may also affect HIV treatment outcomes as it has been associated with decreased antiretroviral adherence and incomplete viral suppression (Weiser et al., 2013).

Diabetes and HIV in low- and middle-income countries.—Diabetes has become a global epidemic, driven by a combination of Western diet and sedentary lifestyle, with cases projected to reach 438 million by 2030 (Emerging Risk Factors Collaboration, 2010). Rates of diabetes among PLWH in low- to middle-income countries (LMIC) have been difficult to assess because treatment is often siloed and there may be no screening for

chronic conditions. In some LMIC, food insecurity among PLWH may be as high as 90% (Benzekri et al., 2015). Successfully managing, supporting, and monitoring for the development of diabetes will be key for decreasing morbidity and mortality. Patient-centered interventions that are tailored to culture and personal preferences, combined with addressing social determinants of health, will improve patients' attainment of diabetes goals.

Epidemiology of chronic kidney disease in the United States and around the globe.—One potential consequence of poorly managed diabetes is chronic kidney disease (CKD). Approximately 10–20% of PLWH have an additional diagnosis of CKD, presenting with proteinuria and reduced glomerular filtration rate (GFR; Park and ZuÑiga, 2018). While it is one of the most common causes of HIV-related morbidity and mortality (Adedeji et al., 2015; Kim et al., 2011; Szczech et al., 2004), less than 1% of PLWH (1.9 per 1,000 patients) with CKD will progress to end stage renal disease (ESRD), a reversible stage of kidney disease that requires dialysis (Bickel et al., 2013).

Unlike many other chronic conditions, CKD is often a negative sequela of other chronic, nephrotoxic conditions, such as hypertension, diabetes, or hepatitis. Additional risk factors include older age, Black race, and injection drug use; high CD4+ T cell counts are protective (Bickel et al., 2013; Bonjoch et al., 2014). Black PLWH are at higher risk for developing CKD than non-Hispanic, White PLWH due to a combination of predisposing genetic polymorphisms and health care inequities, such as delayed referrals (Norton et al., 2016). For all PLWH, an additional risk factor is use of nucleoside reverse transcriptase inhibitors (NRTI) which can damage renal tubules and reduce kidney function; however, the viral suppressive benefits of NRTI may outweigh the risk of developing CKD (Scherzer & Shlipak, 2015).

Prevalence of CKD in LMIC has not been well-characterized due to a paucity of studies in these regions (Stanifer et al., 2018). In LMIC, the prevalence of CKD in PLWH ranges between 4.7% to 12.3%, which is similar to people without HIV (Ekrikpo et al., 2018; Neuen et al., 2017; Stanifer et al., 2016). As Westernized diets become more common and obesity is increasing in LMIC, the rates of CKD are increasing in tandem with diabetes (Neuen et al., 2017). Additional risk factors for CKD in LMIC include poor sanitation and waste disposal, and heavy environmental pollution (Stanifer et al., 2016); in one systematic review, CD4+ T cell count and ART did not significantly contribute to the development of CKD (Ekrikpo et al., 2018).

Screening, prevention and treatment of CKD in PLWH.—Early identification of those at risk for CKD is critical to preserving kidney function in PLWH. Screening labs include eGFR <60 mL/min/1.73 m^2 and/or presence of protein in the urine (Park & Zuniga, 2018). Kidney function is monitored using albuminuria, which is flagged for concern when the albumin/creatine ratio is ≥30 mg/g. A first morning urine catch is the more effective method for screening for CKD than a random urine test (Saydah et al., 2013). Mocroft and colleagues (2015) developed a CKD risk assessment score based on 13 traditional and HIV-related risk factors, that can help identify patients who are not good candidates for certain nephrotoxic HIV medications, such as tenofovir disoproxil fumarate.

The cornerstone for CKD prevention and treatment is the management of chronic conditions that lead to CKD. Limited access to nephrology care is associated with progression to end stage renal disease, which is frequently common in LMIC; linkage to care and referral to specialists will improve outcomes for PLWH (Gillespie et al., 2015; Lucas et al., 2014).

If CKD progresses to ESRD, patients may require renal replacement therapy, dialysis, or renal transplantation. Dialysis for PLWH does not require isolation or precautions above standard precautions. It is recommended that PLWH have an arterial venous fistula placed for vascular access instead of peripheral or subclavian catheters to reduce the risk for a central line associated blood-stream infection. It is recommended that ART dosages be reduced due to the nephrotoxicity, although this does not apply to medications excreted by extra-renal routes (Trullas et al., 2011). NRTI are filtered from the blood during dialysis, therefore, they must be administered after completion of dialysis (Diana & Naicker, 2016).

In 2013, the U.S. Congress passed, and President Obama signed, the HIV Organ Policy Equity Act, authorizing PLWH to donate organs, including kidneys. PLWH are eligible for renal transplant in most countries; however, in addition to the normal restrictions, PLWH must also have a CD4+ T cell count over 200 cells/ml^3, no neoplasms or immune reconstitution, no opportunistic infections in the previous year, and viral suppression (Trullas et al., 2011). Post-transplant, PLWH need to be monitored for potential drug-drug interactions between immunosuppressive medications and ART (Lucas et al., 2014) and for changes in viral load (Trullas et al., 2011). PLWH show a higher rate of rejection and mortality compared to those without HIV (Stock et al., 2010).

Intersections

It is rare that aging PLWH experience just one additional comorbidity (Friedman & Duffus, 2016; Kim et al., 2012). Increasingly, PLWH experience multimorbidities characterized by shared pathways that can interact and lead to the development of other conditions (Wong et al., 2017). For example, increased weight and a poor diet can lead to hypertension and diabetes, vascular disease, and ultimately kidney disease. While prevention of conditions through the non-pharmacological mitigation of these shared pathophysiological pathways is the ideal clinical approach, PLWH often face many challenges to early prevention. If pharmacotherapy is used to treat one or more of these chronic conditions, it is imperative that the clinician recognize the increased risk of polypharmacy–related adverse events in this population (Courlet et al., 2019; Devanathan et al., 2019), particularly as they age. Working with a pharmacist to recognize and reduce these potential drug-drug interactions and adverse events is a critical strategy to maintaining the health and well-being of PLWH confronting multiple comorbidities.

Globally, PLWH often confront social challenges that increase their probability of developing multiple chronic health conditions. Poverty, low socioeconomic position, institutional racism, homophobia, ageism, and sexism can intersect throughout the lifespan to create conditions (e.g., discrimination, segregation, increased domestic work, gender norms that discourage physical activity, sexual abuse) that increase risk for many of the

chronic conditions we reviewed (Caceres et al., 2019; Chrisler et al., 2016; O'Neil et al., 2018; Walsemann et al., 2016; Williams et al., 2019) and for HIV.

Preventing and mitigating these deeply ingrained societal conditions is complex, but also necessary to optimize the health of PLWH. As nurse clinicians, scientists, educators, and activists, we are uniquely positioned at the patients' bedsides, in their communities, and due to the growth of virtual spaces, in their homes, to do what we do best. Assess and ask explicitly, but gently, about poverty, discrimination, sexual and other forms of abuse, and then listen to the patient, student, or the participant (Hardeman et al., 2018). While there are few evidence-based treatments for societal ills, the trauma-informed care model can be a guide when working with individuals (Purkey et al., 2018). At a structural level, we can work with our professional associations and local communities to learn more about these injustices and act to change the policies and systems that perpetuate them.

Finally, as aging PLWH are increasingly diagnosed with chronic conditions, it will be important to re-visit patients' goals for their care. Simply asking them what matters the most to them now can facilitate shared-decision making around the treatment plan. Each encounter is a chance to update their goals of care and, if the patient is willing, to complete advance directives. An individual's preferences can evolve throughout the aging process and a candid conversation about what matters to them is important. This can also be an opportune time to discuss socioeconomic challenges that may limit patients' abilities to achieve their own health goals and strategize ways to overcome those challenges.

Conclusions

Nurses will increasingly encounter PLWH who are also living with one, or multiple, chronic physical comorbidities. Providing excellent, patient-centered care to this growing population will require nurses in all settings to recognize the unique risk HIV poses to the development of these conditions and to understand how to prevent, screen, and potentially treat these often intersecting conditions. While our review provides a summary of this current evidence, it is also clear that the best care will need to be delivered by a coordinated multidisciplinary team. In many settings, HIV care has led the way in detection, treatment, adherence, and self-management – all of which requires a multidisciplinary, egalitarian team approach. We believe that the HIV community comprising nurses, providers, researchers, and advocates can do the same for chronic comorbidity care.

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KEY CONSIDERATIONS

- People living with HIV are aging and are at elevated risk for developing multiple chronic health conditions, including cardiovascular diseases, COPD, cancers, chronic kidney disease, and diabetes mellitus.
- Similar to HIV, each chronic health condition requires its own prevention, screening, and treatment management strategies; yet these strategies often interact with the others, putting PLWH at risk for suboptimal chronic disease management.
- Nurse clinicians, scientists, educators, and activists are uniquely positioned at the patients' bedsides, in their communities, and increasingly in their homes to help mitigate the complex societal and structural challenges that increase risk for these chronic health conditions.
- By adopting multidisciplinary, collaborative care and incorporating evidence-based findings, teams may more effectively address the growing multimorbidity burden in the growing population of people aging with HIV.

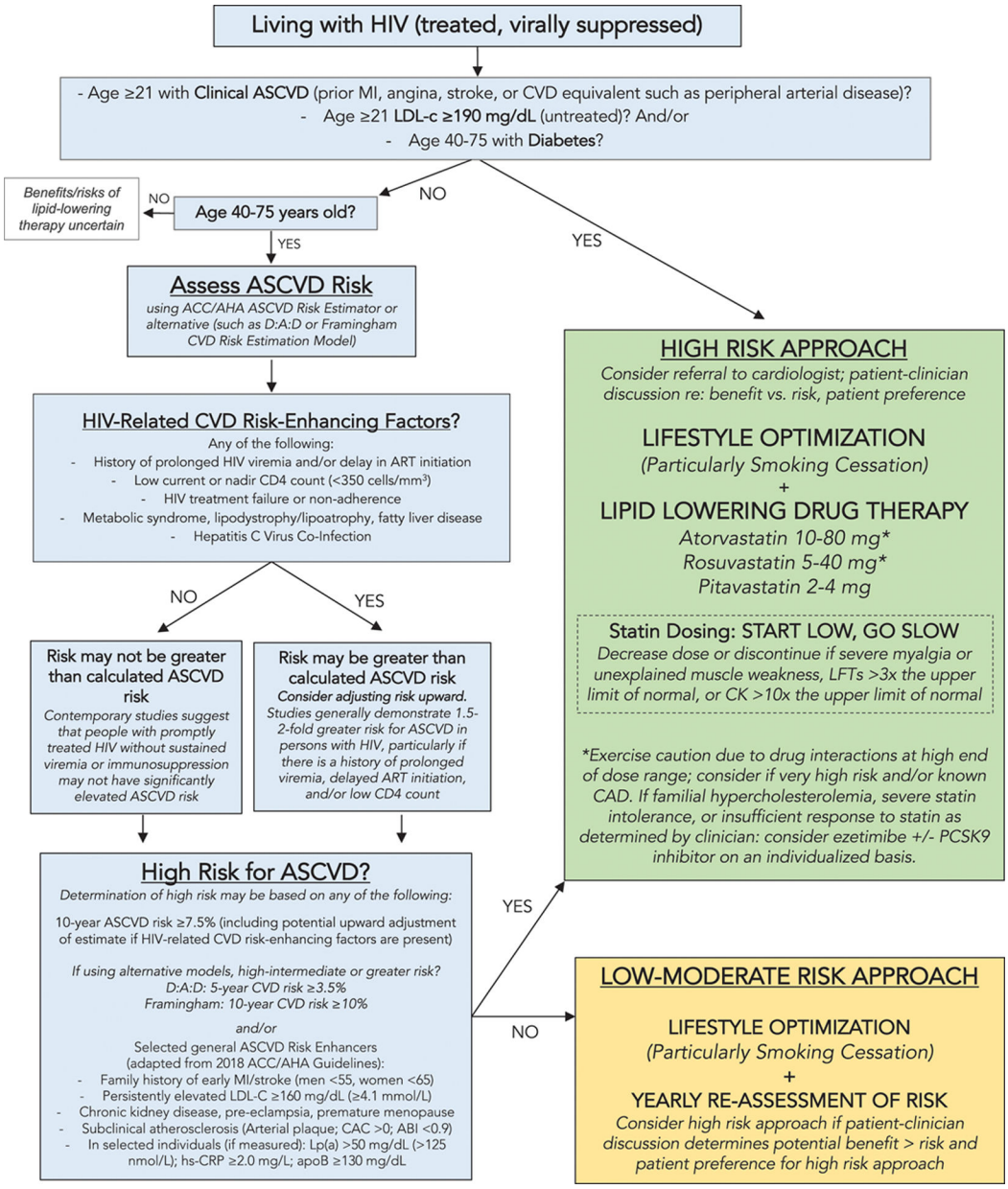

Figure 1. Pragmatic approach to atherosclerotic cardiovascular disease (ASCVD) risk assessment and prevention in treated HIV infection

(Reprinted with permission Circulation [2019], 140:e98-e124 © 2019 American Heart Association, Inc.). This figure applies to people with controlled HIV. For people with uncontrolled HIV, the first priority is appropriate HIV therapy to achieve viral suppression. Thresholds based on findings of elevated CVD risk at current or nadir CD4 count <200, <350, and <500 cells/mm^3 in Silverberg et al. (2014), Lichtenstein et al., 2010 and Triant et al., 2010. Hazard ratios and incidence rate ratios of 1.4 to 2.1 for myocardial infarction (MI) for people living with HIV (PLWH) vs uninfected people demonstrated in Freiberg et al., (2013) Triant et al., 2007 and Silverberg et al. (2014). Hazard ratio of stroke for PLWH vs. uninfected people was 1.40 in Chow et al. (2012).

Note. ABI indicates ankle-brachial index; ACC/AHA, American College of Cardiology/ American Heart Association; apoB, apolipoprotein B; ART, antiretroviral therapy; CAC, coronary artery calcium; CAD, coronary artery disease; CK, creatine kinase; CVD, cardiovascular disease; D:A:D, Data Collection on Adverse Events of Anti-HIV Drugs; hs-CRP, high sensitivity C-reactive protein; LFT, liver function test; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein A; and PCSK9, proprotein convertase subtilisin-kexin type 9.

Table 1.

Prevention, Assessment and Treatment Strategies for Chronic Comorbidities in HIV

Chronic Condition	HIV Risk	Prevention Strategies	Monitoring/Assessment Strategies	Treatment Strategies	Structural Strategies
ASCVD	1.5- to 2-fold greater risk	↓ Hypertension, ↓Hypocholesteremia ↓ Hyperglycemia ↓ Weight 🚭Smoking ↑Physical activity ↑ Healthy diet	• Routine (or at home) blood pressure monitoring • Routine weight, waist circumference, and smoking assessment • Annual fasting lipid panel & HgA1c • ASCVD risk calculator • Exercise vital sign • Coronary calcium scoring • Cardiorespiratory fitness testing	• Maintain a suppressed HIV viral load • Nutrition consultation and follow-up • Physical activity prescription • Lipid lowering agents • Antihypertensive agents	Shift to collaborative care models to include cardiovascular specialist, pharmacist, registered dietician, physical therapy
COPD	~10% higher risk	🚭Smoking (consider using the 5 As) ↓ exposure to environmental pollutants • Administer influenza & pneumococcal vaccines	• Smoking (pack/year) assessment • Pulmonary function tests for those over age 40 and/or with respiratory symptoms	• Maintain a suppressed HIV viral load • Respiratory inhalers • Pulmonary rehabilitation, administration of oxygen therapy	Collaborative care models to include respiratory specialist, pharmacist, smoking cessation counselor Support community and workplace initiatives to reduce tobacco use (e.g., tobacco-free zones, tobacco/vaping taxes, age of purchase)
Lung Cancer	~2-fold greater risk (Hernández-Ramírez et al., 2017)	🚭Smoking (consider using the 5 As) ↑Physical activity ↑ Healthy diet	• Smoking (pack/year) assessment • Annual low-dose CT for those at high risk	• Surgery	
Liver Cancer	4-fold higher risk	↓Injection drug use ↓Alcohol & tobacco use ↑Safe sex Administer Hepatitis B vaccine	• Substance use screening and brief intervention at each encounter • Ultrasonography with or without alpha-fetoprotein tests every 6 months for those at high risk	• Maintain a suppressed HIV viral load • Direct acting antiviral medications • Transarterial chemoembolization & radioembolization, • Stereotactic body radiation therapy • Systemic chemotherapy	Collaborative care models to include hepatology, pharmacist, substance use/behavioral medicine specialist Support use of needle exchanges

Chronic Condition	HIV Risk	Prevention Strategies	Monitoring/Assessment Strategies	Treatment Strategies	Structural Strategies
Anal Cancer	19-fold higher risk	• Administer HPV Vaccine ↓ Exposure to HPV (e.g., condom use) • Treat anal lesions Smoking	• Unclear benefit of routine screening using anal cytology	• Radiation therapy • Chemotherapy • Excision of lesion	
Diabetes Mellitus	~2-fold reduced risk in HIV, but growing (Herrin et al., 2016)	↓ Hyperglycemia ↓ Weight ↑Physical Activity ↑ Healthy Diet	• Daily glucose testing (by the PLWH) • Regular fasting glucose test & HgA1c • Exercise vital sign • Food Insecurity assessment	• Nutrition consultation and follow-up • Physical activity prescription • Blood glucose lowering agents	Adopt collaborative care models to include endocrinology, nephrology, pharmacy, registered dietetics, physical therapy Support increased access to promote food security including SNAP

Note. ASCVD – Atherosclerotic Cardiovascular Disease, COPD – Chronic Obstructive Pulmonary Disorder, 5 As – Ask, Assess, Advise, Agree, Assist, HPV – Human Papillomavirus, PLWH – People Living with HIV, SNAP - Supplemental Nutrition Assistance Program

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