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REVIEW

A review of cardiovascular and renal function monitoring: a consideration of older adults with HIV

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Abstract: The prevalence of human immunodeficiency virus (HIV) infection in older and elderly adults is significant worldwide. This population poses new challenges and opportunities in the management of HIV. In addition to the risks affecting HIV patients of all ages, including risk of opportunistic infection and medication resistance, age-related changes in physiology, higher comorbidity burdens, increased use of medications, and potential adverse drug reactions to HIV medications all factor into the care of older adults with HIV. The risk and progression of cardiovascular and renal comorbidities may be higher in the older adult HIV population and in patients taking specific HIV medications. Understanding these risks is essential when managing a new type of patient: the older adult with HIV.

Keywords: older adult, elderly, geriatrics, cardiovascular disease, kidney disease, renal dysfunction, HIV

Introduction

When discussing human immunodeficiency virus (HIV) in older adults, the nomenclature can differ based on the source of information. Currently, the Centers for Disease Control (CDC) in the United States defines "elderly" in the HIV population as 50 or older;[1] however, this definition differs from study to study. Most HIV studies have defined people 50 or older as "older adults," while people 60 or older in developing countries and people 65 or older in developed countries are defined as "elderly".[2,3] For the purpose of this review, "older adults" will be defined as 50 or older and "elderly" will be defined as 65 or older.

Currently, there are 34 million people worldwide with a diagnosis of HIV.[4,5] In 2006, 15.5% of the patients diagnosed with HIV were 50 or older; this percentage has doubled since 1982.[4,6] Additionally, 25% of patients with a diagnosis of HIV (independent of the age at diagnosis) were 50 or older, which is an increase of 17% over 5 years. It is estimated that more than 50% of the worldwide HIV population will be 50 or older by the year 2015.[7] The addition and evolution of highly active antiretroviral therapy (HAART) is a large contributing factor to HIV-infected adults living longer.[2] When optimal care and combination antiretroviral therapy (cART) are utilized, patients are expected to live an additional 20 years, to a near-normal lifespan.[2,8] In women, the rate of HIV diagnosis is decreasing in all age cohorts except for those 50 or older.[9] Moreover, race and ethnicity assessments in the United States show the rate for HIV infection in older adults disproportionately affects African Americans 12 times more than Caucasians.[10,11]

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Although only identified in descriptive data, there is limited information available for "elderly" patients. In an abstract from a French HIV database (n = 1,680 patients), 3.87% (n = 61) were 65 or older.[12] Of these patients, 21% were women and 79% were men; regarding the status of these patients, 38% had an acquired immunodeficiency syndrome (AIDS)-defining illness, 21% were symptomatic, and 41% were asymptomatic.[12] The initial diagnosis of patients 65 or older worldwide ranges from 1.8%–2%.[13–16] In the United States, the CDC has also compiled data for elderly patients with HIV.[9] From 2008 to 2011, the diagnosed incidence in this age group was 2.0–2.4 per 100,000. When evaluating elderly patients currently living with HIV, the rate is 85.7 per 100,000 persons, which is just one-ninth of the cohort (45–49 year olds) with highest rate of infection.[9]

Many older adults do not consider the risk of acquiring HIV. In a 2010 HIV Surveillance Report published by the CDC, approximately 21,000 "older adults" remained undiagnosed: 10.1% of all undiagnosed HIV patients.[17] There are two main factors that may contribute to a lack of an HIV diagnosis. The first is a lack of testing. Currently, the CDC recommends universal opt-out testing in persons aged 13 to 64. Previously, patients 65 or older were not considered for routine testing because of the increased costs of testing in this population and the low proportion of the elderly thought to be infected with HIV.[2] However, the American College of Physicians, the American Academy of HIV Medicine, the American Geriatric Society, and the AIDS Community Research Initiative of America recently updated their guidelines to recommend no upper age limit for HIV testing.[9,10] The second factor contributing to a lack of diagnosis in older HIV patients is the inability to differentiate symptoms of HIV from symptoms of "typical aging".[9] These symptoms may include dementia, weight loss, fatigue, anorexia, chronic pain, rash, and itching.[8,9,13] Failure to assess risk factors, or patients not fully disclosing risk factors, can prolong the time to diagnosis. Therefore, an accurate history of patients' intercourse and intravenous drug use needs to be solicited regardless of age.[9] When people 50 or older were compared to 20 year olds, older adults were 5 times less likely to be tested and were 6 times less likely to use condoms during intercourse.[18]

Once diagnosed, the prognosis and course of HIV in older adults differs from that in younger counterparts. At diagnosis, older adults typically have lower CD4 counts, approximately 15% less than younger adults, which is thought to result from an increased time to diagnosis and age-related immunological dysfunction.[2,12,13,19,20] It also appears that older patients have a greater virologic response to cART than younger patients; however, their immune response is weaker. Therefore, older adults show a quicker decrease in viral load, with a conversely slower increase in CD4 nadirs.[21]

Additionally, older adults are at higher risk for worse outcomes because of neurocognitive decline, social isolation, lack of social support, and depression.[22] After HIV diagnosis, cART is usually initiated sooner in older adults.[18,20] The risk of developing AIDS or death increases by 1.3 and 1.5 times, respectively, for every increase in age by 10 years.[9] Progression to AIDS and death is highest in the older adult population.[2,4,9] The AIDS-defining illness of HIV-related dementia is also highest in older adults.[9]

The shift toward a population of older adults having HIV brings new treatment considerations to light. When assessing an older adult or elderly HIV patient, the health professional must continue to address cART and opportunistic infections; however, further considerations must also be made for age-related comorbidities such as cardiovascular disease, metabolic disorders, non-HIV related malignancies, osteoporosis, depression, and liver and renal function decline.[8,22,23]

Cardiovascular risk and renal function in older adults

Cardiovascular disease (CVD) and chronic kidney disease (CKD) are highly prevalent in the elderly population. Currently, there are 40.4 million people in the US over the age of 60 diagnosed with CVD; this population comprises one-half of all CVD cases in the US.[24] In patients 60 years or older, 73%–80% of men and 72%–87% of women have CVD. Approximately two-thirds of otherwise healthy adults have some decline in renal function.[25,26] Coresh et al determined that the prevalence of CKD in 60–69 year olds is double that of 40–59 year olds; the prevalence of CKD in adults 65 or older is 38%.[27]

With the increasing number of older adults and the elderly with a diagnosis of HIV, plus the relatively higher prevalence of CVD and CKD in the older adult population, the HIV and Aging Consensus Project published a summary report that highlights specific risk factors that older adults face with concomitant HIV.[28] This summary report discusses: initiation of cART; prevalence of CVD, CKD, diabetes, and hypertension; drug-drug interactions; hepatitis screening; cancer screening; sexual health; pulmonary disease; osteoporosis; advanced directive care; and mental health. The specific aim of the present paper is to further discuss the cardiovascular and renal considerations in older adults with HIV.

HIV: impact on cardiovascular function

Advances in the effective delivery of cART combined with the natural process of aging have raised new questions about risks posed to the older patient with HIV. In a descriptive, cross-sectional analysis of older adults with HIV compared with HIV-positive patients under the age of 50, the frequency of ischemic heart disease, congestive heart failure, vascular disorders, stroke, hypertension, and hyperlipidemia were more prevalent in the older adult cohort.[29] There is evidence to suggest that the presence of HIV has an adverse effect on various biomarkers related to inflammation and coagulation, regardless of age.[30] Additionally, other studies have examined the potential link between CVD and HIV.[31–33] Whereas not all studies have examined this link in older adults, a recent study examined the risk of HIV and myocardial infarction (MI).[34] After adjusting for comorbidities and cardiovascular risk scores, that study found the associated risk for MI with HIV infected patients was 1.48 (hazard ratio [HR]; 95% CI, 1.27–1.72). Of note, the population was stratified by age group, and only HIV infected patients between 50–59 years and 60–69 years had a significantly higher incidence of MI than that of uninfected patients. Patients with HIV between 70–79 years and 80–89 years did not have a higher risk for MI than their non-HIV control group.

The specific rationale for cardiovascular risk in aging patients with HIV is not clear. The process appears to be multifactorial. Potential causes include the use of cART, specific use of antiretroviral agents within regimens, the inflammatory nature of HIV disease itself, and the natural process of aging.

cART versus non cART

There are several studies related to the use of cART and implications for cardiovascular risk. A notable study which found an increased risk for the development of MI was the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study group.[33] Whereas other variables such as age, smoking status, and male sex were associated with increased risk of MI in the D:A:D cohort, there was an independent association of MI in patients exposed to cART, with a risk ratio (RR) of 1.26 (95% CI, 1.12–1.41) per year of exposure. Currier et al assessed coronary heart disease (CHD) based on exposure to cART and found a significantly higher rate of CHD in younger patients (18–33 years of age).[31] Unlike the D:A:D cohort, this study examined risk of CHD for both men and women of various age groups. Of particular importance to the older adult with HIV, the study found a significant reduction in CHD incidence in men aged 45–54 years, 55–64 years, and 65–74 years, and in women aged 55–64 years, on cART therapy compared with untreated controls. Other studies have examined the cardiovascular risk with cART and come to a variety of conclusions (Table 1).[31–33,35–38] In contrast, El-Sadr et al found an increase in cardiovascular, renal, or hepatic failure in the cohort of patients who were not aggressively managed with cART based on a CD4 >250 cells/mm^3, which could not be specifically attributed to treatment.[37]

Specific ARTs within regimens

The D:A:D cohort has accumulated enough data to analyze the association of individual antiretroviral medications with MI. Early studies from the 1990s and early findings from the D:A:D cohort published in 2007 determined that there was an increased risk of MI with the use of protease inhibitors (PI) as a class effect.[39–43] However, more recent data from the D:A:D cohort found an increased RR of MI with the use of indinavir (RR 1.12; 95% CI, 1.07–1.18) and lopinavir/ritonavir (RR 1.13; 95% CI, 1.05–1.21), whereas there was no risk found with nelfinavir or saquinavir.[44] The French Hospital Database Cohort (FHDC) found an association with MI and both cumulative and recent exposure to amprenavir/fosamprenavir with or without ritonavir and lopinavir/ritonavir, but not indinavir, saquinavir or nelfinavir.[38] With the exception of lopinavir/ritonavir, these PIs are used minimally in clinical practice, as evidenced by their place in the Department of Health and Human Services guidelines.[45] The D:A:D cohort recently acquired enough data to analyze atazanavir and found no association between cumulative exposure and risk of MI.[46] Currently, the cohort lacks the data necessary to assess the effects of darunavir, PI, and raltegravir, an integrase inhibitor. Older non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz and nevirapine, and the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) have not been associated with MI in the D:A:D cohort or FHDC.[39,43] Among the individual NRTIs, didanosine and abacavir have been associated with an increased risk for MI in some, but not all, studies.[39,47] No association has been found with the less commonly used thymidine analogs zidovudine and stavudine, or lamivudine.[38,39] Cumulative exposure to didanosine, but not recent or past exposure, was associated with an increased risk of MI in the D:A:D cohort (RR 1.06; 95% CI, 1.01–1.12),[39] but no risk was seen in the FHDC (RR 0.91; 95% CI, 0.82–1.01).[38] Only the assessment by Bozzette et al analyzed admission

Table 1 Major studies of cardiovascular risk in HIV-positive patients with or without cART

Study	Population	Design	Outcomes
Currier et al[31]	HIV+ Males (n = 20,742) HIV+ Females (n = 7,771) Non-HIV+ Males (n = 970,259) Non-HIV+ Females (n = 2,084,437)	Historical cohort	HIV group RR for CHD by ART or not ART (Covariate adjusted) 18–33 y 2.06 (95% CI, 1.42–2.99; $P < 0.001$) 34–49 y 1.08 (95% CI, 0.91–1.28; $P > 0.05$) 50–65 y 0.79 (95% CI, 0.63–1.00; $P > 0.05$) 66 or older 1.15 (95% CI, 0.65–2.04; $P > 0.05$)
Obel et al[32]	HIV+ (n = 3,953) Non-HIV+ (n = 373,856) Age: <45	Historical cohort	Adjusted relative risk was significantly higher in HAART cohort 2.12 (95% CI, 1.62–2.76) RR did not increase after 8 years of follow up
Friss-Moller et al[33]	HIV+ Patients (n = 23,468) Age: 34–45 (IQR)	Prospective cohort	Exposure to cART and rate of MI – RR 1.26 (95% CI, 1.12–1.41; $P < 0.001$)
Bozzette et al[35]	HIV+ Patients (n = 41,213) 98.2% male Age: 35–55	Historical cohort (VA population)	Serious CV event: HR 1.05 (95% CI, 1.05–1.06) Death: HR 1.03 (95% CI, 1.03–1.03) Pre-existing vascular disease: HR 4.01 (95% CI, 3.39–4.76)
Lichtenstein et al[36]	HIV+ Patients (n = 2,005) Age: 42 (median)	Prospective observational cohort	CVD incidence (per 100 person years) 1.32 vs 3.27 ($P = 0.002$) Exposure vs non-exposure to HAART, respectively
El-Sadr et al[37]	HIV+ Patients (n = 5,472) Drug Conservation Group (treatment <250 CD4 cells/mm^3) (n = 2,720) Viral Suppression Group (n = 2,752) Age: 38–50 (IQR)	Open-label, randomized	Major Cardiovascular, Renal, or Hepatic Disease HR 1.7 (95% CI, 1.1–2.5) in Drug Conservation Group as opposed to cART
Lang et al[38]	HIV+ Patients (n = 74,958) Age: 41–54 (IQR)	Case-control	Risk of MI Abacavir OR 2.01 (95% CI, 1.11–3.64) *(Overall exposure to cART not measured)*

Abbreviations: +, positive; ART, antiretroviral therapy; cART, combination antiretroviral therapy; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HAART, highly active antiretroviral therapy; HR, hazards ratio; IQR, interquartile range; MI, myocardial infarction; OR, odds ratio; RR, relative risk; VA, Veterans Affairs; y, years; vs, versus, HIV, human immunodeficiency virus.

rates for cardiovascular disease by class of antiretroviral at various age ranges.[48] Few data are available on the association of MI specifically in the HIV-positive older adult population. Limitations of data include observational design of trials, short duration of follow-up, lack of data on newer antiretroviral agents, and inconsistent control of traditional cardiovascular risk factors (Table 2).[38–44,46–51]

The NRTI abacavir has been associated with possible increased cardiac risk and may pose a risk to older adults with HIV. The FHDC determined there was an increased risk of MI in short term exposure to abacavir (odds ratio[OR] 2.01; 95% CI, 1.11–3.64).[38] Data from the D:A:D cohort also determined there was an increased risk of MI with abacavir use.[44] The ACTG A5001/ALLRT (AIDS Clinical Trial Group A5001/Longitudinal Linked Randomized Trial) historical cohort, using data from previous clinical trials, revealed no association between abacavir use and risk for MI.[51] When data from clinical trials performed by the manufacturer of abacavir were analyzed, no risk was found.[52] The meta-analysis by Ding et al concluded that the risk of cardiac events with the use of abacavir was not clinically meaningful.[53] Due to the inclusion/exclusion of many of these studies, data on older adults were sparse.

Inflammatory nature of HIV and the natural process of aging

Important considerations for the cardiovascular health of the older patient with HIV include modifiable risk factors that have the potential to disproportionately affect HIV patients older than 50 years. In addition to the increased risk of MI listed previously, HIV infection alone is an independent risk factor for atherosclerosis, regardless of CVD history.[54] Smoking is a well recognized risk factor for increased cardiovascular disease in the general population, but further analysis of the D:A:D cohort revealed an increased risk in all-cause mortality, and specifically, an increased risk for cardiovascular events in HIV-infected patients.[55] That analysis is particularly important in relation to the high prevalence of smoking in patients with HIV compared with that in the general population – up to 58% in some demographic groups.[56] Dyslipidemia is common in patients with HIV and specifically in patients taking cART with certain ARTs, including PIs, efavirenz, and elevated triglycerides occur

Table 2 Cardiovascular risks for specific antiretroviral therapies

Study	Population	Design	Outcome
Classes			
Friis-Moller et al[39]	Cohort (n = 23,437) MI (n = 345) Age (median): 39 (with MI)	D:A:D, retrospective case-control	RR of MI per year of PI exposure 1.16 (95% CI, 1.10–1.23) RR of MI per year of NNRTI exposure 1.05 (95% CI, 0.98–1.13)
Worm et al[44]	MI (n = 580) Without MI (n = 32,728) Age (median): 49 (with MI), 44 (without MI)	D:A:D, retrospective case-control	Adjusted RR of MI: Indinavir, cumulative exposure (per year) 1.12 (95% CI, 1.07–1.18) Lopinavir-ritonavir, cumulative exposure 1.13 (95% CI, 1.05–1.21) Nelfinavir, cumulative exposure 1.04 (95% CI, 0.98–1.11) Saquinavir, cumulative exposure 1.04 (95% CI, 0.98–1.11) Efavirenz, cumulative exposure, 1.02 (95% CI, 0.96–1.08) Nevirapine, cumulative exposure 0.97 (95% CI, 0.92–1.03) Didanosine, recent exposure 1.41 (95% CI, 1.09–1.82) Abacavir, cumulative exposure 1.07 (95% CI, 1.00–1.14); recent exposure 1.70 (95% CI, 1.17–2.47) Tenofovir, cumulative exposure 1.04 (95% CI, 0.91–1.18); recent exposure 1.14 (95% CI, 0.85–1.53) No association with zidovudine, stavudine, lamivudine, or tenofovir
Protease Inhibitors (older)			
Holmberg et al[40]	HIV+ (n = 5,672) 17,712.4 person years Age (median/range): 47 (28–67)	HOPS, prospective observational cohort	MIs (n = 21) per number of patients Protease inhibitors: 19/3,247 No protease inhibitors 2/2,425 OR 7.1 (95% CI, 1.6–44.3) Adjusted HR 6.5 (95% CI, 0.9–47.8)
Jutte et al[41]	HIV+ (n = 1,324) PI use (n = 373)	Retrospective cohort	MI PI use (n = 5), 1.06/100 person years (95% CI, 0.42–2.24) No PI use (n = 3), 0.21/100 person years (95% CI, 0.06–0.54; $P = 0.025$)
Klein et al[42]	HIV+ (n = 4,159) 14,823 person-years Age (median): 42	Retrospective cohort	Acute MI: No PI use (n = 19) PI use (n = 28) Age adjusted MI hospitalization rates: No PI exposure: 4.4 (95% CI, 2–6.7) PI exposure 4.3 (95% CI, 2.4–6.1)
Mary-Krause et al[43]	HIV+ (n = 34,976) 88,029 person-years History of MI: Age (mean): 41.9 No MI: Age (mean): 37.7	FHDH, Prospective cohort	Relative hazard for MI PI 2.56 (95% CI, 1.03–6.34; $P = 0.04$) NRTI 0.93 (95% CI, 0.19–4.65; $P = 0.93$); NNRT 1.38 (95% CI, 0.67–2.83; $P = 0.38$) Exposure to PI: <18 months: 8.2 (95% CI, 4.7–11.7) per 10,000 patient-years 18–29 months: 15.9 (95% CI, 7.9–23.9) per 10,000 patient-years ≥30 months: 33.8 (95% CI, 15.4–52.1) per 10,000 patient-years
Bozzette et al[48]	HIV+ (n = 36,766) Age <35 years = 17.6% 25–55 years = 71.3% >55 years = 11%	Retrospective cohort of patients using VA services compared to typical US patients	HR for admission for cardiovascular disease for 24 months of exposure: NRTIs 0.88 (95% CI, 0.63–1.22) PIs 1.23 (95% CI, 0.78–1.93) NNRTIs 1.09 (95% CI, 0.56–2.09)
David et al[49]	Case Angina (n = 8); MI (n = 8) Control (n = 32) Age (median): 43 years (ICVD); 45 years (control)	Retrospective case-control	Number of patients with cardiovascular disease (case vs control) NNRTI Case 0 vs control 0 ($P = 0.09$) NRTI Case 190 vs control 130 ($P = 0.02$) PI Case 118 vs control 64 ($P = 0.46$)

(*Continued*)

Table 2 (*Continued*)

Study	Population	Design	Outcome
Atazanavir			
Monforte et al[46]	301,907 person-years	D:A:D study Prospective cohort	Incidence of MI No drug exposure: 0.28 (95% CI, 0.26–0.3) per 100 person-years Drug exposure (3 or more years): 0.2 (0.12–0.32) per 100 person-years
Didanosine			
Lang et al[38]	HIV+ (n = 74,958) MI (n = 423) Median age Cases (n = 289) Age (median/IQR): 47 (41–54) Age (median/IQR): 46 (40–54)	FHDH, Prospective, observational cohort	Cumulative exposure 0.91 (95% CI, 0.82–1.01; $P = 0.06$) Cumulative, recent, and past exposure 0.88 (95% CI, 0.77–1.01; $P = 0.07$) No risk associated with lamivudine, stavudine, tenofovir, zalcitabine, zidovudine, efavirenz, or nevirapine No risk associated with indinavir +/– ritonavir, nelfinavir, saquinavir +/– ritonavir Amprenavir or fosamprenavir +/– ritonavir Cumulative: 1.57 (95% CI, 1.24–2; $P = 0.001$) Cumulative, recent, and past: 1.56 (95% CI, 1.21–2.01; $P = 0.001$) Lopinavir/ritonavir Cumulative: 1.37 (95% CI, 1.13–1.65;), $P = 0.002$ Cumulative, recent, and past: 1.34 (95% CI, 1.09–1.64; $P = 0.005$)
SMART/ INSIGHT and D:A:D[47]	HIV+ (n = 4,544) Didanosine use (n = 643) Age (median/IQR): 44 (38–50)	Prospective cohort	HR (multivariable) in viral suppression arm CVD, major 1.06 (95% CI, 0.43–2.58) Clinical MI 1.89 (95% CI, 0.35–10.2) CVD, minor 1.03 (95% CI, 0.35–3.03) CVD, expanded definition 0.86 (95% CI, 0.40–1.85) HR (multivariable) for new ischemic abnormalities on EKG in viral suppression arm 0.81 (95% CI, 0.59–1.12)
Sabin et al[50]	HIV+ (n = 33,347) 157,912 person-years Age (median/range): 49 (24–92)	Prospective cohort	Cumulative exposure (per year) 1.06 (95% CI, 1.01–1.12; $P = 0.03$) Recent exposure (within 6 months) 1.49 (95% CI, 1.14–1.95; $P = 0.003$) Past exposure 1.08 (95% CI, 0.84–1.39; $P = 0.54$)
Abacavir			
SMART/ INSIGHT and D:A:D[47]	HIV+ (n = 4,544) Abacavir use (n = 1,019) Median age: 45 (39–51)	Prospective cohort	Adjusted HR (multivariable) in abacavir, not didanosine arm CVD, major 1.80 (95% CI, 1.04–3.11) Clinical MI 4.25 (95% CI, 1.39–13.0) CVD, minor 2.70 (95% CI, 1.51–4.83) CVD, expanded definition 1.91 (95% CI, 1.25–2.92)
ACTG A5001/ ALLRT[51]	HIV+ (n = 5,056) Abacavir use: (n = 1,704) Median age: 37 % population ≥45: 23% (n = 1,182)	Historical Observational cohort	Hazard Ratio of Exposure to abacavir and MI 1 year: 0.7 (95% CI, 0.2–2.6) 6 year: 0.6 (95% CI, 0.3–1.4)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; D:A:D, Data Collection on Adverse Events of Anti-HIV Drugs; FHDH, French Hospital Database on HIV; HR, hazards ratio; hsCRP, high-sensitivity C-reactive protein; HIV, human immunodeficiency virus; HOPS, HIV outpatient study; ICVD, ischemic cardiovascular disease; IL6, interleukin-6; IQR, interquartile range; MI, myocardial infarction; NRTI, non-nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; PY, patient-years; RR, relative risk; vs, versus; SMART, Strategies for Management of Antiretroviral Therapy.

with zidovudine and stavudine treatment.[57] There are also data to suggest that the incidence of diabetes increases with exposure to cART (RR 1.11; 95% CI 1.07–1.15), which can disproportionately affect older patients because of increased exposure to cART.[58] Caution in cART selection should be taken in patients with significant cardiovascular history, regardless of age, as well as other risk factors for cardiovascular disease such as smoking, hyperlipidemia, or a preexisting cardiovascular condition. With the potential for increased comorbidities that exist with aging, older patients with HIV

require aggressive management and monitoring for modifiable risk factors associated with cardiovascular disease.

HIV: impact on renal function

The risks for renal dysfunction in patients with HIV are multifactorial. The first identified renal-specific disease associated with HIV infection was HIV-associated nephropathy (HIVAN). HIVAN primarily affects African-Americans and persons with progressive HIV infection.[59] The utilization of cART has significantly decreased the occurrence of HIVAN in the HIV population. Acute renal failure (ARF) occurs more frequently in patients with HIV compared with a non-HIV population; however, the occurrence of ARF was significantly decreased in patients who have received cART for longer than 3 months.[60] Moreover, patients with stage 3 CKD and an initially depressed CD4 cell count (<200 cells/mm^3) experienced an increase in glomerular filtration rate (GFR) when the viral load was suppressed (<400 copies/mL) following cART.[61]

Recent prevalence data from the CDC's Medical Monitoring Project estimated that 7.6% of patients with HIV have concurrent CKD.[62] Older patients are disproportionately affected by CKD in both the HIV and non-HIV populations. Renal failure is 3 times more likely to occur in HIV-positive older adults compared with those aged 18–49 years without HIV infection.[29] An analysis of HIV positive patients with and without CKD revealed that hypertension (HR 2.39; 95% CI, 1.88–3.04) and history of ARF (HR 2.4; 95% CI, 1.8–3.2) increased the risk for developing CKD, whereas a CD4 count >200 cells/mm^3 reduced the risk of developing CKD (HR 0.63; 95% CI, 0.48–0.81).[63]

The specific rationale for renal risk in aging patients with HIV is not clear. The process appears to be multifactorial. Potential causes have been theorized which include the use of cART, specific use of antiretroviral agents within regimens, and decreased kidney function associated with aging.

cART versus non cART

The benefits of cART far outweigh the nephrotoxic risks associated with therapy, as noted in the Strategies for Management of Antiretroviral Therapy (SMART) trial.[37] Continuous antiretroviral therapy showed a nearly significant increase in fatal or nonfatal renal disease compared to episodic antiretroviral therapy (HR 4.5; 95% CI, 1–20.9). Given the growth in the aging HIV population and the loss of kidney function associated with increased age, kidney impairment is a major concern when treating with specific cART medications.

Specific ARTs

In addition to the potential effects of aging and HIV on the kidneys, the potential risk of kidney toxicity secondary to cART must also be considered. Whereas some negative effects on kidney function have been reported with indinavir, lopinavir/ritonavir, atazanavir, and ritonavir in the published literature,[37,64,65] the antiretroviral associated with kidney impairment with the greatest frequency is tenofovir, a preferred medication according to the Department of Health and Human Services guidelines, and commonly used in clinical practice.[45] In premarketing studies of tenofovir, there was no reported kidney impairment in its safety profile.[66,67] However, following US Food and Drug Administration approval, a number of case reports surfaced describing a variety of toxic effects on the kidneys.[68–84] The majority of those affected were between the ages of 40–50 years, and the exposure to tenofovir ranged from 10 days to 4.5 years. Reports include cases of acute and chronic kidney dysfunction, with most involving cases of tubular dysfunction. A meta-analysis consisting of 17 prospective studies published by Cooper et al found that tenofovir did reduce renal function, as evidenced by reduction in the estimated creatinine clearance (CrCl) using the Cockcroft and Gault (C&G) equation or estimated GFR using the Modification of Diet in Renal Disease (MDRD) study equations, respectively.[85] In the time since these studies were published, the results of several cohorts have been published that demonstrated an association between tenofovir and renal impairment (Table 3).[63–65,86–92] In the ASSERT study, there was no difference in GFR in the tenofovir/emtricitabine arm compared to the abacavir/lamivudine arm; however, there was a greater presence of markers associated with tubular dysfunction in the tenofovir/emtricitabine arm compared with the abacavir/lamivudine arm.[91] Additionally, the D:A:D cohort showed that tenofovir was associated with progression of GFR to 70 mL/min/1.73 m^2 or less but was not associated with progression to CKD.[92] There are numerous limitations of these studies, including the young age of patients, normal baseline renal function, lack of consistent risk factor controls for renal impairment, short duration of follow-up, small sample size in some cohorts, and an overall lack of controls resulting from design limitations.

Other studies that examined the association between tenofovir and renal dysfunction have focused on health issues beyond exposure and dysfunction. Two small observational studies have looked at the recovery of kidney function following the discontinuation of tenofovir. One study found improvements but not complete reversal to baseline renal function, as only 42% of patients achieved their pre-tenofovir level of kidney function.[93] The other study (n = 20), with a median age of 45 years, found an association between the duration of tenofovir exposure and the kidney recovery rate.[94]

Table 3 Renal risks with tenofovir[a]

Study	Population	Design	Outcome
Scherzer[64]	(n = 10,841) Age (mean): 46 (VA population)	Cohort	Tenofovir exposure (Multivariate adjustment) Proteinuria: HR 1.34 (95% CI, 1.25–1.45; $P < 0.0001$) Rapid decline: HR 1.11 (95% CI, 1.03–1.18; $P = 0.0033$) CKD: HR 1.33 (95% CI, 1.18–1.51; $P < 0.0001$)
Dauchy et al[65]	(n = 399) Age (median, IQR): 47.4 (IQR 42.5–54) Aquitaine cohort	Cohort	Tenofovir exposure: Proximal renal tubular dysfunction: OR 1.23 per year (95% CI, 1.02–1.47; $P = 0.028$)
Mocroft et al[108]	(n = 6,843) Age (median, IQR): 43 (38–50) 103 centers in Europe, Israel, and Argentina, EuroSIDA study group	Prospective cohort	Tenofovir exposure (multivariable adjustments) Incidence of CKD per year: 1.16 (95% CI, 1.06–1.25; $P < 0.0001$)
Laprise et al[86]	(n = 1,043) Age (median, IQR): 39.3 years (34–45.2) Montreal, Canada	Prospective cohort	Tenofovir exposure: HR 1.63 (95% CI, 1.26–2.1) Cumulative eGFR loss: 1 year: –3.05 ($P = 0.17$) 2 years: –4.05 ($P = 0$) 3 years: –2.42 ($P = 0.23$) 4 years: –3.09 ($P = 0.119$)
Monteagudo-Chu et al[87]	(n = 230) Age (mean) Tenofovir: 52.6 Abacavir: 50.2 Bronx, NY (VA)	Retrospective chart review assessing progression of CKD from stages 0–1 to 2–5 with abacavir as control	Tenofovir (vs abacavir): progression of CKD Stage 2: 48.8% vs 23.7% ($P < 0.001$) Stage 3: 5.8% vs 0% ($P = 0.28$) Progression to CKD stage 2: HR 2.12 (95% CI, 1.41–3.18; $P < 0.001$) Progression to CKD stage 3: HR 4.91 (95% CI, 1.02–23.7; $P = 0.048$)
Calza et al[88]	(n = 324) Age (median, IQR) Tenofovir exposed: 42.5 (34.2–50.1) Tenofovir unexposed: 42.9 (33.6–51.4)	Retrospective cohort	Tenofovir exposed (Multivariable adjusted) eGFR decline: HR –5.1 (95% CI, –7.6 to –3.28; $P < 0.0021$)
Beaudrap et al[89]	(n = 324) Age (mean): Tenofovir: 40 No tenofovir: 38 Senegal, eGFR 1,215	Cohort	eGFR change from baseline at 12 months Tenofovir: –10.4 mL/min No tenofovir: +4.33 mL/min
Horberg et al[90]	(n = 1,647) Age (median, IQR): Tenofovir: 43 (37.9–49.5) No Tenofovir: 41.5 (35–49) Kaiser Permanente health maintenance organization	Retrospective cohort	Tenofovir exposure vs No tenofovir exposure over 104 weeks eGFR decline: –7.6 mL/min/1.73 m^2 (95% CI, –9.2 to –5.9; $P < 0.001$) Development of proximal tubular dysfunction: RR 5.23 (95% CI, 2.08 to 13.1; $P = 0.004$)
Post et al[91]	(n = 385) Age (median): 37 76 centers in Europe ASSERT study	Randomized Once daily abacavir/lamivudine versus tenofovir/emtricitabine, both with efavirenz	Abacavir/lamivudine/efavirenz vs tenofovir/emtricitabine/efavirenz Change eGFR (from baseline): 0.953 (95% CI, –1.445 to 3.351, $P = 0.435$) Renal tubular dysfunction (marker): increase risk in tenofovir/emtricitabine/efavirenz arm ($P < 0.0001$)
Ryom et al[92]	(n = 22,603) Age (median, IQR): 39 (33–44) D:A:D study	Prospective cohort	Cumulative tenofovir exposure (aIRR) Progression of eGFR ≤70 mL/min/1.73 m^2: 1.18 per year (95% CI, 1.12–1.25) Progression to CKD: 1.08 per year (95% CI, 0.97–1.21)

Note: [a]Published studies completed after the Meta-analysis by Cooper et al.[85]

Abbreviations: CKD, chronic kidney disease; CI, confidence interval; D:A:D, Data Collection on Adverse Events of Anti-HIV Drugs; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IQR, interquartile range; OR, odds ratio; RR, relative risk; VA, Veterans Affairs; vs, versus.

Several studies have shown that tenofovir in combination with a PI has a greater impact on kidney function.[94–98] Additionally, cohorts have examined the effects of tenofovir on patients with baseline CKD and found the worse the dysfunction at baseline, the greater the negative impact on the kidney function.[98–100]

With limited data on the older adult with HIV, extrapolation of the renal effects of tenofovir in the aging population is challenging. Based on the available data, it appears that an older patient with HIV initiated on tenofovir as part of cART may be at higher risk than a younger patient as a result of the age-associated kidney dysfunction and the potential for the presence of additional risk factors for renal toxicity.

Monitoring

Additional cardiovascular considerations for monitoring

Framingham risk score evaluations can be a useful tool for assessing CVD risk in older adult HIV patients. This score can be used to help patients understand the need for behavior modifications, such as increased exercise and smoking cessation. The Nutrition for Healthy Living Study evaluated the role of the Framingham risk score among individuals infected with HIV by comparing both patients with and without cART.[101] That study demonstrated that higher scores were related to surrogate markers for atherosclerosis, such as increased carotid intima-media thickness (c-IMT) and coronary artery calcium (CAC). Intermediate and high scores were associated with internal c-IMT >1.0 mm (26% versus 12%; $P = 0.003$) and with detectable CAC (78% versus 5%; $P < 0.001$).[101] The Framingham score was shown to be accurate even when HIV related variables such as viral load and CD4 counts were present; therefore, it can be a valuable tool in predicting cardiovascular risk in the HIV patient.

The European AIDS Clinical Society (EACS) guidelines recommend consideration of cART changes if the 10 year CVD risk is >20%.[102] In addition to the Framingham risk calculator, the D:A:D 5-year estimated risk calculator and the number needed to harm for abacavir calculator can also be used to assess HIV patients' CVD risks.[103]

Additional renal considerations for monitoring

Monitoring renal function by looking at CrCl should be done at least quarterly in the aging HIV patient. An Amsterdam study by Vrouenraets et al attempted to determine the most accurate way to determine kidney function in HIV patients.[104] That study compared assessments of renal function in a small population of virally suppressed HIV patients to determine the most accurate method. The renal function equations, including the Cockcroft and Gault equation (C&G), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the MDRD study equation, and the cystatin C- and 24 hour urine-based estimated GFR, were compared to measured GFR using [125I]-iothalamate. That study showed that C&G and CKD-EPI appeared to be the best reflections of true renal function and were most practical for clinical use. A recent study from Thailand also compared estimated GFR to measured GFR, and showed that GFR using the MDRD study equation underestimated true GFR in HIV patients.[105] The measurement by cystatin-C was deemed the most accurate for assessing renal function. However, that study also showed that the re-expressed MDRD study equation was the most accurate creatinine-based measurement when adjusting for race. Using cystatin-C to determine kidney function is controversial and has not been readily implemented into clinical practice. Studies are limited and with potential questionable methodology; future studies will be necessary to evaluate its utility in a clinical setting.[106,107] Finally, urinary analysis (UA) should be performed for all patients upon initiation of therapy, at any therapy change, annually for patients on tenofovir, and every 3 months for patients experiencing HIVAN.[45] Special attention should be paid to kidney function and cholesterol levels to evaluate both cardiovascular and renal health in the older patient on antiretroviral therapy.

Conclusion

There is a growing increase in the number of patients over the ages of 50 and 65 years living with an HIV diagnosis. The combination of physiological changes in older adults, comorbidities associated with aging, and potential ADRs of cART may lead to an increased risk for cardiovascular and renal disease in this population relative to younger patients. However, as the long-term impact of HIV on cardiovascular and renal function in the older patient with HIV is unknown, aggressive management and monitoring of comorbidities in the older adult HIV patient is critical, as further studies in patients 50 years and older with HIV are conducted. Managing specific cART therapies, preventing viral progression of the disease, and aggressively treating comorbidities may all play a role in monitoring and decreasing the impact of cardiovascular and renal disease in the older patient with HIV.

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