HIV and the aging kidney

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Purpose of review
To review unique considerations in the epidemiology, diagnosis, and management of kidney disease in older adults with HIV.

Recent findings
HIV infection may accelerate the course of kidney disease associated with traditional risk factors, such as diabetes, which are more common in older adults. The risks of acute and chronic kidney disease are increased both with HIV infection and with older age. Although the prevalence of chronic kidney disease is higher among HIV-infected adults than among HIV-negative adults, the mean age at diagnosis of end-stage renal disease is similar. Recent studies have supported the use of newer creatinine-based kidney function estimates in HIV-infected adults, although data in older adults are limited. These estimates are susceptible to artifact in the setting of newer medications that interfere with the secretion of creatinine, including cobicistat and dolutegravir. The management of kidney disease in older adults with HIV infection may be complicated by polypharmacy and increased risk for medication toxicity.

Summary
With aging of the HIV-infected population, age-related comorbid conditions such as kidney disease are increasingly important causes of morbidity and mortality. Although recent data do not support premature aging of HIV-infected individuals with respect to kidney disease, the risk of acute and chronic kidney disease is increased by HIV infection and its treatment.

Keywords
age, comorbidity, estimated glomerular filtration rate, HIV, kidney disease

INTRODUCTION

Antiretroviral therapy (ART) has increased the life expectancy of HIV-infected adults living in high-income countries by as much as 20 years [1], leading to a near-normal lifespan. The aging of the HIV population has important implications, including a growing burden of age-related comorbidities.

Chronic kidney disease (CKD) is increasing in prevalence in the United States (USA), with the highest prevalence in older adults [2]. The risk of acute kidney injury (AKI) also increases with age [3,4], and both CKD and AKI are strongly associated with adverse long-term outcomes in the general population [5,6]. The risks of CKD and AKI are higher in HIV-infected adults than in the general population [7,8], and the relationship between kidney disease and adverse outcomes is similar [8–11]. In addition, older adults with HIV infection are at increased risk for polypharmacy and related medication nephrotoxicity [12]. The aim of this review is to discuss unique considerations in the epidemiology, diagnosis, and management of kidney disease in older adults with HIV infection.

DEFINITIONS

For the purpose of this review, we have adopted the Centers for Disease Control (CDC) definitions of 'older adults' as 50 years or older and 'elderly' as 65 years or older. The majority of studies included in this review define CKD based on a decrease in estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 and/or the presence of proteinuria. Although expert guidelines require that these abnormalities be persistent for greater than 3 months [13], many studies have based the definition of CKD on a single measure of eGFR or

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KEY POINTS

- Both unique risk factors for chronic kidney disease (CKD), such as low CD4 cell count, high HIV viral load, hepatitis C virus infection, and injection drug use, and traditional CKD risk factors are common in HIV-infected individuals.
- Aging of the HIV-positive population will result in an increase in CKD incidence and faster progression, especially in the presence of comorbid CKD risk factors such as black race, diabetes, and hypertension.
- The increased burden of acute kidney injury in younger individuals with HIV infection may also contribute to higher CKD prevalence as this population ages.
- HIV infection and older age are both associated with polypharmacy, which may increase the risk for medication nephrotoxicity and other adverse outcomes.
- Patients with stage 4 CKD (eGFR <30 ml/min/1.73 m^2) should be referred to a nephrologist for individualized education and planning for end-stage renal disease, including consideration of dialysis, nondialysis medical management, and kidney transplantation as appropriate.

proteinuria. In addition, although several recent studies have demonstrated that the CKD Epidemiology Consortium (CKD-EPI) equations provide the most accurate GFR estimate in HIV-infected adults [14▪▪,15,16▪▪], most published studies have relied on older creatinine-based GFR estimates.

EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE IN THE GENERAL POPULATION

In the USA, CKD affects nearly 12% of the adult population [17]. Diabetes and hypertension are the two leading causes, accounting for 64% of prevalent end-stage renal disease (ESRD) cases in the USA [18]. Black race is a strong risk factor for CKD and CKD progression; although they represent only 13% of the United States population, African-Americans comprise 32% of the ESRD population [18]. Recent studies have confirmed a strong genetic predisposition to progressive CKD in individuals of West African descent [19].

The prevalence of CKD also increases dramatically in older adults, affecting more than 60% of United States adults at least 80 years of age [2]. Older adults are at increased risk for CKD as a result of increasing comorbidity and a physiologic decline in GFR with age. On average, individuals over 60 years of age have 20–30% lower GFR than those younger than 50 years [20], consequent to structural and functional changes in the aging kidney that are accelerated in association with comorbidities including hypertension, diabetes, and cardiovascular disease [21].

EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE IN HIV-INFECTED ADULTS

The epidemiology of CKD in HIV-infected individuals is influenced by traditional CKD risk factors and by HIV-related factors. Traditional CKD risk factors such as diabetes and hypertension are increasingly common among ART-treated adults [22,23]. As in the general population, diabetes [hazard ratio 1.7, 95% confidence interval (CI) 1.3–2.2] and hypertension (hazard ratio 1.9, 95% CI 1.5–2.4) are associated with increased ESRD risk in HIV-infected adults [24]. An analysis of data from 31 072 adults in the Veterans Aging Cohort Study (VACS) demonstrated that, compared with veterans without HIV or diabetes, the relative rate of progression to eGFR less than 45 ml/min/1.73 m^2 was increased in those with HIV only (hazard ratio 2.8, 95% CI 2.5–3.15), diabetes only (hazard ratio 2.5, 95% CI 2.2–2.8), and concomitant HIV and diabetes (hazard ratio 4.5, 95% CI 3.9–5.2) [25▪]. The conclusion that HIV and diabetes may have an additive effect on CKD risk is consistent with data from a mouse model of diabetic kidney disease, which demonstrates a more aggressive phenotype in mice expressing an HIV-1 transgene [26].

As in the general population, black race is a strong risk factor for CKD progression in HIV-infected individuals, resulting in a higher burden of advanced CKD and ESRD among HIV-infected blacks [27]. Among United States patients with ESRD attributed to HIV-associated nephropathy (HIVAN), approximately 90% of incident cases occur in African-Americans [18]. Although the incidence of ESRD is lower among HIV-infected European blacks, there is a similar racial disparity. In an analysis of 20 132 patients in the United Kingdom Collaborative HIV Cohort (UK-CHIC), progression to stages 4–5 CKD was three-fold more frequent in black Europeans compared with whites (rate ratio 2.8, 95% CI 1.6–4.8) [28]. Genetic studies have confirmed a particularly strong link between West African ancestry and HIV-associated CKD and ESRD [19].

Similar to the general population, aging of the HIV-positive population will result in an increase in the incidence of CKD. Existing data from the USA and European cohort studies confirm a higher incidence of CKD among older HIV-infected adults. The effect of age appears to be independent of race; as an example, the data presented in Table 1 demonstrate a graded increase in CKD incidence with older age in both a predominately African-American United States cohort and a predominately white European

Table 1. Increased incidence of chronic kidney disease in older adults with HIV: data from the USA and Europe

Reference	Country	Data source	*n*	Male	Black race	Age strata	Adjusted incidence rate ratio (95% CI)
Morlat *et al.* [29]	France	ANRS CO3 Aquitaine Cohort	4350	74%	<10%	<45 years	1 (referent)
						45–60 years	1.7 (1.2–2.6)
						>60 years	2.6 (1.6–4.1)
Lucas *et al.* [27]	United States	Johns Hopkins HIV Clinical Cohort	4259	68%	78%	<45 years	1 (referent)
						45–55 years	1.45 (1.01–2.09)
						>55 years	3.47 (2.07–5.81)

Both studies defined chronic kidney disease according to the current practice guidelines, as an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2, confirmed on two measurements at least 3 months apart. The Modification of Diet in Renal Disease (MDRD) equation was used to estimate GFR.
CI, confidence interval.

cohort, with similar effect size and overlapping CIs [27,29].

Interestingly, the pattern is less clear for prevalent CKD. In an analysis of 2009 data from the CDC Medical Monitoring Project presented at the 2013 Conference on Retroviruses and Opportunistic Infections (CROI), an estimated 21% of HIV-infected adults aged at least 60 years had CKD [30]. Although this prevalence was higher than that in younger adults with HIV infection, it was lower than that observed in age-matched uninfected adults in the National Health and Nutrition Examination Survey. In adults less than 60 years old, the relative prevalence of CKD was higher among HIV-infected adults. The authors hypothesized that this finding reflects a cohort effect, with premature death among older adults with concomitant HIV infection and CKD. In contrast, the relative prevalence of CKD was increased among older HIV-infected adults in an Italian study, when compared with age-matched uninfected controls [31]. In a cross-sectional analysis of more than 9000 Italian adults, the prevalence of CKD was significantly higher in HIV-positive adults aged 51–60 years compared with age-matched, HIV-negative adults (5.2 vs. 0.29%, $P < 0.001$); the disparity was even greater in those more than 60 years (24.3 versus 0.49%, $P < 0.001$).

Studies such as these have fueled the debate over 'premature aging' in HIV-infected adults. A recent analysis of data from the VACS virtual cohort presented at the 2013 CROI did not find evidence of premature aging for the outcome of ESRD, with a significantly higher prevalence of ESRD, but a similar age at diagnosis in HIV-infected veterans versus uninfected controls [32]. The increased prevalence of CKD in HIV-infected adults reflects a growing prevalence of the traditional CKD risk factors and the contribution of HIV-related factors. Unique risk factors for CKD in this population include low CD4 cell count and high HIV viral load, as well as other exposures that may be more common among HIV-infected adults, including hepatitis C virus infection, cigarette smoking, and injection drug use [24,25▪,27,33▪,34,35]. A growing body of literature, discussed in the next section, suggests that a high rate of AKI may also contribute to CKD risk among HIV-infected individuals.

ACUTE KIDNEY INJURY

AKI is a rapid decline in GFR, typically marked by an increase in serum creatinine or a decline in urine output. There is a high burden of AKI in the HIV population. In hospitalized patients, AKI occurs at three times the rate of uninfected controls [8]. Although age has not been consistently identified as an independent risk factor for AKI in HIV-infected adults, one of the strongest predictors of AKI is preexisting CKD [8,36]. Similar to the observations in the general population, AKI has also been associated with subsequent CKD progression, cardiovascular events, and mortality in HIV-infected adults [8,37,38]. The increased burden of AKI in the younger HIV population may translate into a higher prevalence of CKD in older adults with HIV, whereas preexisting CKD in older adults further increases their risk of AKI.

MEDICATION-INDUCED NEPHROTOXICITY

HIV-infected adults are at risk for nephrotoxicity from medications used to treat HIV, opportunistic infections, and associated comorbid conditions. Both HIV infection and older age have also been associated with polypharmacy [12,39], further increasing the risk of medication toxicity in older adults with HIV infection [40]. The literature on ART nephrotoxicity was recently reviewed by Ryom *et al.* [41] in this journal. Although only the nucleotide reverse transcriptase inhibitor (NRTI) tenofovir disoproxil fumarate (TDF) and the first-generation protease inhibitor indinavir have well established potential for acute nephrotoxicity, these agents and several ritonavir-boosted protease inhibitors

have been associated with an increased risk of CKD in observational studies. Risk factors for potentially reversible proximal tubulopathy and AKI with TDF include factors that increase systemic tenofovir exposure, such as older age, lower GFR and body weight, and concomitant use of other nephrotoxic agents or medications that increase tenofovir concentration, including some boosted protease inhibitors. Older age and lower baseline GFR have also been identified as risk factors for the development of CKD in patients receiving TDF [42]. The investigational prodrug tenofovir alafenamide fumarate (TAF) achieves high intracellular tenofovir concentrations in target cells at significantly lower plasma tenofovir concentrations, and phase 2 studies suggest an improved renal and bone safety profile [43,44]. If phase 3 studies confirm efficacy and safety, TAF may eventually provide a safer alternative for older adults with HIV infection and for patients with preexisting CKD. In addition to the potential for ART toxicity, older adults with HIV infection may also be at risk for nephrotoxicity from drugs used in the treatment of opportunistic infections and age-related comorbid conditions, including antivirals, antibacterials, nonsteroidal anti-inflammatory drugs, and proton pump inhibitors.

DIAGNOSIS OF CHRONIC KIDNEY DISEASE IN OLDER ADULTS WITH HIV

Updated guidelines for the diagnosis and management of CKD in HIV-infected individuals are expected from the Infectious Disease Society of American/ HIV Medicine Association this year, and will provide a comprehensive overview of CKD diagnosis and management. The following sections focus on the key decision points faced by HIV providers, including the timing and approach to CKD screening and the timing of referral to nephrology.

Expert guidelines define CKD as the presence of kidney damage (including proteinuria) and/or eGFR less than 60 ml/min/1.73 m^2 that persists for more than 3 months [13]. Although commonly used GFR estimates were not derived in HIV-infected individuals or in older adults, recent studies have demonstrated that the CKD-EPI equations provide a reasonable estimate of GFR in HIV-infected adults, when compared with a direct measurement of GFR [14▪▪,15,16▪▪]. Available data suggest that serum cystatin C should not be used alone to estimate GFR in HIV-infected adults, although the combination of cystatin C and creatinine may be useful in situations in which a more accurate GFR estimate is necessary [14▪▪,15,16▪▪]. GFR estimates are known to be less accurate in older adults [45] and no studies have focused on the validation of GFR estimates in older adults with HIV. Although approximately one-third of participants in a single study were greater than 50 years of age, the mean age of HIV-infected participants in the available studies ranged from 46 to 49 years [14▪▪,15,16▪▪]. Given the limitations of existing equations, providers should use the same estimate to follow GFR over time in an individual. At present, the Cockcroft Gault estimated creatinine clearance remains the accepted kidney function estimate for drug dosing, although there is increasing evidence to support a change in this practice [46]. All creatinine-based kidney function estimates are influenced by medications that interfere with tubular secretion of creatinine, including cobicistat and dolutegravir, and to a lesser extent rilpivirine [47–49]. The resulting increase in serum creatinine is immediate, nonprogressive, and typically less than 1–2 mg/dl, and the observed decline in eGFR does not reflect a decline in measured GFR. Because cystatin C is not affected, it may be useful as an adjunct measure to exclude deterioration of kidney function in patients with marginal eGFR who are starting therapy with one of these agents.

Assessment of proteinuria is currently recommended at the time of diagnosis in all HIV-infected adults and annually in those with additional risk factors for CKD, including black race, diabetes, and hypertension [13]. Dipstick urinalysis is a reasonable screening tool for low-risk patients, although a quantitative assay such as an untimed urine protein : creatinine ratio is more sensitive and should be the preferred test in patients with documented urinalysis proteinuria or who are at high risk for CKD. Microalbuminuria is more common in HIV-infected adults and has been associated with adverse outcomes in this population [9–11]; however, in the absence of a proven intervention, there are currently no data to support routine microalbuminuria screening in nondiabetics.

MANAGEMENT OF CHRONIC KIDNEY DISEASE IN OLDER ADULTS WITH HIV

With aging of the HIV-positive population, HIV providers will encounter a growing number of patients with comorbid CKD. The burden of age-related CKD is greatest in minority populations at highest risk for HIV infection and for whom specialty care may be the least accessible. As such, HIV providers should be comfortable with the routine management of early CKD, including awareness of CKD complications and recommendations for referral to nephrology.

As in the general population, CKD is associated with increased cardiovascular risk in HIV-infected adults. This risk may be more pronounced than in the general population as HIV and CKD are

independent risk factors for cardiovascular disease [50]. The diagnosis of CKD should prompt consideration of cardiovascular risk modification, with the caveat that no studies have been performed to evaluate the impact of risk modification in this population. HIV providers should also be aware of other common complications of CKD, including anemia, secondary hyperparathyroidism, and renal hypertension. Nephrology referral should be considered for co-management of these complications, for definitive diagnosis, and for ESRD planning [13].

All patients with stage 4 CKD (eGFR <30 ml/min/1.73 m^2) should be referred to a nephrologist for ESRD planning [13]. In elderly patients, the symptoms of advanced CKD may be difficult to distinguish from frailty [51], and these distinctions may be even more challenging in individuals with symptomatic HIV disease. There is growing appreciation of the need to individualize ESRD planning and to offer non-dialysis medical management as an active alternative to all patients, in particular older adults with significant comorbidities [52]. Validated tools to assess mortality risk are available for both CKD (http://www.ctsu.ox.ac.uk/cribcalculator/) and HIV (http://vacs.med.yale.edu/), and could serve as useful resources for ESRD planning in such patients.

HIV-infected patients who choose to pursue dialysis should be educated about both hemodialysis and peritoneal dialysis. Patients who choose hemodialysis should be evaluated early for creation of an arteriovenous access, in order to avoid or minimize the use of tunneled central venous catheters [13]. Kidney transplantation is also an alternative in patients with well controlled HIV infection. A large observational study in the USA demonstrated 1-year and 3-year allograft survival rates of 90 and 74%, respectively [53▪▪]. When compared with the general kidney transplant population and recipients greater than 65 years of age, HIV-infected recipients had intermediate graft and patient survival. Acceptable outcomes have also been reported in smaller studies in Europe and the UK [54–56]. Higher rates of acute rejection observed in HIV-infected recipients are largely attributed to drug interactions between antiretroviral agents, in particular protease inhibitors, and calcineurin inhibitors, the backbone of immunosuppressive therapy [53▪▪,56], although differences in immunosuppressive regimens may also contribute [57].

Of note, the median age of HIV-infected transplant recipients in the United States study was 46 years, with no recipients over the age of 65 years [53▪▪]. Similar age trends have been reported in Europe [54–56]. Although there are limited data regarding kidney transplantation in older adults with HIV infection, there is evidence in the general population that allograft survival is more closely associated with comorbidities than with age [58]. Older adults with well controlled HIV infection may be acceptable candidates for kidney transplantation after a thorough and accurate assessment of comorbidities, mortality risk, and patient preferences.

CONCLUSION

The diagnosis and management of kidney disease in HIV-infected adults are increasingly important with aging of the population. Studies should consider the mechanisms by which HIV infection accelerates CKD progression in the setting of traditional risk factors, in order to optimize treatment and slow progression to ESRD. HIV-infected adults should be included in studies evaluating the management of CKD and ESRD in older adults, including studies of nondialysis medical management and kidney transplantation. Future studies should evaluate the impact of kidney transplantation on survival and quality of life in older adults with HIV infection and ESRD. In addition, future clinical trials of new ART agents should include older adults with HIV infection, who are at increased risk for medication toxicity, including kidney injury, but who have the most to gain from the beneficial effects of viral suppression on age-related comorbidities such as kidney disease.

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Conflicts of interest

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