World Journal of Nephrology

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DOI: 10.5527/wjn.v4.i3.388

World J Nephrol 2015 July 6; 4(3): 388-395
ISSN 2220-6124 (online)

MINIREVIEWS

Epidemiology, clinical characteristics, and management of chronic kidney disease in human immunodeficiency virus-infected patients

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Conflict-of-interest statment: None declared.

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Received: June 24, 2014
Peer-review started: June 25, 2014
First decision: September 16, 2014
Revised: October 10, 2014
Accepted: April 8, 2015
Article in press: April 9, 2015
Published online: July 6, 2015

Abstract

Antiretroviral therapy has markedly reduced acquired immune deficiency syndrome-related deaths and opportunistic infectious diseases. This has resulted in prolonged survival of individuals infected with the human immunodeficiency virus (HIV). However, this improvement in survival has been accompanied by an increase in the incidence of chronic kidney disease (CKD) and end-stage renal disease. CKD is now epidemic among HIV-infected populations in both Western and Eastern countries. Risk factors associated with CKD in HIV-infected populations include aging, hypertension, diabetes mellitus, co-infection with hepatitis C virus, a low CD4 cell count, and a high HIV viral load. Clinical experience has shown that HIV-infected individuals often have one or more concurrent risk factors for CKD. The cumulative effect of multiple risk factors on the development of CKD should be noted in this population. Glomerular disease directly related to HIV infection, so-called HIV-associated nephropathy, remains an important cause of CKD among a limited HIV population of African descent, but is less likely to be common among other urban HIV populations. The impact of exposure to nephrotoxic antiretroviral agents on the development of kidney disease is both an old and a new concern. In particular, the association of tenofovir with kidney tubular injury has been an area of great interest. The findings regarding tenofovir's adverse effect on long-term kidney function vary among studies. The early identification and treatment of CKD is recommended for reducing the burden of patients requiring dialysis in HIV-infected populations. Periodic monitoring of urinary concentrations of albumin, protein, and tubular injury markers such as low-molecular-weight proteins may be useful for the early diagnosis of patients at risk for incident CKD. This review focuses on recent epidemiology, clinical characteristics, and management of CKD in a contemporary HIV-infected population.

Key words: Antiretroviral therapy; Tenofovir; Human immunodeficiency virus-associated nephropathy; Albuminuria; Renal tubular biomarkers; Cystatin C; Diabetes mellitus; Hypertension

Core tip: Kidneys are affected by the human immunodeficiency virus (HIV) and its associated therapies. As HIV subjects now have longevity while they receive combination anti-retroviral therapy (cART), kidney disease has been prominent among the current HIV subjects on cART. HIV subjects often have several coexisting risk factors of kidney disease, including diabetes and hypertension. Measurements of albuminuria, proteinuria, urinary low-molecular weight proteins, and serum cystatin C are necessary for early detection of kidney disease. Collaborative discussions between HIV experts and nephrologists are warranted to achieve the good treatment of chronic kidney disease in HIV patients.

Ando M, Yanagisawa N. Epidemiology, clinical characteristics, and management of chronic kidney disease in human immunodeficiency virus-infected patients. *World J Nephrol* 2015; 4(3): 388-395 Available from: URL: http://www.wjgnet.com/2220-6124/full/v4/i3/388.htm DOI: http://dx.doi.org/10.5527/wjn.v4.i3.388

INTRODUCTION

Although combination anti-retroviral therapy (cART) has contributed to the longevity in individuals affected by human immunodeficiency virus (HIV), the life-span extension is followed by the emergence of chronic kidney disease (CKD), leading to their high morbidity and mortality[1-9]. Now, nephrologists are faced with several problems related to CKD among HIV populations, including how to find out subclinical kidney insults, to identify incipient stage of kidney illness, and to collaborate with HIV healthcare staff to offer how to treat CKD. The frequency of CKD is increasing in HIV patients living in Asian countries[10,11] likewise in Western countries[12,13]. Generally speaking, as the early identification of kidney disease gives a chance to exert treatments that inhibit progression of kidney dysfunction[14-16], it could be most crucial to find out HIV patients at high risk of incident CKD as the first step in weakening the frequency of CKD in this population[17-19]. The 2012 KDIGO guidelines elaborated the identification and prognosis of CKD by combining albuminuria with estimated glomerular filtration rate (eGFR)[20,21]. The review attempted to summarize recent advances in the study on CKD in the current HIV individuals.

PREVALENCE OF CKD: PROTEINURIA, ALBUMINURIA, AND A LOSS IN RENAL FUNCTION IN HIV INDIVIDUALS

A simple and reliable biomarker of renal insult is persistent urinary excretion of protein or albumin. Whereas 7.2%-13.7% of HIV-infected subjects manifest proteinuria on a urine dipstick test[7,9,10,22-26], 8.7%-17.8% of those subjects have albuminuria, based on the urinary excretion of albumin[10,27,28]. The frequency of a persistent loss in renal function less than 60 mL/min per 1.73 m^2 varies between 3.5% and 9.7% in different HIV populations[9-12,26]. When both of the existence of urinary protein and a decline in glomerular function were considered, the frequency of CKD stages 1 to 5 ranged 15% to 24%[2,9,10,12,26]. Difference of the CKD prevalence across various countries has not been studied yet. Table 1 demonstrates the frequency of kidney disease in Japan, China, Europe, and the United States, as previously reported.

Numerous reports have shown that albuminuria seems to be one of independent risk factors of a poor prognosis among HIV-infected individuals[27,28]. A quite recent paper has shown that low-grade proteinuria is highly prevalent in a large HIV-infected white cohort on cART[29]. It is therefore reasonable to assume that the KDIGO classification would be more practical for the identification of CKD and for estimating prognosis in HIV-infected individuals than the conventional KDOQI staging. However, the measurement of albuminuria is expensive, with public health care insurance systems in most countries limiting the application to follow-up for diabetic nephropathy. Therefore, a total of 1447 HIV-infected Japanese (1351 males, 96 females; mean age, 44.4 ± 11.5 years) were classified using the 2012 KDIGO guidelines for estimating CKD risk: a combination of eGFR and dipstick proteinuria, as a convenient alternative to albuminuria[30]. Proteinuria was classified into 3 grades: [A1] $\leqslant$ +/-, [A2] 1+ to 2+, and [A3] 3+ $\leqslant$ eGFR was classified into 6 grades: [Gade 1] $\geqslant$ 90, [Grade 2] 60-89, [Grade 3a] 45-59, [Grade 3b] 30-44, [Grade 4] 15-29, and [Grade 5] < 15 mL/min per 1.73 m^2, using colored heat map zones. It was shown that the prevalence rates of individuals in the green, yellow, orange, and red zones were 85.9%, 11.0%, 2.1%, and 1.0%, respectively. The prevalence of individuals at high and very high risk for a poor prognosis in the KDIGO classification was nearly halved, compared with the risk for CKD $\geqslant$ stage 3 in the KDOQI system (3.1% *vs* 6.6%) (Figure 1).

GLOMERULAR AND TUBULAR DISEASES IN HIV-INFECTED PATIENTS

Glomerular and tubular diseases that are often identified in HIV-infected patients are summarized in Table 2. The traditional problems of HIV-associated nephropathy (HIVAN), HIVIC, and TMA are still crucial because of the delay in HIV diagnosis or the non-response to ART even in the contemporary cART years[31]. Patients at the earlier stage of HIVAN may manifest almost normal kidney glomerular function, albuminuria, or subclinical proteinuria. Their renal function often remains constant over some years after the start of cART[32,33]. HIV-

GFR grade	eGFR (mL/min per 1.73 m^2)	A1	A2	A3
G1	⩾ 90	G1A1 518 (35.8%)	G1A2 25 (1.7%)	G1A3 0 (0.0%)
G2	60-89	G2A1 725 (50.1%)	G2A2 79 (5.5%)	G2A3 4 (0.3%)
G3a	45-59	G3aA1 55 (3.8%)	G3aA2 21 (1.5%)	G3aA3 3 (0.2%)
G3b	30-44	G3bA1 5 (0.3%)	G3bA2 5 (0.3%)	G3bA3 1 (0.1%)
G4	15-29	G4A1 2 (0.1%)	G4A2 3 (0.2%)	G4A3 1 (0.1%)
G5	< 15	G5A1 0 (0.0%)	G5A2 0 (0.0%)	G5A3 0 (0.0%)

Figure 1 Distribution of human immunodeficiency virus-infected individuals determined by the KDIGO 2012 classification. The percentage of HIV-infected individuals in each category is expressed in each color box. The cohort includes 1447 HIV-infected patients. The prevalence of individuals in the green, yellow, orange, and red zone was 85.9%, 11.0%, 2.1%, and 1.0%, respectively. KDIGO: Kidney Disease: Outcomes Quality Initiative; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; A1: No proteinuria (dipstick - or +/-); A2: Mild proteinuria (dipstick 1+ or 2+); A3: Heavy proteinuria (dipstick ⩾ 3+); HIV: Human immunodeficiency virus.

Table 1 Comparisons of prevalence of chronic kidney disease in human immunodeficiency virus-infected patients across previous studies

	Prevalence (%)	Countries	Ref.
Proteinuria			
	7.20	United States	[7]
	9.50	Japan	[11]
	13.70	China	[10]
Albuminuria			
	8.70	Norway	[25]
	11.00	United States	[26]
	17.80	Japan	[11]
CKD stages 1-5			
	15.40	Japan	[11]
	15.50	United States	[23]
	16.80	China	[10]
	23.70	United States	[13]
CKD stages ⩾ 3			
	3.50	EuroSIDA	[12]
	5.60	China	[10]
	5.90	United States	[23]
	9.70	Japan	[11]
	9.70	United States	[13]

CKD: Chronic kidney disease; EuroSIDA: European study of patients with HIV-1 infection including 93 centers across Europe.

infected individuals with African pedigree have been considered being at higher risk of HIVAN arising from podocyte proliferation and tubular dilatation with atrophy and flattening of the tubular epithelial cells[34,35].

RISK FACTORS OF CKD IN HIV SUBJECTS

Known risk factors of CKD in HIV patients are shown in Table 3. Epidemiologic investigations showed that variates associated with CKD in HIV-infected patients include traditional risks including elder age, hypertension, and DM[9-12,22-26]. This has been confirmed by a report from a prospective study with a 6-year median follow-up including a large white HIV cohort receiving antiretroviral treatment[36]. Lipids levels, decreased CD4 cell counts, and elevated HIV RNA load are perhaps specific risks for HIV-infected subjects[10,11,23-25]. Moreover, HCV infection contributes to renal insults in HIV people[11,25,31]. Nearly 30% of subjects with HIV are affected with HCV[37]. Liangpunsakul *et al*[38] performed a study to see the association between non-diabetic patients concurrently having HCV and albuminuria, based on a database from the NHANES Ⅲ. Adjusted for known variates, they demonstrated that HCV co-infection was independently involved in microalbuminuria in individuals without diabetes mellitus. Furthermore, Tsui *et al*[39] showed a significant relationship between albuminuria and HCV seropositivity in people who were classified by age.

ART AND CKD

Some antiretroviral agents are related to kidney disease, hyperlipidemia, diabetes mellitus, and hypertension which may intensify the risk of incidence of CKD[40]. Whereas HIVAN was the major renal involvement before the era of ART, comorbidities and adverse renal effects of various drugs for ART now complicate the landscape of kidney disease in HIV[41]. Drug-induced decrease in kidney function was shown in some NRTIs, TDF, and protease inhibitors (PIs). In those PIs, indinavir is predisposed to generate crystalline stones and it has been changed by PIs with safer agents with integrase inhibition. In addition, atazanavir (ATV) is likely associated with acute interstitial nephritis[42,43] and sub-acute or chronic renal insufficiency due to granulomatous interstitial nephritis characterized by the coexistence of crystalline deposition[44-46]. TDF is secreted from proximal renal tubules, and may be associated with its tubular damage representing mitochondrial dysfunction[47,48]. Although studies of the Gallant *et al*[49] did not show that tenofovir was responsible for renal failure, HIV-infected groups on TDF at the Johns Hopkins Clinical Cohort had a significant decrease in creatinine clearance for 3 years, as compared to patients not having tenofovir[50]. Nevertheless, another study using the same cohort

Table 2 Glomerular or tubular diseases in human immunodeficiency virus-infected patients

Diseases	Clinical characteristics
HIV-specific glomerular disease	
HIVAN	Detectable viral load, a high amount of proteinuria, albuminuria, RPGN
HIVIC	Proteinuria and/or hematuria, variable manifestation including AKI
TMA	AKI, proteinuria, hematuria with microangiopathic hemolytic anemia and thrombocytopenia
HIV-non-specific glomerular disease	
HCV-related MPGN/ cryoglobulinemia	Proteinuria and/or hematuria, nephritic syndrome, a decrease in serum complements
Diabetec nephropathy	Proteinuria (microalbuminuria to nephrotic syndrome), a decrease in GFR
Glomerular sclerosis	Older patients, hypertension, no or low amount of proteinuria, coexistence of atherosclerotic diseases
Membranous glomerulopathy	Nephrotic syndrome; idiopathic and secondary causes associated with HBV or cancers
Minimal change disease	Nephrotic syndrome, use of NSAIDs
IgA nephropathy	Hematuria and/or proteinuria with or without renal failure
Post-infectious glomerulonephritis	Hematuria and/or proteinuria with or without renal failure
ART-associated tubular injury	
Acute tubular necrosis	Use of TDF
Cristal nephropathy	Use of IDV and ATV
Acute or chronic interstitial nephritis	Use of ATV

HIVAN: HIV-associated nephropathy; HIVIC: HIV-associated immune complex kidney disease; TMA: Thrombotic microangiopathy; HCV: Hepatitis C virus; HBV: Hepatitis B virus; AKI: Acute kidney injury; GFR: Glomerular filtration rate; NSAID: Non-steroidal anti-inflammatory drug; ART: Antiretroviral therapy; TDF: Tenofovir disoproxil fumarate; IDV: Indinavir; ATV: Atazanavir.

showed that kidney function did not significantly change between HIV-infected subjects on cART with or without the regimen including tenofovir[51]. These differences between the two studies may be derived from the difference in the cumulative time for cART. The latter included only cART-naïve subjects, while the former included both cART-naïve and -experienced subjects. These disparate results on the TDF's nephrotoxicity remain conflicting, but a recent meta-analysis showed that the relevance of the adverse impact of TDF is mild, which may imply that restriction of "TDF use without regular monitoring of renal function" is not basically necessary[52]. Table 3 shows the known factors related to CKD in HIV-infected individuals.

HOW TO IDENTIFY HIV-INFECTED INDIVIDUALS AT HIGH RISK OF CKD

Measurement of albuminuria and proteinuria

The early diagnosis of renal illness in HIV patients is critical for preventing progression of prevalent renal injury and adding suitable treatment promptly. To help

Table 3 Traditional and human immunodeficiency virus-related factors associated with chronic kidney disease

Variables	Ref.
Black race	[34,35]
Older age	[9-12,22-26]
Low CD4 cell count	[10,11,23-25]
High HIV-RNA viral load	[10,11,23-25]
Diabetes mellitus	[9-12,22-26]
Hypertension	[9-12,22-26]
Hepatitis C virus coinfection	[11,25,31,37]
Proteinuria	[3,27,28,30]
Albuminuria	[3,29,55]
eGFR < 90 mL/min per 1.73 m^2	[10,12,23-25]
Elevation of urinary tubular markers	[56-64]
Use of TDF or ATV	[40-52]

eGFR: Estimated glomerular filtration rate; TDF: Tenofovir disoproxil fumarate; ATV: Atazanavir.

HIV experts with the identification of kidney disease, the IDSA guidelines suggest to conduct urinalysis and the evaluation of glomerular function at the diagnosis of HIV infection[3]. Although a dipstick test is a simple measure to use, it is unable to identify subclinical levels of urinary albumin. A comparison of a dipstick test and urinary protein concentration corrected for creatinine (PCR) in HIV-infected patients showed that the dipstick test could not detect individuals with mild or moderate proteinuria[53]. Therefore, the screening of proteinuria should be done according to PCR than dipstick test[54]. Ando *et al*[55] have found that a moderate to mild level of ACR (30 mg/g > ACR $\geqslant$ 10 mg/g) is an indicator of the incidence of CKD, likely emphasizing that the measurement of the ACR may be of higher relevance than that of the PCR for the detection of new CKD among HIV individuals.

Urinary low-molecular weight proteins for detection of tubular damage

The measurement of urinary biomarkers for identifying early tubular damage in HIV subjects, especially receiving cART has special importance. Some researchers measured urinary low-molecular weight proteins to examine whether patients on cART may have kidney tubular injury in the absence of renal dysfunction[56-62]. Approximately a quarter of HIV-infected patients on cART could have prevalent kidney tubular injury in the absence of renal dysfunction, probably resulting in a near future decrease in glomerular function and a higher emergence of urinary protein[63]. Also, Shlipak *et al*[64] indicated that novel urine biomarkers for tubular injury including KIM-1 and interleukin-18 identify risk for ensuing decrease in renal function in HIV-infected women in the Women's Interagency HIV Study cohort. Measuring urinary low-molecular-weight proteins could be helpful to the early detection of subjects, particular those who take tenofovir, who have high risk of definite CKD. In addition, Peralta *et al*[65] showed that some urinary indices of tubular damage are relevant to mortality in the Women's Interagency HIV Study.

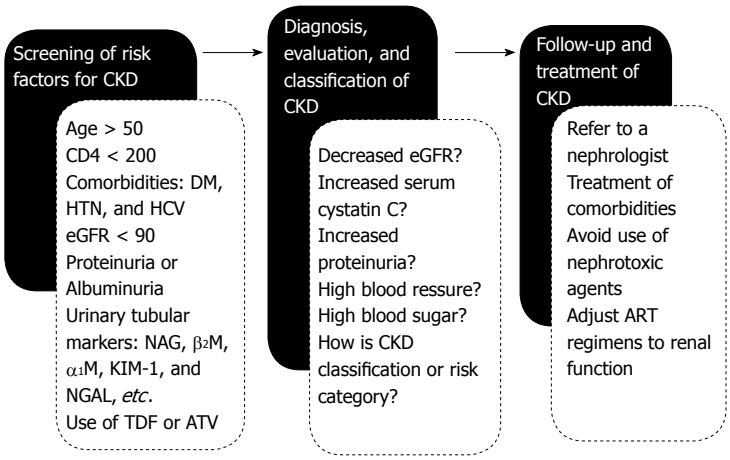

Figure 2 Flow chart for management of chronic kidney disease in human immunodeficiency virus-infected patients. This algorithm includes a clinical flow from screening of risk factors to identification, evaluation and follow-up care of patients for prevalent or incident CKD. CKD: Chronic kidney disease; HTN: Hypertension; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; NAG: N-acetyl-D-glucosaminidase; M: Microglobulin; ART: Antiretroviral therapy; ATV: Atazanavir; TDF: Tenofovir disoproxil fumarate.

Comprehensive assessment of risk factors

HIV-infected subjects usually possess several co-existing risks associated with renal illness, but the clinical impact of them on the emergence of chronic renal disease has remained unknown. A clinical model of predicting the incidence of CKD has been constructed. This model including age, CD4 cell count, diabetes, proteinuria, and a loss in glomerular function less than 90 mL/min per 1.73 m^2 were related to the incident CKD and predicted the development of CKD[66]. In addition, Scherzer *et al*[67] developed a point-based score to discriminate an HIV patient's risk of CKD over 5 years. Figure 2 shows a screening algorithm of the detection and practical management for patients infected with HIV.

CLINICAL SIGNIFICANCE OF CYSTATIN C FOR HIV-INFECTED PATIENTS

Cystatin C is an index for early glomerular dysfunction and may be a potential marker of chronic inflammation. Accordingly, cystatin C is something more than a marker of renal function. In fact, its elevation portends the incidence of heart and vessel diseases and all-cause mortality in the older people[68]. Moreover, it may be associated with a high likelihood of developing cancers[69,70]. However, serum cystatin C concentration are sometimes affected by non-renal factors including age, sex, race, and others[71]. The serum cystatin C level among HIV-infected patients could be greater in those with HIV infection than those without[72], as the serum cystatin C concentration is influenced by prevalent inflammatory diseases and the HIV viral replication[73]. Validation would be needed to confirm the utility of serum cystatin C level for assessing kidney function in HIV individuals.

MAHAGEMENT OF HIV-INFECTED INDIVIDUALS WITH CKD

A careful examination of the medical history and cumulative ART exposure is important for the past and further investigation of HIV individuals with CKD. The cART has beneficial effects on HIV-related diseases, such as HIVAN and HIVIC, but has adverse effects due to the long-term cumulative exposure. In addition to the metabolic changes of glucose and lipids induced by ART, some antiretroviral drugs may directly affect kidney function. Therefore, the detection of patients at high risk of CKD by the periodic measurements of ACR, PCR, and tubular biomarkers is most crucial with special reference to renal protection.

Further examination includes the follow-up of glomerular function, the test of urinary sediments, the ultrasonography of kidneys, and the pathological assessment of biopsied kidney tissues. Renal biopsy study is required for differentiating HIVAN from other glomerular nephtitis including diabetic nephropathy and HCV-related glomerulonephropathies, however, the risk of biopsy-related complications should be fully considered.

Adverse effects of cART on kidney are likely based on the overdosing of medications[74], and thus drug dosages have to be correctly altered according to eGFR. The major treatments for CKD may involve the strict control of high blood pressure, serum sugar and lipids. ART initiation in those having HIVAN is advocated, being independent on the control of $CD4^+$ cell count and HIV infection[75,76]. Prednisolone and ACE inhibitors could be useful for caring HIVAN[77,78].

KEY MESSAGE

The periodic examination of proteinuria or albuminuria combined with eGFR, serum cystatin C, and markers for renal tubular damage may enable the early detection of CKD in HIV-infected subjects.

ACKNOWLEDGMENTS

We thank all doctors in the Department of Infectious Diseases in Komagome General Hospital for their invaluable help with writing this review.

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