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HIV AND CARDIOVASCULAR DISEASE REVIEW SERIES

Cardiac and Renal Comorbidities in Aging People Living With HIV

Keir McCutcheon, Unati Nqebelele, Lyle Murray, Teressa Sumy Thomas, Dineo Mpanya, Nqoba Tsabedze

ABSTRACT: Contemporary World Health Organization data indicates that ≈39 million people are living with the human immunodeficiency virus. Of these, 24 million have been reported to have successfully accessed combination antiretroviral therapy. In 1996, the World Health Organization endorsed the widespread use of combination antiretroviral therapy, transforming human immunodeficiency virus infection from being a life-threatening disease to a chronic illness characterized by multiple comorbidities. The increased access to combination antiretroviral therapy has translated to people living with human immunodeficiency virus (PLWH) no longer having a reduced life expectancy. Although aging as a biological process increases exposure to oxidative stress and subsequent systemic inflammation, this effect is likely enhanced in PLWH as they age. This narrative review engages the intricate interplay between human immunodeficiency virus associated chronic inflammation, combination antiretroviral therapy, and cardiac and renal comorbidities development in aging PLWH. We examine the evolving demographic profile of PLWH, emphasizing the increasing prevalence of aging individuals within this population. A central focus of the review discusses the pathophysiological mechanisms that underpin the heightened susceptibility of PLWH to renal and cardiac diseases as they age.

Key Words: aging ■ cardiovascular diseases ■ heart failure ■ HIV ■ inflammation ■ interleukin

There are approximately 39 million people living with human immunodeficiency virus (HIV [PLWH]) globally, with an estimated 2 million new infections occurring annually.[1] Although 70% of PLWH reside in low- and -middle-income countries, an estimated 1 189 700 PLWH live in the United States, and >50% of these are over the age of 50 years, with 26% in the sixth decade alone.[2] In sub-Saharan Africa, the HIV infection prevalence rate for older adults is already higher than the prevalence rate in the total population.[3] In 2011, about 1 in 7 PLWH in South Africa were 50 years or older; by 2040, this proportion is estimated to be one in 4.[4] Recent modeling data suggests that up to 47% of PLWH in Kenya will be 50 years of age or older by 2040.[5]

With improved survival, PLWH are increasingly likely to experience age-related and HIV-related comorbidities, including cardiac diseases and renal insufficiency.[6,7] Compared with people without HIV (PWoH), the increase in absolute cardiovascular disease (CVD) burden in older PLWH on combined antiretroviral therapy (cART) is due to higher rates of heart failure (HF) with and without reduced ejection fraction,[8] coronary artery disease[9] and sudden cardiac death.[10] Similarly, chronic kidney disease (CKD) remains an important noncommunicable disease among aging PLWH, with prevalence rates varying depending on geographic region and formulae used to estimate the glomerular filtration rate.[11] This narrative review will describe the interplay between chronic inflammation, HIV, and endothelial dysfunction leading to cardiac and renal comorbidities commonly encountered in aging PLWH.

EPIDEMIOLOGY OF CVD AND CKD IN AGING PLWH

Aging is an inevitable biological process accompanied by distinct challenges, such as a heightened burden

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Nonstandard Abbreviations and Acronyms

ART	antiretroviral therapy
ASCVD	atherosclerotic cardiovascular disease
cART	combination antiretroviral therapy
CKD	chronic kidney disease
CVD	cardiovascular disease
DAD	Data Collection on Adverse Events of Anti-HIV Drugs
EVERE2ST-HIV	Evaluation of Residual Platelet Reactivity After Acute Coronary Syndrome in HIV
FSGS	focal segmental glomerulosclerosis
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HIVAN	human immunodeficiency virus-associated nephropathy
IL	interleukin
INSTI	integrase strand transfer inhibitor
LDL-C	low-density lipoprotein cholesterol
Lpa	lipoprotein a
NNRTI	nonnucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors
PI	protease inhibitor
PLWH	people living with human immunodeficiency virus
PWoH	people without HIV
VACS	Veterans Aging Cohort Study

of comorbidities, polypharmacy, frailty, oxidative stress, and increased risk of myocardial and renal dysfunction.[12,13] Age is an important contributor to increasing comorbidities among PLWH. Data from the United States predicts that by 2030, nearly 50% of PLWH will have multiple comorbidities, with significant increases in CKD, dyslipidemia, diabetes, and myocardial infarction.[14] In South Africa, PLWH over 50 years of age have a 2-fold increased risk of having multiple comorbidities, including diabetes and hypertension.[15] Among 450 PLWH from Tanzania, age was the only independent predictor of diminishing renal function.[16] Therefore, as PLWH age, they are at greater risk of cardiac and renal comorbidities. These noncommunicable diseases, particularly CKD, are a global public health challenge whose burden has increased in the last 2 decades, with an increase in ranking among the global causes of disability-adjusted life-years, rising from 29th in 1990 to 18th in 2019 and from 14th to 8th in the individuals aged ≥50 years.[17]

In a meta-analysis on the prevalence of CKD in PLWH, the global prevalence of CKD was 6.4% using the Modification of Diet in Renal Disease (MDRD) equation and 4.8% using the CKD Epidemiology Collaboration (CKD-EPI) equation.[18] Based on the World Health Organization region classification, on subgroup analysis, Africa had the highest CKD prevalence among PLWH of 7.9%,[18] as depicted in Figure 1A.

Among the 9 African countries included in the systematic review by Ekrikpo et al,[18] PLWH in Nigeria had the highest prevalence of CKD at 19.3%, followed by Uganda at 15.1% and Ghana at 13% (Figure 1B). In another meta-analysis by Stanifer et al[19] evaluating the epidemiology of CKD in the general population residing in sub-Saharan Africa, the overall prevalence of CKD was 13.9%, with estimates ranging from 2% in Cote d'Ivoire to 30% in Zimbabwe. Some of the challenges encountered by Stanifer et al were a paucity of data and a lack of good quality studies, with only 3% of studies being of high quality.[19] There was also heterogeneity in the measurement of renal function, and different formulas were used to estimate the glomerular filtration rate.[19]

The virological and immune status of PLWH are important risk factors for CVD. There is substantial evidence that viral suppression and improved immunologic status are associated with lower CVD risk.[20] Demographic and geographic factors also play a role in the development of CVD. PLWH from high-income countries with access to cART are more likely to develop atherosclerotic CVD (ASCVD). In contrast, >95% of CVD among individuals from low-and-middle-income countries are not related to ASCVD.[21] As access to HIV treatment evolves, cardiac and renal complications also change over time.

Biological sex may be an important cardiovascular risk as PLWH age. One systematic review showed that women with HIV are more likely to enter menopause earlier than matched PWoH controls.[22] Early menopause would put aging women with HIV at an increased risk of ASCVD compared with the general population. Furthermore, women living with HIV are already at increased risk of myocardial infarction (relative risk, 2.7–2.9 compared with PWoH) versus the risk in men living with HIV (relative risk, 1.4).[23] The reasons for this higher risk are unclear. It may be related to higher levels of immune activation in women.[23]

A substantial risk of CVD events remains even when HIV infection is controlled.[24] Large observational studies of PLWH in high-income countries have shown that there is a pooled ≈2-fold increased risk for developing

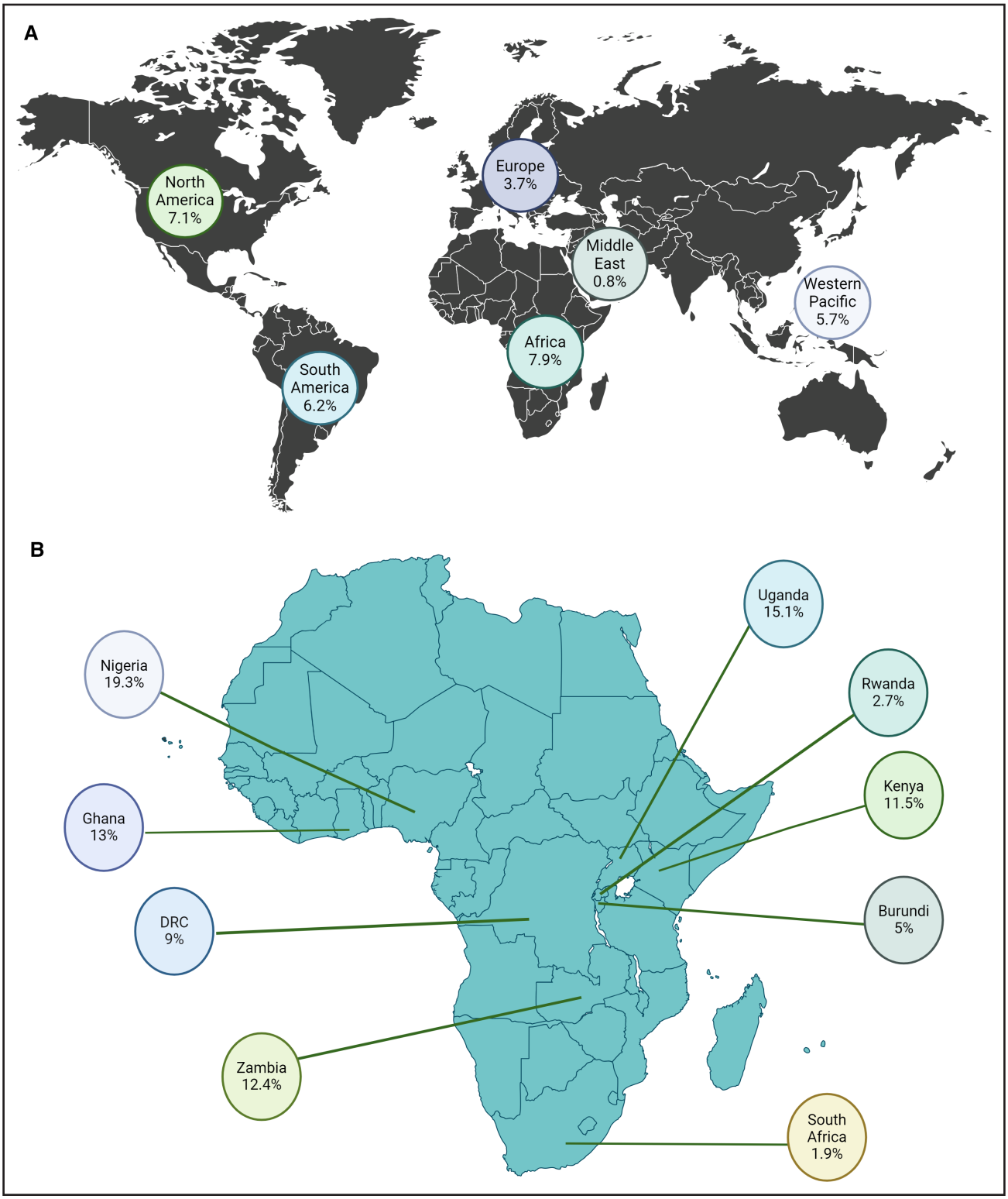

Figure 1. Prevalence of chronic kidney disease (CKD) in people living with HIV (PLWH).
A, World map showing the prevalence of CKD in PLWH. **B**, The prevalence of CKD in PLWH in 9 African countries. The data on the prevalence of CKD in PLWH in 60 countries emanates from a systematic review and meta-analysis by Ekrikpo et al.[18] Globally, the highest prevalence of CKD among PLWH is in Africa, followed by North America. Renal impairment was defined as creatinine clearance <60 mL/min. The glomerular filtration rate was estimated using the Modification of Diet in Renal Disease (MDRD) equation. DRC indicates Democratic Republic of Congo.

ASCVD-related events due to HIV infection, even when adjusting for age, sex, race, hypertension, diabetes, and cholesterol levels.[9] This is similar to the attributable ASCVD risk of hypertension, smoking, diabetes, and hyperlipidemia in PWoH. CVD is now an important cause of death in PLWH, contributing to 6.5% to 11.5% of overall mortality.[25,26] Moreover, PLWH who have CVD are generally treated less aggressively by being subjected to fewer cardiovascular interventions, have a greater risk of developing cardiovascular complications, and have higher CVD-related death rates compared with PWoH.[27] The rising prevalence of CVD and CKD in PLWH calls for collaboration between epidemiologists, policymakers, and health care practitioners to implement early screening and preventative campaigns, focusing on public health interventions that promote a healthy lifestyle incorporating physical activity.

HIV INFECTION, AGING, AND INFLAMMATION

Inflammation is central to the aging process and the pathogenesis of most age-related chronic conditions, including cardiovascular and renal comorbidities.[28,29] The term inflamm-aging has been used to describe the chronic inflammation that develops with age.[30] This complex process includes immunosenescence, garbaging, alterations in the gut microbiome, clonal hematopoiesis, and genetic dysregulation that occur with aging.[29] Similarly, aging PLWH are characterized by evidence of chronic inflammation.[31] Data from rural South Africa comparing inflammatory markers in PLWH and PWoH aged 50 years and older showed that, even with cART, markers of inflammation remain elevated in PLWH.[32] Compared with age-matched controls, the low-grade inflammation associated with aging contributes to frailty in PLWH.[33] Furthermore, PLWH are biologically older than matched controls, especially if coinfections exist.[34] In addition to the earlier onset of aging-related chronic conditions in PLWH, analysis of epigenetic DNA methylation patterns has shown significant epigenetic age acceleration and telomere length shortening in PLWH compared with matched PWoH.[35,36] These changes only partially improve on cART.[36]

The HIV itself initiates a process of inflammation and immune activation that, although significantly reduced on cART, persists despite apparent HIV viral suppression.[37] Understanding the mechanisms by which HIV infection causes inflammation and immune activation is key to the development of therapeutic strategies to mitigate cardiovascular and renal comorbidities in aging PLWH. The chronic inflammation seen in aging PLWH is caused by an interplay between aging and multiple HIV-associated factors (Figure 2).

Persistent Viral Replication

HIV replication in the absence of cART is associated with CD4+ T-cell depletion and the elevation of cellular and soluble markers of inflammation.[38] This is demonstrated by increased levels of activation markers on cellular components of the adaptive and innate immune responses to HIV as well as the elevation of proinflammatory cytokines.[38] The level of immune activation is correlated with the magnitude of viremia and is caused by the direct antigenic stimulation of the virus and its products.[39]

Multiple HIV proteins have been detected in a large proportion of patients on cART with undetectable viral loads.[40] The HIV protein negative factor (*nef*) plays a prominent role in inflammation through its effect on immune activation and impact on cholesterol metabolism and lipid rafts.[40,41] Elite controllers, who can maintain healthy CD4+ T-cell counts and suppress viremia to below 50 copies/mL in the absence of cART, demonstrate significantly lower levels of T-cell activation than individuals with chronic untreated HIV infection.[42] Levels of immune activation in cART-treated individuals are lower still; however, they remain above healthy PWoH controls.[43] cART can suppress HIV viral loads below the level of detection of conventional assays. However, they do not eradicate the viral DNA integrated into the host long-lived cells that comprise the latent HIV reservoir. Ultrasensitive assays can detect HIV RNA in plasma in cART-treated individuals with undetectable viral loads on commercial assays.[44] The source of this viremia may well be the product of low-level ongoing viral replication or the activation of resting CD4+ T cells harboring latent proviruses resulting in immune stimulation despite cART.

Immune Cell Activation

The cellular drivers of inflammation in HIV infection involve pathways involved in the innate and adaptive immune responses to HIV. The characteristic immunosenescence that drives inflammation in aging is also present in PLWH.[38] HIV infection is characterized by CD4+ T-cell activation, depletion, and CD8+T-cell activation. This activation is evidenced by the expression of CD38 and Human Leukocyte Antigen-DR isotype (HLA-DR) on the cell surface.[45] Persistent HIV-mediated T-cell activation can lead to T-cell exhaustion and the expression of markers, such as PD-1, TIM-3, and LAG-3, which are associated with impaired proliferation, cytokine production, and cytotoxic ability.[46] Interestingly, parallels can be observed between the impact of HIV infection and aging on T-cell exhaustion and functionality.[38,47] The balance between CD4+ and CD8+T cells, as reflected by a reduced CD4+:CD8+ ratio, and perturbations in other T-cell subsets such as Th17 CD4+ and gamma delta ($\gamma\delta$) T cells contribute as drivers of inflammation.[48] Elevated activation has also been shown in natural killer and B cells. While the role of hyperactivated neutrophils,

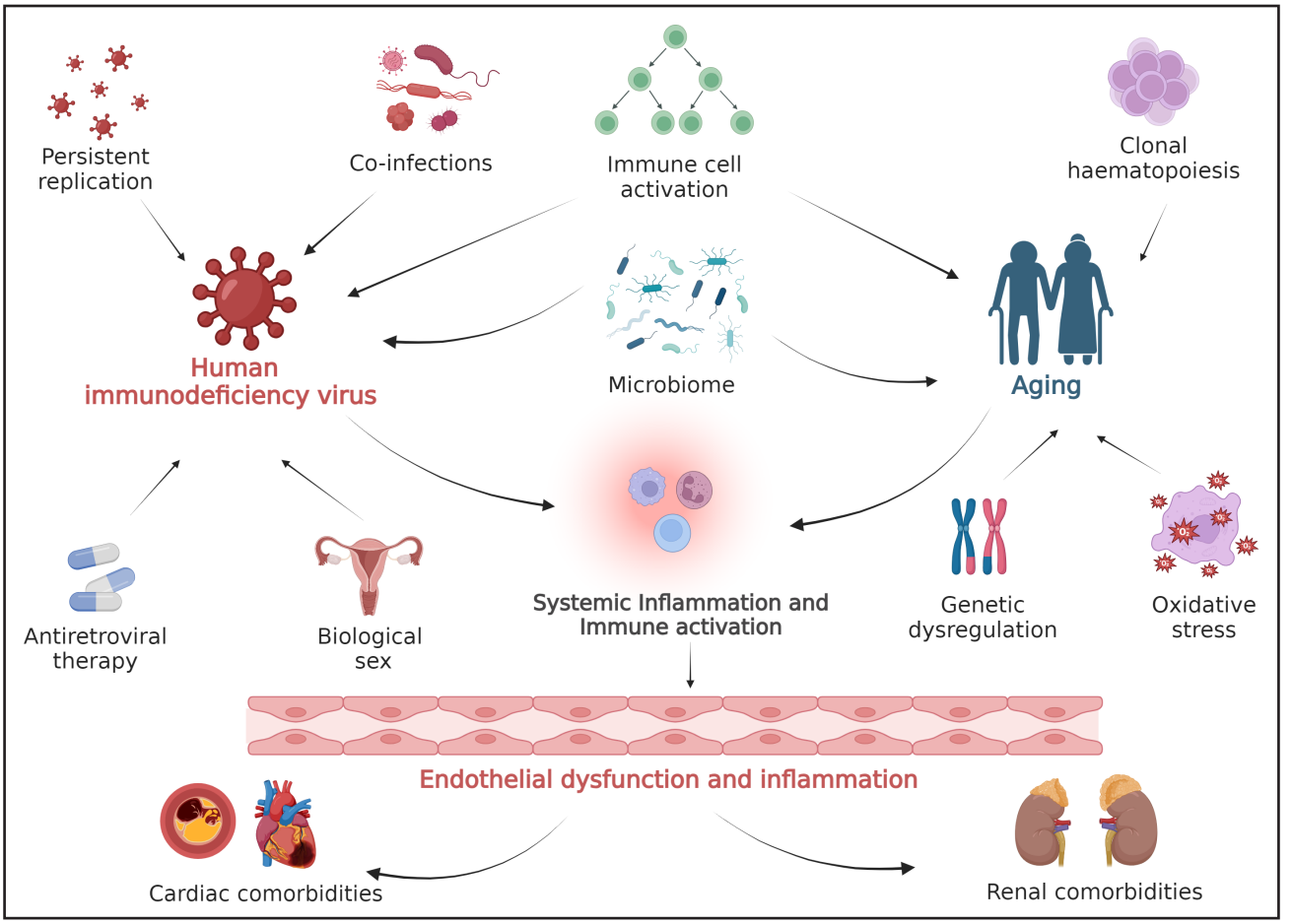

Figure 2. Inflammation is central to the aging process and the pathogenesis of HIV-associated comorbidities.
HIV infection causes systemic inflammation and immune activation that age-associated inflammation exacerbates. Chronic inflammation induces endothelial dysfunction and subsequent cardiac and renal disease. As people living with HIV (PLWH) age, oxidative stress, genetic dysregulation, and clonal hematopoiesis predispose them to chronic inflammation. Coinfections, including hepatitis B and C, contribute to persistent inflammation in aging PLWH.

inflammatory monocytes, and plasmacytoid dendritic cells is well established, the chronic activation of these various components of the immune response in HIV infection results in the elevation of proinflammatory cytokines and chemokines that maintain and potentiate inflammation.[38]

Coinfections

Individuals coinfected with Mycobacterium tuberculosis, hepatitis B or C have been shown to have higher levels of inflammation than mono-infected or uninfected controls.[49,50]

Microbiome

The microbiome plays a prominent role in the pathogenesis of inflammatory processes in PLWH and aging PWoH. In PLWH, the loss of predominantly Th17 CD4+ T cells in the gut leads to a disrupted microbiome, reduced mucosal integrity, and translocation of microbial products into the systemic circulation, triggering inflammation.[51] The mechanism for altered immune activation is complex but appears to include altered levels of bacterial metabolites such as tryptophan, trimethylamine-N-oxide, and short-chain fatty acids.[52]

Antiretroviral Therapy

Although not reducing to levels seen in PWoH, cART is undoubtedly associated with improved levels of inflammation and immune activation.[53] Older patients are more likely to have been exposed to early-generation ARTs—with the legacy of early antiretroviral therapy (ART) toxicity leading to long-term adverse effects. Dyslipidemia induced by protease inhibitors (PIs) has been shown to contribute to inflammation, which improved when switching to an integrase inhibitor-based regimen.[54] In other comparisons, integrase inhibitors have been associated with larger decreases in markers of inflammation and immune activation than nonnucleoside reverse transcriptase inhibitors (NNRTIs) and PIs. However, these differences were not consistent or applicable to all measured surrogates of

immune activation.[55,56] Where specific ART agents within the same class have been assessed in head-to-head comparisons, there has been no evidence of differential effect on measures of inflammation.[57]

CARDIAC COMORBIDITIES IN PLWH

A high prevalence of traditional cardiovascular risk factors has been reported in PLWH on cART.[58] With cART, these individuals now aging, and the cumulative effect of these traditional and novel CVD risk factors has led to an increasing incidence of CVD in PLWH. In the pre-cART era, HIV-associated pericardial effusions and HIV-associated left ventricular systolic dysfunction were common manifestations. However, in the cART era, these conditions have largely been replaced by HIV-associated dyslipidemia, ASCVD, arrhythmias and sudden cardiac death.[24,58] Other noteworthy CVDs are HIV-associated pulmonary hypertension and cerebrovascular disease. However, their in-depth discussion is beyond the scope of this review. We conducted a systematic literature search to identify original clinical research studies evaluating cardiac disease on PLWH 50 years of age and older (Table 1). These studies were conducted primarily in the United States and were association studies. A comprehensive search criteria is attached as a Supplemental Material.

HIV and cART Associated Dyslipidemia

There is a cumulative risk of dyslipidemia as PLWH age. Soon after the index episode of HIV infection, the typical lipid abnormalities noted are increased triglyceride levels and decreased total cholesterol, LDL-C (low-density lipoprotein cholesterol), and HDL-C (high-density lipoprotein cholesterol).[77,78] Depending on the selection of ART used, the initiation of cART may further induces dyslipidemia. However, the true lipid impact of individual ART is difficult to determine as these agents are routinely combined to effectively halt in vivo HIV replication by targeting multiple pathways. Generally, first-generation PIs, nucleoside reverse transcriptase inhibitors (NRTIs), and NNRTIs increase triglyceride levels and are prone to increase LDL-C. The contemporary INSTI (integrase strand transfer inhibitor) and the C-C chemokine receptor type 5 antagonists have more neutral lipid effects.[77] In a recently published Italian study in stable HIV-1 positive virologically suppressed patients, the switching to a darunavir/cobicistat based antiretroviral regimen from a ritonavir-boosted PI/r (protease inhibitor)-based regimen in virologically suppressed HIV-positive patients was beneficial in terms of low rates of virological failure and adverse events due to its high tolerability and improvement in triglycerides.[79] This strategy may be considered in PLWH with significant cART-related dyslipidemia.

A meta-analysis of 14 HIV cART trials conducted in sub-Saharan Africa concluded that cART was associated with an increased risk of hypertriglyceridemia. In this study, among 10615 individuals, cART was associated with a 2-fold higher probability of raised hypertriglyceridemia (risk ratio, 2.05 [95% CI, 1.51–2.77]; I^2=45.2%). However, the associations between cART and raised blood pressure, glucose, glycated hemoglobin, and other lipids were inconsistent across studies.[80] These findings further highlight the unmet need for more prospective studies in sub-Saharan Africa, where most PLWH live, to determine the risk of long-term cART on CVD.

Atherosclerotic CVD

Infection with HIV is independently associated with a 2-fold increased risk of ASCVD, which is thought to be the result of complex interactions between inflammation, endothelial dysfunction, and coagulation disorders.[81] As discussed above, aging with HIV contributes to chronic inflammation. Despite appropriate cART, persistent viral replication and immunodeficiency (CD4+ cell counts <200 cells/mm^3 or a low CD4+/CD8+ ratio) have been associated with a higher risk of ASCVD.[82] Unlike atherosclerosis in PWoH, the typical plaque in PLWH appears to be noncalcified atherosclerotic plaque.[83] Computed tomography coronary angiography showed an increased prevalence of subclinical atherosclerosis in PLWH compared with the general population.[83] And plasma levels of Lpa (lipoprotein a) have recently been shown to correlate with markers of monocyte activation and greater peri-coronary inflammation in PLWH compared with HIV-negative individuals.[84]

Not all PLWH develop subclinical ASCVD, even when inflammatory markers are raised.[21,85] Therefore, predicting ASCVD risk and determining who needs primary prevention remains challenging. The DAD study (Data Collection on Adverse Events of Anti-HIV Drugs) data, showed that HIV-specific factors such as the CD4+ count, abacavir use, and exposure to PI and NRTI, have been used to generate a model predicting ASCVD risk in PLWH.[86] However, this model has not been validated in other populations. In terms of therapy, cART is recommended for all PLWH as soon as possible after HIV diagnosis.[87] Smoking cessation is crucial since the life expectancy of HIV-infected smokers is reduced by 8 years compared with HIV-infected nonsmokers[88] and interventions to help with smoking cessation can be safely considered in PLWH.[89] Smoking cessation should be considered not only in cigarette or tobacco smokers, but also in individuals vaping or using other substance such as cannabis.

People living with HIV presenting with acute coronary syndromes are often younger, more likely to be smokers, more likely to have severe single-vessel disease, present with a thrombotic ST-segment elevation myocardial infarction rather than non–ST-segment–elevation myocardial infarction and less likely to have a drug-eluting stent placed than matched HIV-negative controls.[90–92]

Table 1. Summary of Original Research Studies Reporting on the Risk of Cardiac Disease and Related Outcomes in Aging People Living With HIV

Author	Study design	Research question	Population	Follow-up, y	Sample size	Age, y	Female (%)	Black (%)	Outcome	Conclusion
Surial et al[59]	Prospective cohort	What is the impact of starting INSTI-based ART on CV events among treatment-naive PLWH?	Treatment naive PLWH on INSTI	4.9 y (IQR, 2.4–7.4)	1823 (INSTI)	39 (IQR, 31–50)	16.0		MI=31.9%, stroke=31.0%, and invasive CV-related procedures=37.1%	CV event risk was similar between treatment-naïve PLWH started on INSTI-based ART and those started on other ART combinations
			Treatment naive PLWH on other ART		3525 (other ART)	38 (IQR, 31–46)	24.0			
Foldyna et al[60]	Multicenter trial (31 United States sites)	What is the relationship between PCAT density on CT imaging and coronary plaque indices, inflammation, and immune activation in PLWH?	PLWH on ART with low-to-moderate traditional ASCVD risk		727			35.4		Increased PCAT density independently associated with the prevalence and severity of coronary plaque
Thakkar et al[61]	Observational, prospective cohort	What is the association between HIV infection with angiopoietin levels and endothelial dysfunction?	PLWH on ART	Measurements collected every 4 mo	47	48 (IQR, 43–57)	10.6	21.3		CRP and IL-6 showed weak correlations with ANG1 and ANG2, in PLWH and uninfected controls
			Treatment naive PLWH		39	43 (IQR, 32–54)	25.6	25.6		Not much difference seen in the macrovascular dysfunction between treated and untreated PLWH and uninfected controls
			PWoH (controls)		46	53 (IQR, 45–55)	2.2	43.1		Compared with PWoH, PLWH on ART had significantly impaired microvascular dysfunction
Doria de Vasconcellos et al[62]	Observational, prospective cohort	Are there differences in cardiac structure and function evaluated by 2-dimensional echocardiography among men living with and without HIV?	Men living with and without HIV who have sex with other men	None	533 (PWoH)	62 (IQR, 55–69)	0.0	22.3		HIV seropositivity was independently associated with greater LV mass index, left atrial and RV size, lower RV function and diastolic abnormalities
					662 (PLWH)	55 (IQR, 49–62)	0.0	34.4		

(*Continued*)

Table 1. Continued

Author	Study design	Research question	Population	Follow-up, y	Sample size	Age, y	Female (%)	Black (%)	Outcome	Conclusion
Postigo et al[63]	Retrospective observational study	Are there differences in outcomes after ACS in PLWH and PWoH?	PLWH with ACS	3	92 (PLWH)	51.3±9.0	7.6		3-year mortality, CV or non-CV rehospitalisation	HIV status was not independently associated with long-term mortality. PLWH with previous CAD had worse prognosis
			PWoH (controls) with ACS		184 (PWoH)	51.3±9.0	7.6			PLWH with ACS present more frequently with multivessel disease and heart failure than uninfected controls
Heravi et al[64]	Prospective cohort	Is HIV serostatus associated with ventricular repolarization lability using the QTVI?	Men living with and without HIV who have sex with other men		534 (PWoH)	60.1±11.9	0.0	19.3		Men living with HIV have greater beat-to-beat variability in QTVI compared with uninfected controls, especially in the setting of HIV viremia and heightened inflammation
					589 (PLWH)	54.2±11.2	0.0	29.4		Higher QTVI in men living with HIV suggests ventricular repolarization lability which can increase susceptibility to arrhythmias
Fourman et al[65]	Observational study	Is there a relationship between IL-10, coronary atherosclerosis (coronary plaque on coronary CT), and immune parameters in the setting of chronic HIV infection?	Asymptomatic PLWH and controls without a history of CVD	None	144 (PLWH)	46.8±7.0	30.0		None	Inverse relationship between IL-10 and atherosclerosis in PLWH. IL-10 may be atheroprotective in PLWH
					66 PWoH (controls)	45.6±7.0	38.0			
Reinsch et al[66]	Prospective multicentre trial	Do BNP levels improve risk prediction of CV events and mortality in PLWH?	Therapy naive and combined ART-receiving PLWH	10	808	43.8±10.3	16.8		CV events were defined as MI, new diagnosis of CAD, coronary revascularisation, stroke/TIA and PAD.	Increased BNP levels were associated with adverse CV events and mortality

(*Continued*)

Table 1. Continued

Author	Study design	Research question	Population	Follow-up, y	Sample size	Age, y	Female (%)	Black (%)	Outcome	Conclusion
Alenezi et al[67]	Retrospective observational cohort study	What is the prevalence of abnormal GLS in PLWH with preserved LVEF and HIV-associated immune dysfunction? Could GLS serve as a predictor of preclinical abnormalities in PLWH who might be candidates for enhanced CVD prevention?	PLWH on ART	None	253	44 (IQR, 37–50)	38.0	72.0		Proximal and nadir CD4 cell count are independently associated with GLS despite normal LVEF
Nadel et al[68]	Retrospective observational study	What is the utility of CTCA in the assessment of CAD among PLWH? Are PLWH at greater risk of associated morbidity and mortality compared with HIV-negative controls?	Asymptomatic PLWH referred for CTCA due to suboptimal medical management, poor metabolic control or clinician uncertainty regarding patient management	3	32 PLWH	60 (IQR, 56–63)	0.0	0.0	Primary end point: ACS	PLWH were at an increased risk of developing high-risk coronary plaques, higher rates of adverse cardiac events and less aggressive further coronary intervention
					65 PWoH (controls)	60 (IQR, 56–64)	0.0	0.0	Secondary end point: invasive angiography, with or without interventions	PLWH are at greater risk of CAD independent of traditional risk factors
Rider et al[69]	Prospective cohort study	Is HIV infection independently associated with increased arterial stiffness (aortic pulse wave velocity and regional aortic distensibility) on cardiovascular MRI?	PLWH with and without metabolic syndrome* and controls with and without metabolic syndrome	None	92 (HIV uninfected, no metabolic syndrome)	45±10				HIV infection is independently associated with increased aortic PWV and decreased aortic distensibility. HIV infection is an independent predictor of both increased pulse wave velocity and decreased aortic distensibility
		What is the magnitude of the detrimental effect of HIV on aortic elastic function when compared with the metabolic syndrome?		44 (PWoH with the metabolic syndrome)		49±11				PLWH on ART have reduced vascular function, which is independent of the metabolic syndrome and other traditional cardiovascular risk factors. This suggests that there might be a virus-related cause, such as chronic inflammation

(*Continued*)

Table 1. Continued

Author	Study design	Research question	Population	Follow-up, y	Sample size	Age, y	Female (%)	Black (%)	Outcome	Conclusion
				73 (PLWH with no metabolic syndrome)		44±10				
				17 (PLWH and metabolic syndrome)		48±8				
Lucas et al[70]	Multi-center, international, randomized controlled trial	Is there an association between baseline GFRcr, GFRcys, and GFRcr-cys with mortality, cardiovascular events, or opportunistic disease in the SMART study?	PLWH with a CD4 cell count >350 cells/mm^3, with 50.3% of PLWH in the episodic ART arm	4614		44 (IQR, 38–50)	25.4	27.7	All-cause mortality, CV events and opportunistic infections	GFR estimates that used plasma cystatin C had stronger associations with mortality, CVE, and opportunistic disease than GFR based on plasma creatinine in PLWH
Gupta et al[71]		What is the relation of inflammatory and coagulation biomarkers (hsCRP, IL-6, and D-dimer) with ECG evidence of myocardial ischemia?	PLWH on ART with plasma HIV RNA level of ≥400 copies/mL and no history of CVD	2.3	3085	44 (IQR, 38–50)	26.0	25.0		The prevalence of baseline ECG abnormalities indicative of cardiac ischemia increased with greater biomarker levels. However, after adjustment for age and other risk factors, none of the associations remained significant.
Dawood et al[72]	Multi-center, international, randomized controlled trial	What is the prognostic significance of the widening of the spatial QRS-T angle in PLWH in the SMART trial?		2.4	4453	43.5±9.3	28.0			Widened spatial QRS-T angle is independently predictive of CVD events in PLWH on ART
Neuhaus et al[73]	Two large international randomized clinical trials	What is the risk of all-cause mortality after experiencing AIDS and serious non-AIDS (CVD, renal, hepatic or malignancies) events?	PLWH with a CD4+ count above 350 cells/mm^3 were randomized to either CD4+ guided episodic use of ART or to continuous use of ART	2.4 (IQR, 1.8–3.5)	5472	49 (IQR, 43–56)	0.1	21.9	Among PLWH with CD4+ counts >350 cells/mm^3, serious non-AIDS events occur more frequently and are associated with a greater risk of death than AIDS events	
Rathbun et al[74]	Randomized clinical trial	What are the pharmacokinetics, safety, and tolerability of combined ATV and LPV/r therapy using contemporary formulations?	HIV-seropositive subjects receiving ATV or LPV/r with 2 to 3 NRTIs	19		45.2 (IQR, 37–52)	20.0	0.0		Concurrent ATV and LPV/r administration was associated with PR and QRS interval changes
Carr et al[75]		Are ischemic changes common in asymptomatic PLWH?	PLWH with a CD4 cell count >350 cells/mL	4831		44.0±9.3	28.4	29.6		ECG evidence of asymptomatic IHD was common in PLWH. This was more common than a history of symptomatic IHD

(*Continued*)

Table 1. Continued

Author	Study design	Research question	Population	Follow-up, y	Sample size	Age, y	Female (%)	Black (%)	Outcome	Conclusion
Coplan et al[76]	Systematic review	What is the incidence of MI among participants receiving treatment with PIs with or without nRTIs compared to nRTI therapy alone?	PLWH on ART	10986						There is no dramatic increase in MI risk during the first year of PI therapy

ACS indicates acute coronary syndrome; AIDS, acquired immunodeficiency syndrome; ANG, angiopoietin; ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; ATV, atazanavir; BNP, B-type natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; CRP, C-reactive protein; CT, computed tomography; CTCA, computed tomography coronary angiography; CV, cardiovascular; CVD, cardiovascular disease; CVE, cardiovascular events; DBP, diastolic blood pressure; GFR, glomerular filtration rate; GLS, global longitudinal strain; HDL, high-density lipoprotein; hsCRP, high sensitivity c-reactive protein; IFG, impaired fasting glucose; IL, interleukin; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; LPV/r, lopinavir/ritonavir; LPV, lopinavir; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRI, magnetic resonance imaging; NRTI, nucleoside reverse transcriptase inhibitors; PAD, peripheral artery disease; PCAT, pericoronary adipose tissue; PI, protease inhibitors; PLWH, people living with HIV; PWoH, people without HIV; QTVI, QT variability index; RV, right ventricle; SMART, Strategies for the Management of Antiretroviral Therapy Study; and TIA, transient ischemic attack.

*Subjects were diagnosed with the metabolic syndrome when at least 3 of 5 risk determinants increased waist circumference, increased systolic BP) or DBP, elevated serum triglycerides, HDL cholesterol, and IFG were present.

Coronary revascularization in PLWH is more complicated than in the general population because of coagulopathy, persistent inflammation, drug-to-drug interactions, and insufficient data guiding decision-making.[93] Data regarding major adverse cardiovascular events after revascularization are conflicting. Death from ASCVD has increased among PLWH, and long-term outcomes remain worse for PLWH after a cardiovascular event.[94] Some studies have shown that there are no significant differences in major adverse cardiovascular events or target vessel revascularization rates between PLWH and PWoH.[95,96] In contrast, others found an increased risk of stent thrombosis and recurrent acute coronary syndromes among PLWH.[96] The EVERE$_2$ST-HIV (Evaluation of Residual Platelet Reactivity After Acute Coronary Syndrome in HIV) study demonstrated high platelet reactivity after percutaneous coronary intervention in PLWH.[91] People living with HIV are at increased risk for stent thrombosis because of this platelet activation, the elevation of D-dimers, fibrinogen, factor VII, von Willebrand factor, soluble thrombomodulin, and tissue factor levels, which are independently associated with the risk for ASCVD.[97] Therefore, prolonged dual antiplatelet therapy or more potent dual antiplatelet therapy should strongly be considered after acute coronary syndromes in PLWH unless contra-indicated. Coronary artery bypass graft (CABG) surgery is considered feasible and safe, and the rate of perioperative complications is similar to PWoH.[98,99] Indeed, CABG is now the most frequent cardiac surgery performed in PLWH.[100]

HIV-Associated Myocardial Dysfunction

HIV-associated myocardial dysfunction refers to the full spectrum of myocardial disorders that may manifest in PLWH. The dominant clinical phenotype depends mainly on the socio-geographic location and access to cART. In the pre-cART era and in geographic regions where access to cART is limited, HF with reduced ejection fraction (HFrEF [left ventricular ejection fraction <40%]) and a dilated cardiomyopathy phenotype are very common.[101] This manifestation usually presents in advanced HIV infection where the CD4 count is <200 cells/mm^3 and the viral load is very high.[102] All of these are features portending a poor clinical prognosis. In a cohort with rigorous HF adjudication, PLWH had ≈2-fold increased risk of developing HF than PWoH after adjustment for demographics and cardiovascular risk factors.[103]

As PLWH age the prominent manifestation of HIV-associated myocardial dysfunction is diastolic dysfunction.[104] In the United States VACS (Veterans Aging Cohort Study) of uninfected and HIV-infected United States veterans, 2636 HF events occurred over 7.1 years of follow-up.[105] HF with preserved ejection fraction (HFpEF) accounted for 34.6% of these, and borderline HFpEF for 15.5%, HFrEF for 37.1% and HF of unknown type for 12.8%.[105] HIV-infected veterans had an increased risk of HFpEF (hazard ratio, 1.21 [95% CI, 1.03–1.41]), borderline HFpEF (hazard ratio, 1.37 [95% CI, 1.09–1.72]), and HFrEF (hazard ratio, 1.61 [95% CI, 1.40–1.86]) compared with their uninfected counterparts.[105] In this study, a high CD4 count was protective against HFpEF and HFrEF. However, a low viral load was only protective against HFrEF and not HFpEF.[105]

The pathogenesis of HIV-associated HFrEF is most likely multifactorial. It predominates in regions with little access to cART and where there is a concomitant high background of cardiac-specific infectious diseases such as tuberculosis, rheumatic fever, and subsequent rheumatic heart disease.[106,107] This form of cardiomyopathy is seen in advanced acquired immunodeficiency syndrome and is associated with immune dysregulation, acute and chronic inflammation, cardiac myocyte necrosis, and focal myocarditis. There is usually ongoing viral replication causing myocardial injury and remodeling to ultimately

cause a dilated cardiomyopathy phenotype and left ventricular systolic dysfunction.[108] With the widespread use of cART in high-income countries, aging PLWH are more likely to complicate with ischemic cardiomyopathy as the dominant driver for the HFrEF phenotype.[58,109]

Similarly, the pathogenesis of HIV-associated HFpEF is multifactorial. This phenotype is largely seen in areas with good cART coverage, where most patients attain virological suppression. HIV-propagated chronic inflammation is implicated in causing microvascular dysfunction and endothelial injury, which are associated with proinflammatory monocyte and tissue macrophage infiltration. All of these increase the risk of diastolic dysfunction and HFpEF.[110,111] As PLWH age, they are more likely to develop HFpEF due to the higher prevalence of comorbidities, such as ASCVD, hypertension, and diabetes in the aging population.

CARDIAC RHYTHM DISTURBANCES IN PEOPLE LIVING WITH HIV

Aging PLWH have a higher burden of arrhythmia than the general population. This is due to a higher prevalence of CVD among PLWH, drug-to-drug interactions, recreational substance abuse and electrolyte imbalances.[112] Sudden cardiac death is 4.5× higher in PLWH and is the third leading cause of mortality, responsible for 86% of cardiac deaths in PLWH.[113] Atrial fibrillation is more common and more likely to recur among aging PLWH.[114] Low CD4+ T-cell count and high HIV viral load are associated with ≈2-fold elevated odds of atrial fibrillation or atrial flutter, even after adjustment for demographics and CVD risk factors.[115,116]

There is a higher prevalence of prolonged QT interval in PLWH.[117] This may be related to several non-cART drugs commonly used in PLWH that are known to prolong the QT interval, such as macrolides, antifungals, fluoroquinolones, pentamidine, and methadone. In vitro studies have demonstrated that antiretroviral drugs such as atazanavir, efavirenz, and ritonavir bind to and modulate the function of RyR2 (type 2 ryanodine receptor), which interferes with calcium influx,[118] and protease inhibitors have been shown to block the human ether-a-go-go (*h*ERG) related gene, which codes for the rapidly activating delayed rectifier potassium current (I_{Kr}).[119] However, these in vitro findings have not translated to clinically significant QT prolongation[120] or an increase in ventricular tachycardia or ventricular ectopy burden among PLWH, underscoring the continued equipoise surrounding HIV-associated ventricular arrhythmia risk.[121]

RENAL COMORBIDITIES IN PEOPLE LIVING WITH HIV

With effective cART, the life expectancy in PLWH has increased, resulting in a broader spectrum of kidney diseases. The pathogenesis of kidney disease in aging PLWH is multifactorial, often related to an interplay between the HIV infection itself (local infection and immune dysregulation) and antiretroviral therapy-related toxicity (caused by NRTI, PI, integrase inhibitors), genetic susceptibility (*APOL1* [apolipoprotein L1] gene), and comorbid CKD risk factors such as diabetes, hypertension, and hepatitis B and C (Figure 3). Studies done both in vivo and in vitro have shown that HIV can directly infect both glomerular and tubular epithelial cells.[122,123] Renal epithelial cells do not express HIV surface receptors (CD4) or coreceptors (CXCR4 or CCR5), thus making the exact mechanism of entry of HIV into tubular cells unclear. However, in vitro studies have demonstrated cell-cell transfer without these receptors.[124] Thus, infection of kidney epithelial cells by HIV could be a source of viral rebound after cART interruption, even after viral suppression.[125] The presence of latent viral reservoirs is an important obstacle in ongoing efforts toward HIV eradication or cure.[126]

Role of HIV Genes in Promoting Kidney Injury

In transgenic mice, renal expression of HIV genes, such as *nef* and *vpr*, has been shown to cause a glomerular disease that is similar to HIV-associated nephropathy (HIVAN).[127] Inflammation has also been implicated in the pathogenesis of HIV-induced kidney disease, with HIV infection of the renal tubules resulting in an increased expression of nuclear factor κβ-controlled proinflammatory mediators.[128] This chronic inflammation has been shown to accelerate aging and increase the risk of renal insufficiency.[129]

APOL1 Risk Alleles Contribute to HIV-Associated Renal Disease

APOL1 gene missense mutations underlie the higher incidence of endstage kidney disease in patients of African descent and the greater prevalence of classic HIVAN in black PLWH not yet on cART.[130] This health disparity was identified many years before the landmark discovery of the *APOL1* renal risk variants. The high-risk *APOL1* genotype encompasses 2 renal risk variants, G1 and G2 alleles. These alleles are most prevalent in West Africa and are thought to have emerged as a resistance mechanism to endemic human African Trypanosomiasis.[131] A single variant confers a minimal increased risk of kidney disease. However, the presence of 2 variant alleles (G1/G1, G1/G2, or G2/G2) promotes the risk of HIVAN with increased odds that vary by region (odds ratio, 29–89).[132] The disease spectrum varies among PLWH; with suboptimal virological control, *APOL1* variants are associated with HIVAN, and in those who obtain viral suppression, the risk of kidney disease remains, specifically hypertension-related CKD, noncollapsing focal segmental glomerulosclerosis (FSGS) and progression to endstage kidney disease.[133,134]

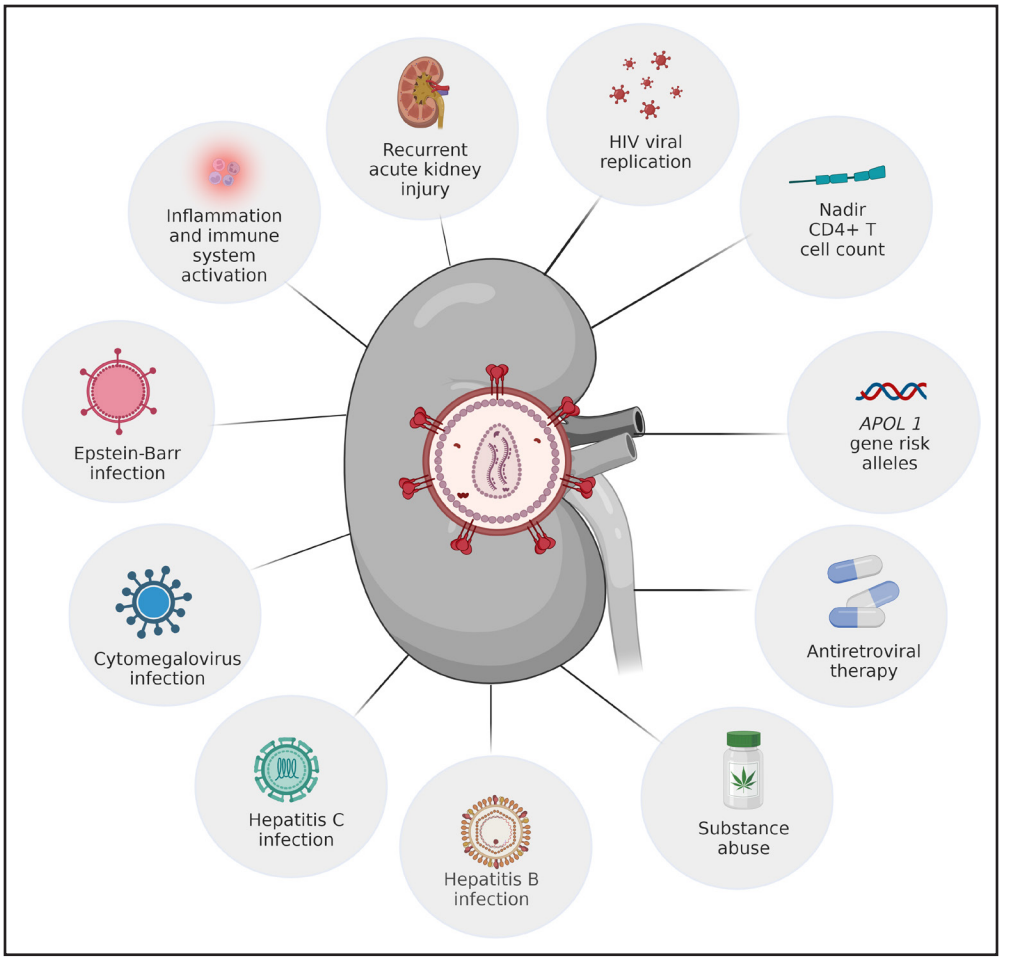

Figure 3. HIV-associated risk factors for kidney disease.
The resultant kidney disease occurs as an interplay between traditional risk factors, such as obesity, smoking, and hypertension, and HIV-associated risk factors, such as viral infections, antiretroviral therapy, and recurrent acute kidney injury. *APOL 1* indicates apolipoprotein L1.

Not all individuals identified to have *APOL1* risk alleles develop kidney disease. Therefore, a second hit is believed to be essential for disease manifestation.[135] The exact mechanism underlying this second hit in PLWH is not fully elucidated but is postulated to be related to interferons.[136] The gene product of *APOL1* is ApoL1, which enters the circulation following hepatic secretion and is expressed in various organs, including the kidney. The true function of the ApoL1 is obscure but relates to innate immunity, and many of the immune pathways upregulate ApoL1 expression. This is particularly true of interferons administered exogenously or increased as a host defense against HIV (type 1 interferons).[135,136] Further mediators of excess ApoL1 are postulated, including Stimulator of interferon genes, RIG-1, JAK/STAT (Janus kinase/signal transducer and activator of transcription) pathways, and NF-κβ in the setting of HIV.[136,137]

Insight has been gained into the pathogenic mechanisms inciting podocyte injury, but the clinical application of genetic testing outside a research setting remains to be determined. Despite a lower prevalence of HIVAN following cART initiated at HIV diagnosis, *APOL1* G1, and G2 alleles remain a contributor to worsening renal function.[137] In one study, 2 renal risk variants were associated with higher level HIV viraemia (odds ratio, 2.37 [95% CI, 1.0–5.63]; *P*=0.05). However, compliance with cART could not be confirmed.[138] Studies are ongoing to determine the contribution of *APOL1* risk variants in managing CKD.[139]

Emerging therapies targeting *APOL1*-related pathogenic mechanisms have been investigated. Preclinical studies in transgenic mice demonstrate effectiveness at reducing *APOL1* variant levels using antisense oligonucleotides and subsequently improved markers of renal disease.[135] Human studies using antisense oligonucleotides are awaiting results.[137] Inaxaplin, an *APOL1* small molecule inhibitor, has been shown to reduce proteinuria successfully in phase II clinical trials.[140] With ongoing clinical trials, JAK/STAT pathway inhibitors are promising therapies targeting *APOL1*-mediated inflammatory pathways.[137]

HIV-RELATED KIDNEY DISEASE

Classic HIV-Associated Nephropathy

With the introduction of cART, there has been a decline in the incidence of classic HIVAN, characterized by a unique pattern of collapsing FSGS, with tubular dilatation with micro cysts and interstitial inflammation.[141] HIVAN is the result of direct viral infection of the kidney in a genetically susceptible host and used to be a leading cause of end-stage renal disease.[142] Classic HIVAN, occurring typically in young adults of African ancestry with advanced HIV disease, is strongly associated with *APOL1* high-risk variants, with *APOL1* variants conferring 29-fold higher odds (95% CI, 13–68) for HIVAN in a recessive genetic model.[143] Clinical presentation of HIVAN includes nephrotic range proteinuria and rapid progression to end-stage kidney diseases and necessitates prompt initiation of cART on diagnosis.[144] Kidney biopsy series from both high-income[145] and low and middle-income[146,147] countries have shown a decline in the prevalence of HIVAN. Nevertheless, HIVAN persists, though at reduced rates, possibly due to the patient's late presentation with advanced immunosuppression, undiagnosed HIV infection and challenges with access and adherence to cART.[135]

Noncollapsing FSGS

With the widespread use of cART, noncollapsing FSGS has now become the more commonly seen pattern of FSGS in PLWH and is thought to be due to partially treated HIVAN.[142] It is imperative to exclude secondary causes of FSGS as the foot process effacement may be indistinguishable from that in the secondary cause of FSGS, which may be due to a maladaptive response to renal injury from diseases like hypertension, diabetes, obesity or sickle cell anemia. Infectious agents (Parvovirus B19, Epstein-Barr Virus, cytomegalovirus) and drug toxicity (lithium and heroin) may also directly lead to glomerulosclerosis and must be excluded.[148]

Immune Complex-Mediated Glomerular Disease

A variety of immune-complex mediated glomerulonephritides have been described in the setting of HIV. Due to the heterogeneous nature of these immune complexes and lack of absolute certainty as to HIV being the etiological agent, a description of the immune complex deposition pattern in the setting of HIV is preferred.[132] Lupus-like nephritis, IgA nephropathy, and membranoproliferative glomerulonephritis have all been described in the setting of HIV. Once secondary causes of immune-complex mediated glomerulonephritis have been excluded, HIV is assumed to be the causative agent.[132] Presentation of these immune complex-mediated diseases varies from hematuria, to proteinuria, and a decrease in glomerular filtration rate, and prompt cART initiation is critical.[144]

Tubulointerstitial Disease

Common causes of tubulointerstitial disease in the setting of HIV include drug-induced acute tubular necrosis, secondary to intake of antibiotics, proton-pump inhibitors, or nonsteroidal anti-inflammatory drugs, and infectious agents such as viruses, bacteria, including *Mycobacterium tuberculosis* or fungi. These are common therapies used by aging PLWH as part of therapy for other comorbidities. An abnormal immune response to HIV antigens can result in an uncommon disease called diffuse infiltrative lymphocytosis syndrome, which presents with dense lymphocytic tubulointerstitial infiltrates predominantly composed of CD8(+) T cells on kidney biopsy, treated by initiation of cART, with the possible addition of corticosteroids.[149] Rarely an immune reconstitution syndrome can also present as a tubulointerstitial nephritis at the initiation of cART.[150] Table 2 depicts original research studies published in the past 5 years evaluating renal dysfunction in PLWH above the age of 50 years.

Renal Transplantation in People Living With HIV: A New Era

Before effective cART, HIV was believed to confer a limited life expectancy and owing to this, PLWH were not considered transplant donors or recipients. Longevity afforded by viral suppression allows several factors, including multi-morbidity, drug toxicity and genetic influences, to culminate in higher rates of kidney disease in aging PLWH.[163] Barriers to referral of suitable candidates for transplantation hinged on misconceptions regarding graft survival and outcomes in HIV-positive recipients. Pioneering work in South Africa released outcomes data of the first 4 successful HIV+ donor to HIV+ recipient transplantation (D+/R+) in 2010.[164] The same group published cohort data detailing 27 kidney D+/R+ transplants, with low mortality and graft survival comparable HIV negative donors.[165] This prompted the HIV Organ Policy Equity Act to be passed in 2013,[164] with D+/R+ transplants becoming more widespread. Despite the leaps and bounds made in HIV transplant medicine, studies still indicate that PLWH are less preferentially referred for kidney transplantation and tend to remain on the waiting list for longer.[166] Other studies show that time on the waiting list for D+ donation has reduced waiting times.[135]

Studies reveal that PLWH on dialysis have poorer outcomes compared to PWoH.[166] This is not true for renal transplantation, where equivalent survival benefit is found in PLWH and PWoH, and further to this PLWH demonstrating increased survival with transplant compared with remaining on dialysis.[135] Concerns following

Table 2. Summary of Original Clinical Studies Conducted on Aging People Living With HIV Evaluating the Prevalence of Renal Dysfunction

Author % (year published)	Study design	Research question	Population	Follow-up, y	Sample size	Age	Female (%)	Black	Results	Conclusion
Heron, et al[151]	Retrospective longitudinal open cohort study	What is the rate of sustained renal impairment (eGFR of <60 mL/min twice at least 30 d apart), between PLWH on TDF and those on PrEP?	PLWH and PrEP users on TDF	3	1973 (PLWH)	PLWH: 44 (IQR, 36–52), PrEP users: 36 (IQR: 29–46)	7.2 (PLWH)		Rate of renal impairment: 4.01/1000 person-years (95% CI, 2.93–5.48) in the PrEP cohort and 16.18/1000 person-years (95% CI, 13.01–20.11) in PLWH (P<0.001)	Patients prescribed TDF-based PrEP had lower rates of renal impairment than PLWH on TDF
					5973 (PrEP users)		1.3 (PrEP users)		Renal impairment: 0.7% in PrEP users vs 3.9% in PLWH. Predictors of renal impairment: older age (40–49 y; HR, 5.09 [95% CI, 2.12–12.17]) and 50–82 y (HR, 13.69 [95% CI, 5.92–31.67])	
Manavalan et al[152]	Randomized double-blind placebo-controlled	What is the mean eGFR decline from baseline over time and risks factors associated with eGFR decline?	Hypertensive PLWH, with 93% on ART		91	51.1±11.2	82.4	100.0	28.6% had 1+ proteinuria	The prevalence of kidney disease was 28.6%.
Garza Tovar et al[153]	Observational	Which risk factors are associated with biochemical alterations in renal function in PLWH undergoing ART?	Seropositive PLWH on ART		179	39.3±10.9	22.9		Ten-year ASCVD risk, 18.9% high risk and 29.7% low risk. CKD prevalence, 7.3% (CKD-EPI equation). GFR between 60 and 89 mL/min per 1.73 m^2 associated with dyslipidemia (P=0.02; OR, 2.2 [95% CI, 1.1–4.5]). Creatinine levels ≥1.5 mg/dL in 2.8% PLWH. Plasma urea levels higher than normal values in only 5.6% (n=10).	Prevalence of CKD in PLWH was 7.3%
Schrader et al[154]	Prospective observational cohort	Is medium-grade proteinuria (100–500 mg/g) creatinine a risk factor for incident renal dysfunction in PLWH?	PLWH on ART without a history of renal disease	4.6	241		23.0	12.0	Medium grade proteinuria (uPCR 100–500 mg/g) associated with a >2-fold risk for developing signs of CKD (aR, 2.4; P=0.024)	Medium-grade proteinuria of 100–500 mg/g creatinine is frequent in PLWH.

(*Continued*)

Table 2. Continued

Author % (year published)	Study design	Research question	Population	Follow-up, y	Sample size	Age	Female (%)	Black	Results	Conclusion
Overton et al[7]	Randomized control trial	What is the baseline renal function in PLWH on ART with a low- to -moderate risk of ASCVD?	PLWH with low to moderate risk of ASCVD		7770	50 (IQR, 45–55)	31.0	43.0	The median CKD-EPI eGFR was 97 mL/min per 1.73 m^2, and 38% had a eGFR <90 mL/min per 1.73 m^2	Protenuria is a risk factor for developing markers of CKD, especially in the absence of TDF. Tenofovir disoproxil fumarate exposure and traditional ASCVD risk factors were associated with decreased renal function.
Moulignier et al[155]	Prospective cross sectional	Do PLWH with microalbuminuria have more neurocognitive impairment than those without?	PLWH with microalbuminuria (UACR on urine sample: 3–30 mg/mmol)		30 (PLWH and microalbuminuria)	52 (IQR, 47–58)	37.0	47.0	PLWH with microalbuminuria performed worse than controls for information-processing speed (P=0.01) and motor skills (P=0.02)	cART-treated PLWH with a history of microalbuminuria have worse cognitive performances for the information-processing-speed domain.
			PLWH without microalbuminuria (control group)	49 (control group)	48 (IQR, 45–55)	29.0	41.0			
Ibrahim et al[156]	Observational cohort study	What are the effects of TDF and TAF on renal function?	PLHW with prior TDF exposure		309	50 (IQR, 42–59)	19.0	17.0	Median duration of TDF exposure: 4.8 (IQR, 1.9–7.9) years	Improvement in eGFR seen when switching from TDF to TAF containing ART.
			PLWH without prior exposure to TDF		48	49 (IQR, 34–58)	25.0	23.0	PLWH with prior TDF exposure experienced eGFR decline (mean, 2.20 [95% CI, 2.36–2.03] mL/min per 1.73 m^2/y) while receiving TDF and improvement in eGFR (mean, +1.16 [95% CI, +0.55 to +1.82] mL/min per 1.73 m^2/y) while receiving TAF	
Hoang et al[157]	Cross-sectional study	What are the clinical and demographic variables that affect renal function in participants on TDF-based ARV regimens over a 36 mo period?	PLWH >18 y on a TDF-based regimen	3	400 (PLWH)	39.8±8.8	48.5		Renal impairment was associated with older age >60 y (prevalence ratio, 26.75 [95% CI, 3.38–211.62]), and negatively associated with BMI, 18.5–25 (prevalence ratio 0.31 [95% CI, 0.15–0.62]) and those not exposed to isoniazid (prevalence ratio, 0.35 [95% CI, 0.14–0.91])	Longitudinal studies are needed to corroborate findings in this study and target the maintenance of the low prevalence of renal impairment in PLWH in Vietnam

(*Continued*)

Table 2. Continued

Author % (year published)	Study design	Research question	Population	Follow-up, y	Sample size	Age	Female (%)	Black	Results	Conclusion
Ryom et al[158]	Prospective cohort study	What are the clinical outcomes in PLWHs with CKD, and which modifiable risk factors are associated with these outcomes?	PLWH with CKD defined as eGFR<60 mL/min per 1.73 m^2	2.7	2467 (PLWH and CKD)	60 (IQR: 52–67)	0.2		24.1% of participants developed a serious clinical event (CVD, ESRD, death, malignancy, AIDS), with smoking status being a predictor of all serious clinical events	PLWH with CKD have a high incidence of serious clinical events, with several modifiable risk factors that can be targeted
Louis et al[159]	Observational study	What is the spectrum of hospitalized PLWH with kidney disease and which factors are associated with hospitalization?	PLWH who are hospitalized in France with an identity code representing kidney disease.	None	10862 PLWH	65±18	52.7		PLWH had a 1.5 times higher prevalence of hospitalization than those in the general population, which represents a significant increase from 2008 to 2013 (3% vs 3.7% $P<0.01$), respectively. The most prevalent condition was acute renal failure	The likelihood of hospitalization for kidney disease is higher in PLWH compared with the general population and appears to be increasing over time
Lavinya et al[160]	Clinical trial	What additional biomarkers could supplement current methods of assessing kidney function in PLWH with CKD?	PLWH with CKD (with and without proteinuria), and matched controls without CKD	None	8 PLWH/nonproteinuric CKD, 5 HIV/proteinuric CKD and matched controls (no CKD)	53 (IQR, 45.08–59.28) CKD. 49.39 (IQR, 45.9–57.2) Controls	23 CKD, 23 Controls		Of 5 protein candidates, identified using mass spectrometry and confirmed by Western blot, 2 were increased in nonproteinuric and 3 were increased in proteinuric CKD	Four potential biomarkers of CKD in PLWH were identified, that need validation in further studies with a larger sample size
			PWoH with renal impairment, and matched controls	None	3 non-HIV/renal impairment and matched controls (normal renal function)	64.98 (IQR, 61.54–77.11) renal impairment; 70.51 (IQR, 63.92–71.44) Controls	33 Renal impairment, 33 controls		No increase in protein candidates in non-HIV subjects	
Davidson et al[161]	Observational cohort study	What is the prevalence, clinical and renal outcomes of GIN in PLWH in a cohort in South Africa?	Renal biopsies taken from PLWH from 2005 to 2012 showing GIN	7	45 PLWH who underwent biopsies showing GIN	33 (IQR, 29–37)	57.8	91.1	TB was the most common cause of GIN (60% of biopsies with GIN) and factors associated with mortality were TB coinfection, higher UPCR, and lower eGFR	TB-GIN confers a high mortality and needs to be considered as part of diagnostic workup of PLWH with an AKI

(*Continued*)

Table 2. Continued

Author % (year published)	Study design	Research question	Population	Follow-up, y	Sample size	Age	Female (%)	Black	Results	Conclusion
Camargo et al[162]	Single center retrospective study	Have outcomes changed in HIV and hepatitis C coinfected patients postkidney transplant with the advent of direct-acting antivirals?	PLWH coinfected with hepatitis C who are postkidney transplant (with and without direct-acting antiviral treatment)	1.98	13 PLWH/ Hepatitis C postkidney transplant, 7 of whom were treated with direct-acting antivirals	55 (IQR, 47–63)	15.0	77.0	Improved outcomes were observed in the post direct-acting antiviral vs pre direct-acting antiviral groups (graft survival, 100% vs 67%; mortality, 0% vs 17%; serious infections, 0% vs 67%; and acute rejection, 0% vs 17%)	Direct-acting antiviral therapy confers superior outcomes compared with no therapy in PLWH co-infected with hepatitis C following kidney transplant

AKI indicates acute kidney injury; ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; cART, combination antiretroviral therapy; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; EPI, Epidemiology Collaboration; ESRD, end-stage renal disease; GIN, granulomatous interstitial nephritis; HR, hazard ratio; IQR, interquartile range; PLWH, people living with HIV; PrEP, preexposure prophylaxis; PWoH, people without HIV; TAF, tenofovir alafenamide; TB, tuberculosis; TDF, tenofovir disoproxil fumarate; UACR, urine albumin creatinine ratio; and UPCR, urine protein creatinine ratio.

transplant include an increase in opportunistic infections and HIV superinfection leading to resistant strains, with results largely being reassuring.[167] The rates of acute graft rejection are higher in PLWH compared with PWoH, thought to be related to dysregulated immune responses, but with overall outcomes being similar.[164,168] In an older person with HIV, the burden of polypharmacy can be confounded following the development of significant renal disease and regular monitoring of dosing of ARV's and other medication is needed. Fixed-dose ART regimens may be unsuitable in a patient with fluctuating renal function or on dialysis,[169] and attention must be given to dose adjustment of agents that are impacted by the cytochrome P450 enzyme system, especially interactions between protease inhibitors and tacrolimus, that may result in toxic tacrolimus levels.[135] Individualized management by a specialized team ensures favorable outcomes following transplant. It is recommended to adjust ART regimens before transplant, and protease inhibitors are cautioned against, with integrase inhibitors being first line.[135]

NONHIV–RELATED KIDNEY DISEASE

Noncommunicable diseases such as diabetes and hypertension remain the leading cause of kidney disease in PLWH.[170–172] Furthermore, as the life expectancy of PLWH on cART continues to increase, there is a growing number of PLWH with comorbidities such as diabetes, hypertension and CKD. The prevalence of type 2 diabetes has been shown to be ≈4 times higher in PLWH compared with the general population.[173] The presence of both HIV and diabetes has been associated with a significantly higher risk of progressive CKD, even after adjustment for traditional CKD risk factors.[174] In murine models, expression of HIV genes and upregulation of local inflammation accelerates diabetic kidney disease.[175] Measures to slow the progression of CKD are imperative, and health care services need to be improved to ensure adequate management of both HIV and coexisting noncommunicable diseases.

CARDIOVASCULAR AND RENAL DISEASE IN PLWH

The association between CVD and kidney disease is well established, particularly in PWoH. Both these conditions share a similar risk factor profile, such as diabetes, hypertension, obesity, and smoking. Ryom et al[176], studied 35 357 PLWH with two or more estimated glomerular filtration rate measurements. These patients were followed for a median duration of 8 years. The incidence rate of CVD was 5.2 cases per 1000 person years. The relationship between CVD and renal disease is partly related to accelerated atherosclerosis mediated by the increased inflammation and oxidative stress. The coexistence of CVD and renal disease leads to a poorer prognosis and premature death.[177] As such, CVD and CKD risk should be assessed together.[178]

MANAGEMENT OF CARDIAC AND RENAL COMORBIDITIES IN AGING PEOPLE LIVING WITH HIV

Similar to the general population, lifestyle optimization, including regular exercise, is recommended in PLWH to reduce inflammation and improve cardiometabolic health. Diabetes and hypertension should be managed according to current guidelines in the general population because there is insufficient data for a separate recommendation in aging PLWH.[179] According to the American

College of Cardiology/American Heart Association, lipid-lowering therapy is indicated for secondary prevention, LDL cholesterol levels ≥190 mg/dL, or in older diabetics.[180] Beyond this, the identification of aging PLWH who may benefit from statins for primary prevention is less clear, especially since several drug-to-drug interactions need to be considered.[181]

Pitavastatin, which has minimal interaction with antiretroviral drugs, may be preferred in aging PLWH on cART. In the REPRIEVE trial (Randomized Trial to Prevent Vascular Events in HIV), a lower risk of major adverse cardiovascular events was demonstrated in 3888 PLWH randomized to pitavastatin compared with those who received a placebo over a median follow-up duration of 5.1 years.[182] Subsequent computed tomography coronary angiography analysis in 611 REPRIEVE patients demonstrated a reduction in noncalcified plaque volume and progression and markers of lipid oxidation and arterial inflammation. These changes may contribute to the observed major adverse cardiovascular event reduction in REPRIEVE.[183] Ezetimibe does not interact with cytochrome P450 3A4 and can be safely added to statins to decrease LDL levels.[181] PCSK-9 inhibitors reduce LDL-C by ≈60% in patients receiving standard lipid-lowering therapy. Whether PCSK-9 inhibitors will prove equally effective in aging PLWH is currently being investigated in the Effect of PCSK-9 inhibition on Cardiovascular Risk in Treated HIV Infection (EPIC-HIV study; NCT03207945).[184]

Drug to Drug Interactions and Polypharmacy in Older PLWH

A detailed review of drug-drug interaction and contraindications is provided elsewhere.[181] However, it is important to appreciate that several common cardiac agents, such as clopidogrel, are metabolized by several cytochrome P450 liver enzymes, which predispose to interactions with antiviral agents and drugs used to treat opportunistic infections, including azole antifungals, rifampicin, and isoniazid.[185] The effects of cART on patient outcomes are complex and evolving as new, less toxic agents and combination therapies become available. As mentioned above, older patients are more likely to have been exposed to early generation cARTs and will have to live with the long-term toxic consequences of early cART.[37] Furthermore, as PLWH age, increasing drug burden, polypharmacy, and metabolic changes, especially in the presence of renal or cardiac disease, may predispose patients to adverse drug toxicities.[186]

Suppressing Inflammation

Targeting the persistent inflammation and immune activation may reduce the risk of ASCVD in PLWH.[187] However, current options are limited. The reduction in cardiovascular events in REPRIEVE was larger than predicted based on the reduced LDL cholesterol levels, suggesting additional cardiovascular benefits beyond LDL cholesterol lowering.[182] The monoclonal anti-IL (interleukin)-1B, canakinumab reduced plasma IL-6 and hsCRP (high sensitivity c-reactive protein) after a single dose in 10 suppressed PLWH.[188] Low-dose methotrexate (LDMTX) decreased CD8+T-cell activation without significant changes in inflammatory biomarkers in 86 PLWH randomized to LDMTX compared with controls.[189] However, larger studies with longer follow-up are still required.

FUTURE DIRECTIONS

The emergence of multiple chronic conditions in aging PLWH calls for a multidisciplinary approach to patient management. All allied health professionals, including dietitians and medical specialists, should be accessible to patients. Significant advancements in cART can be anticipated, such as injectable medication, stem cell-based therapies, genome editing, and the introduction of broadly neutralizing antibodies.[24] At least 25 ongoing and completed clinical trials evaluate the efficacy of cholesterol-lowering medication and anti-inflammatory drugs in PLWH.[190] Contemporary data from these trials will hopefully shed more light on preventative strategies that reduce inflammation and the severity of comorbidities in aging PLWH.

CONCLUSIONS

The advancing age of PLWH underscores the heightened risk of cardiac and renal comorbidities within this population. Chronic inflammation, a hallmark of HIV infection, plays a pivotal role in the development of these comorbidities. Among PLWH, dyslipidemia, hypertension, coronary artery disease, and HIV-associated cardiomyopathy are prominent cardiac conditions, while acute and chronic kidney injury are also increasing. It is imperative to prioritize screening and primary prevention strategies targeting young PLWH to mitigate the emergence of severe and challenging-to-manage comorbidities as they age. Addressing cardiac and renal comorbidities necessitates a cohesive and interdisciplinary approach to patient care, involving collaboration among cardiologists, nephrologists, and other health care providers. Embracing such a unified approach holds promise for optimizing the management and outcomes of cardiac and renal health in aging PLWH.

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