in mean serum cystatin C level and the proportion of patients with serum cystatin C elevation were significant between patients who developed cancer and those who did not.

Incidence of cancers in the 3-year follow-up period

Cancers developed in 14 (2.7%), and all-cause death in this cohort was 10 (1.9%), including 4 from cancers. There were 4 colon, 3 lung, 1 pancreas, 1 bile duct, 1 oropharynx, 1 buccal mucosa, 1 testicular, 1 tongue, and 1 hepatocellular cancer and 1 case of Hodgkin lymphoma. One patient developed 2 types of cancer. All participants completed the 3-year follow-up study.

Cumulative incidence of cancers

Figure 1 presents the Kaplan-Meier curve of the cumulative proportion of patients who developed cancers, according to the presence or absence of serum cystatin C elevation. The Kaplan-Meier estimate significantly increased in patients with an elevated level of serum cystatin C ($\geq$ 1.0 mg/L).

An association of serum cystatin C elevation with the development of cancers

The results of the multivariate analyses are summarized in Table 2. Age, CD4 cell count, smoking habit, eGFR<60 mL/min/1.73 m^2, serum albumin, CRP, and the presence of comorbidities including DM, hypertension, and hepatitis virus infection were assessed using univariate analysis. Age, serum albumin, and CRP met the entry criteria of a P value $\leq$ 0.10. The multivariate analysis demonstrated that the HR (95% CI) of cancer incidence was 3.56 (1.08 - 11.2) for serum cystatin C elevation and 1.11 (1.05 - 1.19) for age.

Discussion

This study highlighted the clinical significance of serum cystatin C elevation beyond its role as an index of a decrease in renal function among HIV-infected men under good infection control with HAART.
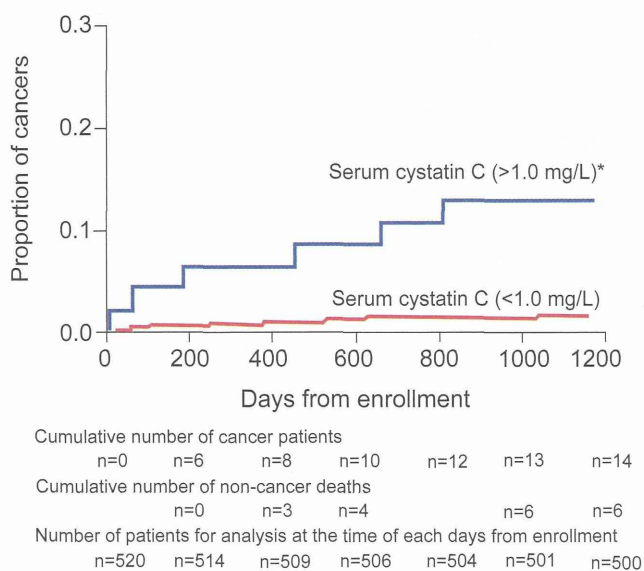

Figure 1: Kaplan-Meier estimate of cancers according to the presence or absence of elevated serum cystatin C at baseline. The difference between the 2 groups was highly statistically significant (P < 0.0001). Elevated serum cystatin C was defined as $\geq$ 1.0 mg/L. Asterisk (*) indicates log-rank test, P < .0001.

Variates	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, per year	1.12 (1.06-1.19)	<.0001	1.11(1.05-1.19)	0.0003*
Hypertension (+)	1.27 (0.35-3.81)	0.6880	-	-
DM (+)	0.95 (0.05-4.80)	0.9653	-	-
HBV or HCV infection (+)	1.29 (0.20-4.74)	0.1556	-	-
Smoking (+)	1.29 (0.45-4.20)	0.6426	-	-
CD4 cell count, cells/µL	0.997 (0.994-1.001)	0.1390	-	-
Serum albumin, g/dL	0.13 (0.06-0.41)	0.0013	0.26 (0.06-1.44)	0.1202
eGFR < 60mL/min/1.73 m^2(+)	2.73 (0.62-8.74)	0.1637	-	-
Serum cystatin C elevation (+)	8.01 (2.64-23.0)	0.0006	3.56 (1.06-11.2)	0.0408*
C-reactive protein, mg/dL	1.27 (1.05-1.42)	0.0200	1.18 (0.96-1.38)	0.1052

The multivariate Cox proportional hazards model was adjusted for age, serum albumin, and C-reactive protein, all of which showed significance (P $\leq$ 0.10) in the univariate analysis. Asterisk (*) indicates that the parameter is significantly associated with the incidence of the outcome.

Abbreviations: DM: diabetes mellitus; HBV: hepatitis B virus; HCV: hepatitis C virus; eGFR: estimated glomerular filtration rate

Table 2: Hazard ratios for cancer incidence in HIV-infected men.

Our results have suggested an impact of serum cystatin C elevation on the probability of cancers in HIV-infected subjects under good infection control with HAART.

Serum cystatin C is not only a sensitive marker for renal dysfunction, but also a potential marker for inflammation, which may suggest that this marker is something more than a measure of renal function [22,23]. Underlying inflammation has become one of the leading causes of morbidity and mortality in HIV-infected subjects while HAART is routinely employed [24]. Common comorbidities of HIV-infected patients including DM, hypertension, chronic kidney disease (CKD), and hepatic viral infection may exacerbate the inflammatory status in HIV-infected subjects. Chronic inflammation is considered to play a key role in the pathogenic process in cancer [15,25]. Our multivariate analysis has shown a significant association between serum cystatin C elevation and incident cancer, after adjusting for relevant covariates including age, serum albumin and CRP which were significant in the univariate analysis. CKD is a proinflammatory state, and likely associated with cancer risk [26]. Thus, serum cystatin C elevation may reflect the wide spectrum of abnormalities, including predisposition to cancer, accompanying renal dysfunction [15,27]. In fact, some reports have shown that the mRNA expression of cystatin C in malignant extracted tumor tissues was increased compared with that in normal tissues, and that increased extracellular levels of cystatin C correlated significantly with high risk of poor outcome in cancer patients [28,29]. Taking this together with our results, serum cystatin C may be of significant value in providing prognostic information for cancers among HIV-infected individuals.

CRP, an acute phase protein, which is generated in liver cells in response to systemic or local inflammation and tissue damage, is a widely used in everyday practice. Previous reports have demonstrated that elevated CRP is important in the diagnosis, prognosis, and cause of cancers, including lung and colon [30-32], with which the majority

in our subjects developing cancers was affected. In addition, low serum albumin concentration is considered to be a risk or poor prognosis factor for colon cancer [33,34]. Nevertheless, our multivariate analysis showed that neither an elevation in CRP nor a decrease in serum albumin were not statistically associated with the incidence of cancers, although both parameters were significant in univariate analyses. From this point of view, serum cystatin C may be more specific in order to alert clinicians to possible cancer incidence in HIV-infected individuals, as compared to such conventional inflammation markers.

In the contemporary era of HAART, epidemiological studies reveal that the incidence of AIDS-defining cancers (ADCs) has decreased, whereas the rate of non-AIDS-defining cancers (NADCs) is rising and now accounts for the majority of cancers in HIV-infected persons [35,36]. In our cohort, 2.7% developed cancers, all of which were classified into NADCs. In particular, colon and lung cancers were the most common, which was comparable to previous reports [36]. It is worth noting that the diversity of cancers observed in our study, which could be comparable to the fact that HIV-infected subjects have higher incidence of NADCs such as anal, Hodgkin lymphoma, liver, lung, melanoma, oropharyngeal, leukemia, colorectal, and renal than the general population [37]. Clinicians have to take into account not only the rising incidence of NADCs but also the diversity of the cancers observed among HIV-infected subjects.

Several limitations must be considered in this study. First, this study did not compare the impact of serum cystatin C on cancer incidence with serum interleukin-6, which is an inflammatory marker involved in pathophysiologic processes including carcinogenesis. Second, we were unable to provide detailed patient characteristics including a prior diagnosis of AIDS, prior serious non-AIDS events, CD4 nadir, and time since starting HAART. Third, the statistical robustness of this study may be limited owing to the small number of incidence of cancers.

In conclusion, our study shows that the presence of serum cystatin C elevation is a risk factor for cancer in HIV-infected men on HAART with their infection under good control. Monitoring of serum cystatin C level may enable earlier recognition of cancers in subjects with HIV infection.

Acknowledgments

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REVIEW ARTICLE

How to manage HIV-infected patients with chronic kidney disease in the HAART era

Minoru Ando · Ken Tsuchiya · Kosaku Nitta

Abstract As human immunodeficiency virus (HIV)-infected patients now live longer while receiving highly active antiretroviral therapy (HAART), chronic kidney disease (CKD) has emerged as a significant cause of morbidity and mortality among urban HIV population. Risk factors associated with CKD in such HIV-infected population include aging, hypertension, diabetes mellitus, co-infection with hepatitis C virus, low CD4 cell count, and 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 limited HIV population of African descent. 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 disease has been an area of great interest. The findings regarding tenofovir's adverse effect on long-term kidney function vary among studies. Early identification and treatment of kidney disease is imperative for reducing the burden of patients requiring dialysis in HIV-infected populations. Periodic monitoring of urinary albumin excretion, tubular parameters such as low-molecular-weight proteinuria, and the estimated glomerular filtration rate may be useful for early diagnosis of patients at risk for incident CKD. This review focuses on recent developments in epidemiology, risk factors, identification, estimation, and management of CKD in HIV-infected population in the HAART era.

Introduction

Although highly active antiretroviral therapy (HAART) has almost certainly contributed to the prolongation of survival in patients infected with human immunodeficiency virus (HIV), this prolongation has been accompanied by the emergence of chronic kidney disease (CKD) and subsequent end-stage renal disease (ESRD) as major causes of morbidity and mortality in these patients [1–8]. Now, nephrologists are faced with several challenges regarding kidney disease in HIV-infected population including means of raising awareness of the problem of undiagnosed kidney disease, identifying early signs of kidney disease, and working in collaboration with HIV experts to provide the best treatment for patients with renal impairment. The prevalence of CKD is increasing among Asian HIV populations [9, 10] as well as HIV populations in Western countries [11, 12]. In general, since early identification of CKD provides an opportunity to implement strategies known to inhibit the progressive loss of kidney function [13–15], early identification of HIV-infected individuals at risk for developing CKD could be important as the initial step in modifying the progression of CKD [16–18]. This review addresses recent advances regarding the epidemiology, risk factors, identification, estimation, and management of CKD among contemporary HIV-infected populations.

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Epidemiology of HIV infection and its kidney disease

Japan is a unique advanced country in which the number of patients newly diagnosed with HIV has increased yearly. The accumulated number of HIV/acquired immunodeficiency syndrome (AIDS) patients in Japan reached 18,447 in December 2008, with a constant increasing rate of approximately 1,000 or more individuals per year, according to the annual data report of the HIV epidemic by the Japan Ministry of Labor, Health, and Welfare (http://api-net.jfap.or.jp/status/2010/10nenpo/nenpo_menu.htm). However, little is known about the epidemiology of kidney disease in Japanese HIV-infected patients. In contrast, in the USA, 1.5% (range 0.3–3.4%) and 0.4% (range 0–1.0%) of dialysis patients were reported to have HIV infection and AIDS, respectively, in 2000 [19]. However, as dialysis patients in the USA have not necessarily undergone routine screening for HIV infection since then, true incidence and prevalence estimates are probably higher than those reported by the US Renal Data System (USRD). Black persons account for 10% of the general population in the USA but account for more than 30% of patients with ESRD [20]. Young and male blacks have an 11-fold increased risk of CKD, compared with their White counterparts [21]. In fact, among persons with HIV infection who receive dialysis, 91% are Black [20]. Consequently, when the difference of racial background between the USA and Japan is considered, the burden of kidney disease in Japanese individuals with HIV is likely to be less than that in Western countries.

The paradigm shift in outcomes of kidney disease after the HAART era

Current guidelines for treatment of HIV infection recommend the combination of three antiretroviral agents (HAART), basically including two nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs) as backbone drugs plus one protease inhibitor or non-NRTI (NNRTI) as a key drug. HAART has been used since the late 1980s and has dramatically reduced the morbidity and mortality of HIV infection. The first reports of AIDS-related renal failure, published in the mid 1980s, described cases of what we now recognize as HIV-associated nephropathy (HIVAN) [22]. Much virologic and histologic evidence suggests that HIVAN, the most usual form of HIV-related nephropathy—a focal segmental glomerulosclerosis or its collapsing variant associated with severe cystic tubular lesions—may be the consequence of HIV replication in the kidney. The possible relation of HIVAN with HIV replication in the kidney corresponds with epidemiologic and clinical data showing that HAART may improve HIVAN. The incidence and spectrum of kidney disease in HIV-infected patients have been altered by the widespread use of HAART. The clinical course of kidney disease is more indolent, the risk of ESRD has been reduced, the survival rate of HIV-infected patients with kidney disease has increased, and kidney transplantation is a viable option in the USA [20]. However, one consequence of this success may be the emergence of new kidney diseases related to the potential nephrotoxicity of antiretroviral therapy (ART). The growing population of patients treated with HAART and the predicted use of HAART in patients with prevalent HIV- or non-HIV-related nephropathies requires consideration of the potential renal side-effects of ART. This important issue is discussed in a later section ("Impact of antiretroviral therapies on kidney function").

Prevalence of proteinuria, albuminuria, and decrease in kidney function

CKD is defined as kidney damage or reduced kidney function which persists for more than 3 months [23]. A simple yet most important clinical marker of kidney damage is sustained proteinuria or albuminuria. While 7.2–32.6% of HIV-infected individuals have proteinuria, which is mostly diagnosed based on urine dipstick examination [7, 9, 10, 24–28], 8.7–17.8% of these individuals have albuminuria, which is mostly defined according to the urinary albumin to creatinine ratio (ACR) [10, 29, 30]. The prevalence of renal dysfunction, defined as a sustained decrease in the estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2 for 3 months or more, varies from 3.5% to 9.7% depending on the social and demographic characteristics of the HIV population that is being studied [9–12, 28]. When the presence of proteinuria and reduced eGFR are combined, the prevalence of CKD stages 1–5 ranges from 15.4% to 23.7% [2, 9, 10, 12, 28]. Comparisons of prevalence of CKD in different countries have not yet been fully analyzed. Figure 1 summarizes the prevalence of CKD as previously reported.

Risk factors of CKD

HIV-specific and HIV-non-specific glomerular diseases

When assessing causes of kidney disease, it is important to distinguish between HIV-specific and HIV-non-specific disease. Traditional HIV-specific glomerular disease can be caused by direct infection of renal epithelial cells by HIV (HIVAN), deposition of immune complexes composed of viral antigen–antibody complexes (HIVIC), and HIV-related thrombotic microangiopathy (TMA). The differential diagnosis of glomerular disease in this group includes
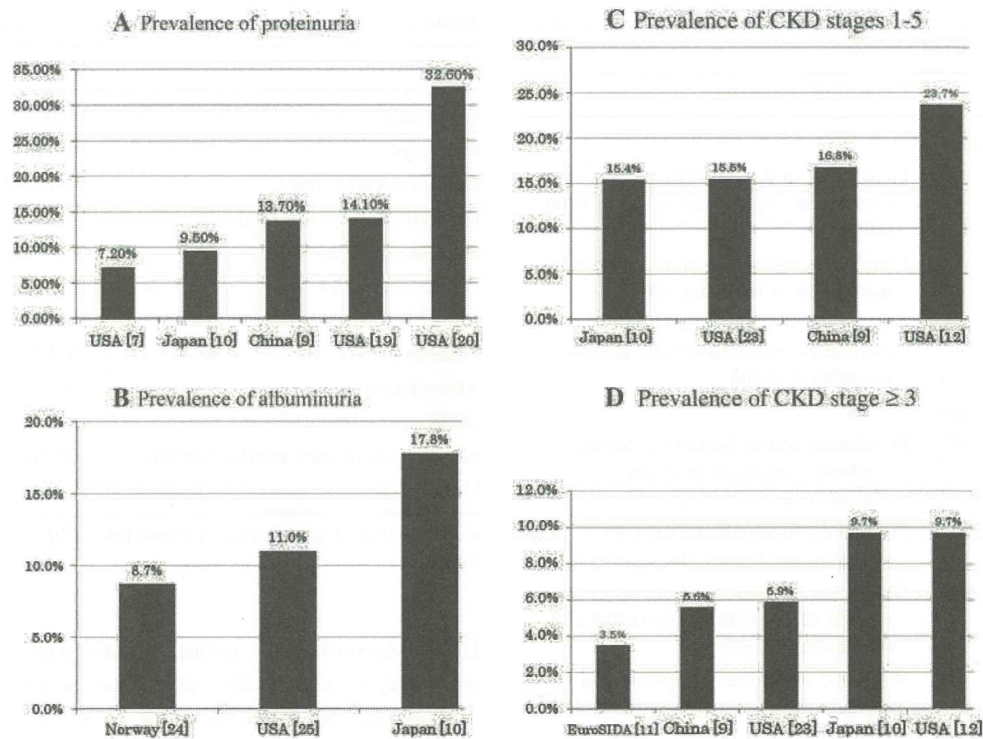
Fig. 1 Comparisons of prevalence of proteinuria (**a**), albuminuria (**b**), CKD stages 1–5 (**c**), and CKD stages ≥3 (**d**) across previous studies. The *number in brackets* indicates the reference number

many HIV-non-specific causes and is often difficult in the clinical setting. Comorbidities including hypertension and diabetes mellitus, co-infections of hepatitis C and/or hepatitis B virus, use of drugs including nonsteroidal anti-inflammatory drugs (NSAIDS), and prevalent primary glomerular diseases have to be considered for differential diagnosis. Possible glomerular diseases in patients with HIV infection are presented in Table 1. Rates of HIV-specific kidney diseases have remained stable after an initial decrease in the mid 1990s, which is likely attributable to the widespread use of HAART [31]. The traditional problems of HIVAN, HIVIC, and TMA remain important because of the late diagnosis of HIV infection or the unavailability or nonresponse to HAART even in the HAART era [32]. Patients with early HIVAN lesions may have normal function, microalbuminuria, or mild proteinuria, and renal function may remain stable for many years following HAART initiation [33, 34].

Race/ethnicity

Race is considered to be an important risk factor for CKD. HIV-infected individuals of African descent, especially those who have family history of ESRD, have been recognized as having greater risk for HIVAN [35, 36]. In addition, among HIV-infected patients who receive dialysis, 91% are African-American, according to the USRD [20].

African descent also increases the risk of microalbuminuria and proteinuria by at least twofold [25, 30], and these individuals have an increased risk of hypertension [37]. These observations may intensify the role of genetic susceptibility in the development of CKD.

Prevalent kidney damage prior to HAART

Acute kidney injury (AKI) is highly prevalent among HIV-infected individuals prior to HAART initiation, in particular in those who have had AIDS-defining illness including opportunistic infection. Ten percent of patients in a large ambulatory clinic experienced at least 1 episode of AKI over a 2-year period [38]. More than one-half of these episodes were attributed to underlying infections, 76% of which were AIDS-defining illness, and almost three-quarters of them needed hospitalization. Drug-related complications accounted for nearly one-third of cases. The conventional uses of amphotericin, acyclovir, ganciclovir aminoglycosides, pentamidine, trimethoprim-sulfonamide, and NSAIDs are often involved [39].

Comorbidities

Epidemiological studies have shown that independent risk factors for the prevalence of CKD among HIV-infected patients include traditional risk factors such as older age,

Table 1 HIV-specific and HIV-non-specific glomerular diseases observed in HIV-infected patients

Diseases	Clinical characteristics
HIV-specific disease	
HIVAN	Detectable viral load, high amount of proteinuria, rapid progression of renal failure
HIVIC	Proteinuria and/or hematuria, variable manifestation including AKI
TMA	AKI, proteinuria, hematuria with microangiopathic hemolytic anemia and thrombocytopenia
HIV-non-specific disease	
HCV-related MPGN/ cryoglobulinemia	Proteinuria and/or hematuria, nephritic syndrome, decrease in serum complements
Diabetic nephropathy	Proteinuria (microalbuminuria to nephrotic syndrome), 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
Postinfectious glomerulonephritis	Hematuria and/or proteinuria with or without renal failure

HIVAN HIV-associated nephropathy, *HIVIC* HIV-associated immune complex kidney disease, *TMA* thrombotic microangiopathy, *MPGN* membranoproliferative glomerulonephritis, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *AKI* acute kidney injury, *GFR* glomerular filtration rate, *NSAID* nonsteroidal anti-inflammatory drug

Table 2 Factors associated with CKD in HIV-infected patients

Variable	References
Black race	[4–6, 12, 25, 28, 30]
Older age	[9–11, 26–28, 55, 64, 65]
Low CD4 cell count	[9–11, 25, 27, 73]
High HIV-RNA viral load	[12, 25, 27]
Diabetes mellitus (+)	[10–12, 27, 55, 64, 65]
Hypertension (+)	[11, 12, 25, 27, 29, 30]
Hepatitis C virus co-infection (+)	[25, 55, 73]
Proteinuria	[9–12, 26, 64, 65]
Albuminuria	[10, 29, 30, 55]
eGFR <90 ml/min/1.73 m^2	[29, 55, 64]
Elevation of urinary tubular markers	[57–64]
Use of TDF	[3, 11, 48, 51, 52, 55]

eGFR estimated glomerular filtration rate, *TDF* tenofovir disoproxil fumarate

HCV seropositivity among adults who were stratified according to age. Latent existence of glomerular disease such as membranoproliferative or membranous glomerulonephritis associated with HCV infection might also be involved. Table 2 summarizes the factors associated with CKD among HIV-infected patients.

Impact of antiretroviral therapies on kidney function

Some antiretroviral agents included in HAART may be associated with nephrotoxicity or with increased rates of dyslipidemia, hypertension, and diabetes mellitus, which in turn may increase the risk of CKD [43]. Drug-induced kidney dysfunction has been reported for several nucleoside reverse transcriptase inhibitors, a nucleotide reverse transcriptase inhibitor [tenofovir disoproxil fumarate (TDF)], protease inhibitors, and a fusion inhibitor (enfuvirtide). Among the protease inhibitors, indinavir (IDV) is notorious for its nephrotoxicity and propensity to form crystals and has been replaced by protease inhibitors with safer drug profiles. TDF is actively and primarily secreted at the proximal tubule, and may induce tubular damage as a result of severe mitochondrial dysfunction [43, 44]. In trials of HAART-naive persons comparing TDF-containing HAART regimens with regimens that did not contain TDF, the median eGFR decreased in a similar manner in both groups [45, 46]. While data from the Chelsea and Westminster HIV cohort did not show an association between TDF and kidney dysfunction [47], TDF-treated individuals in the Johns Hopkins Clinical Cohort experienced greater decline in creatinine clearance over a period of 3 years compared with persons not receiving TDF (−13.3 versus 7.5 ml/min) [48]. However, a more recent study from the

hypertension, and diabetes mellitus [9–12, 24–27, 30, 36]. Lipoprotein concentrations, low CD4 cell count, and high HIV load are likely to be identified as specific risk factors for HIV-infected populations [9, 10, 25–27]. In addition, co-infection with hepatitis C virus (HCV) is an important contributor to kidney disease in HIV-infected populations [10, 25, 28]. Approximately one-third of HIV-infected individuals are co-infected with HCV [40]. Liangpunsakul and Chalasani [41] conducted a nested case-controlled study to examine the relationship between nondiabetic subjects with HCV co-infection and microalbuminuria using a database from the Third National Health and Nutrition Examination Survey (NHANES III) that was performed in the USA from 1988 through 1994. After controlling for relevant covariates, they showed that HCV infection was independently associated with microalbuminuria in subjects without diabetes, insulin resistance, or metabolic syndrome. In addition, Tsui et al. [42] confirmed an independent association between microalbuminuria and

same clinical cohort demonstrated only minor differences in kidney function changes over time between HIV-infected patients starting HAART treatment with or without inclusion of TDF [49]. The disparate results between the two studies reported by Gallant et al. may be due to the difference in the history of HAART exposure between the two cohorts; that is, the latter study contained only HAART-naive patients, whereas the former study contained both HAART-naive and HAART-experienced patients. The contradictory findings regarding TDF's effect on long-term kidney function among studies may also be a consequence of differences in the study populations, differences in the methods used to estimate kidney function, or differences in the CKD definitions. The boosted use of protease inhibitors with TDF may enhance the tubulotoxic potential of TDF, as Fanconi syndrome is sometimes observed in patients treated with a combination of TDF and boosted protease inhibitors [50]. Patients who receive TDF with protease inhibitors may have greater reduction in kidney function, compared with those in whom TDF is administered without protease inhibitors [51]. Taken together, the results from both observational and prospective studies on the nephrotoxicity of TDF remain conflicting, but a recent review based on a meta-analysis concluded that, although use of TDF is associated with a statistically significant loss of renal function, the clinical magnitude of this effect is modest, suggesting that restrictions against "TDF use without regular monitoring of renal function" are not needed [52].

Early identification of patients at increased risk for CKD

Measurements of proteinuria and albuminuria

Early recognition of kidney disease in HIV-infected persons is imperative for preventing further renal damage and instituting appropriate management efficiently. To assist clinicians in recognition of CKD, the Infectious Diseases Society of America (IDSA) guidelines recommend urinalysis and estimation of kidney function for all HIV-infected persons at the time of HIV diagnosis [3]. While urine dipstick examination is more readily available and simple to use, this test might not detect lower levels of clinically significant albuminuria. A comparison of urine dipstick test results and random urine protein-to-creatinine ratios in HIV-infected individuals has shown that the former test may miss up to 21% of individuals with low to moderate proteinuria (300–999 mg/g) [53]. Proteinuria screening, therefore, should rely on random urine protein-to-creatinine ratios rather than urine dipstick examination [54]. In addition, we recently found that a middle to high level within the normal range of albuminuria (30 mg/g > ACR ≥ 10 mg/g) is a strong predictor of near-term incidence of CKD [55], suggesting that measurements of albumin-to-creatinine ratio may be of greater clinical significance than measurements of protein-to-creatinine ratio for early identification of incident kidney disease in HIV-infected populations.

Measurement of urinary tubular markers

Data from animal models and from human renal biopsies suggest HIV infection of renal tubular cells and podocytes as being responsible for the lesions observed in HIVAN. Moreover, renal tubular cells in patients with HIVAN constitute a viral reservoir where active replication of HIV is independent of that in peripheral blood mononuclear cells [56]. In addition, tubular damage could be induced by several NRTIs including TDF, as described above. The usefulness of urinary biomarkers for tubular injury in screening for early kidney disease in HIV-infected patients receiving or not receiving HAART is of increasing importance. In this context, several recent studies have measured urinary tubular markers to test whether HIV-infected patients receiving HAART may have renal tubular damage in the absence of impaired glomerular function [57–63]. Ando et al. [64] showed that at least 25% of HIV-infected patients receiving HAART may have kidney tubular damage in the absence of glomerular defects, likely leading to near-term decline in eGFR and higher incidence of proteinuria. Periodic monitoring of urinary low-molecular-weight proteins, such as N-acetyl-β-D-glucosaminidase, β_2 microglobulin, α_1 microglobulin, etc., might be useful for early identification of patients, especially those receiving TDF, who are at risk for future overt kidney disease.

Predicting near-term CKD in HIV-infected patients

CKD develops as a result of both viral-related risk factors and more traditional risk factors for kidney disease in HIV-infected individuals. Clinical experience has shown that HIV-infected individuals often have 1 or more concurrent risk factors for CKD, but the cumulative effect of multiple risk factors on the development of CKD in HIV-infected population has not been previously investigated. We recently constructed a simple model for predicting incidence of CKD in HIV-infected patients. According to this model, five variables (age, CD4 cell count, diabetes, proteinuria, and eGFR less than 90 ml/min/1.73 m² at baseline) were independently associated with incidence of CKD and had a cumulative impact [65]. Figure 2 shows a protocol for identification and follow-up care of patients at risk for incident CKD.
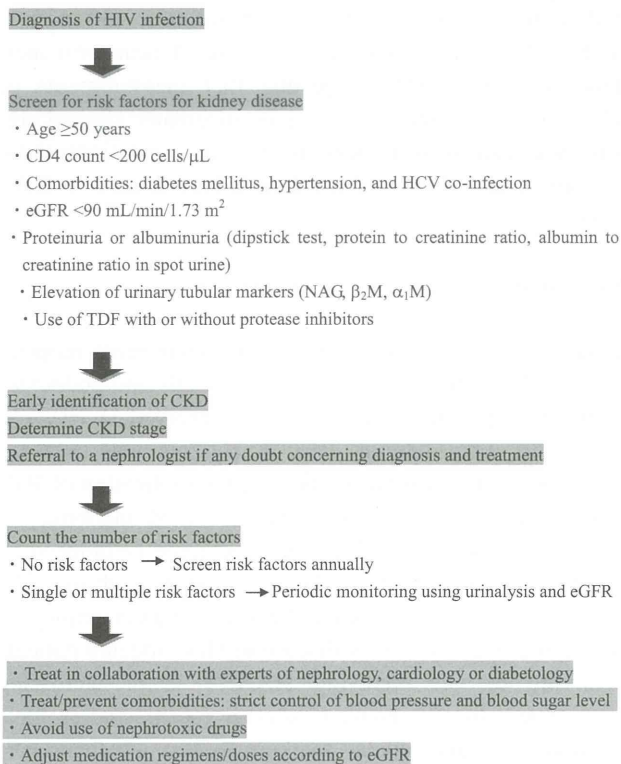
Diagnosis of HIV infection

⬇

Screen for risk factors for kidney disease
· Age ≥50 years
· CD4 count <200 cells/μL
· Comorbidities: diabetes mellitus, hypertension, and HCV co-infection
· eGFR <90 mL/min/1.73 m²
· Proteinuria or albuminuria (dipstick test, protein to creatinine ratio, albumin to creatinine ratio in spot urine)
  · Elevation of urinary tubular markers (NAG, β₂M, α₁M)
  · Use of TDF with or without protease inhibitors

⬇

Early identification of CKD
Determine CKD stage
Referral to a nephrologist if any doubt concerning diagnosis and treatment

⬇

Count the number of risk factors
· No risk factors → Screen risk factors annually
· Single or multiple risk factors → Periodic monitoring using urinalysis and eGFR

⬇

· Treat in collaboration with experts of nephrology, cardiology or diabetology
· Treat/prevent comorbidities: strict control of blood pressure and blood sugar level
· Avoid use of nephrotoxic drugs
· Adjust medication regimens/doses according to eGFR

Fig. 2 Algorithm for early identification and follow-up care of HIV-infected patients at risk for kidney disease. *N*-acetyl-β-D-glucosaminidase (*NAG*), β_2 microglobulin (β_2M), and α_1 microglobulin (α_1M)

Controversy regarding estimations of renal function

Estimates of GFR

Several GFR-estimating equations based on the serum creatinine level exist. The abbreviated modification of diet in renal disease (MDRD) equation contains only four of the variables from the original equation, while the MDRD equation is constructed using standardized serum creatinine measurements [66]. The new Japanese coefficient for GFR estimation based on inulin clearance data has been shown to be more accurate for the Japanese population than the previously reported equations [67, 68]. However, no equations have been thoroughly validated in HIV-infected individuals. Additional validation studies that include large study populations of HIV-infected individuals are warranted. The CKD Epidemiology Collaboration (CKD-EPI) equation, which was developed in a larger population, is thought to provide more precise and accurate estimates of GFR, compared with the MDRD equation [23, 69]. Although the current IDSA guidelines recommend using the MDRD equation to estimate kidney function in HIV-infected individuals based on the authors' observations in clinical practice and unpublished data, the CKD-EPI equation might provide a more precise and less biased estimate of kidney function in HIV-infected populations. Further evaluation of this equation is expected.

Cystatin C

Serum cystatin C has been evaluated as an alternative or additional renal biomarker for estimating kidney function. In addition, cystatin C predicts subsequent cardiovascular disease and mortality better than serum creatinine among elderly general population [70]. However, the serum cystatin C level can be influenced by age, sex, race, and other nonrenal factors [71]. Estimates of GFR using the equation with cystatin C alone or with adjustments for age, sex, and race were slightly less accurate, compared with estimates based on an equation using both cystatin C and serum creatinine, with 83% versus 89% of the eGFRs within 30% of the measured GFR, respectively [72]. The serum cystatin C level in HIV-infected individuals has been shown to be higher in HIV-infected individuals than in HIV-uninfected persons [73], likely because the serum cystatin C level is affected by the existence of inflammation and the degree of HIV viral replication [74, 75]. A comparison of cystatin-based GFR estimates with measured GFR values in HIV-infected persons showed that cystatin C-based eGFR generally underestimated the measured GFR and had poor accuracy, with only 41% of the eGFR values within 30% of the measured GFR values [76]. However, this study was quite small and did not use a cystatin C-based equation to adjust for age, sex, and race. The poor performance of the cystatin C-based eGFR values in this study may also have been due to the influence of additional extrarenal factors more commonly found in HIV-infected persons [77]. Further validation studies are warranted to examine the use of either the serum cystatin C level or cystatin C-based estimated GFR values for estimating renal function in HIV-infected subjects.

Management of CKD

General considerations

1. Careful review of medical history and recent drug exposure are imperative for further work-up and management of kidney disease in HIV-infected individuals. The impact of HAART on long-term kidney function encompasses both beneficial effects on the progression of HIV-related diseases, including HIVAN, and potential adverse effects associated with prolonged HAART exposure. In addition to the impact of metabolic changes related to HAART upon kidney function, certain antiretroviral medications may

directly affect kidney function longitudinally. Therefore, early identification of patients at increased risk for kidney disease by periodic monitoring of urinary albumin and tubular proteins are most important from the perspective of renal safety. Nephrology consultation is necessary if there is any doubt in regard to diagnosis or treatment plan.

2. For CKD stages 3–5 and CKD stages 1–2 with a great amount of proteinuria, additional work-up includes assessment of kidney function trends, examination of urinary sediments, kidney ultrasound examination, and kidney biopsy. A study of kidney biopsies performed at a single center showed similar incidence of complications between HIV-infected and HIV-uninfected individuals, suggesting that ultrasound-guided percutaneous kidney biopsies are well tolerated when performed by experienced operators. However, patients who were dually infected with HIV and HCV had greater risk of biopsy-related complications compared with individuals infected with either HIV or HCV alone [78]. Although kidney biopsy is important for making a definitive diagnosis and for differentiating HIVAN from other common glomerular diseases such as diabetic nephropathy and HCV-related glomerulonephropathies, these patients should be carefully assessed in terms of the risk of biopsy-related complications.

3. HAART initiation in persons diagnosed as having HIVAN is now advocated regardless of CD4$^+$ cell count and HIV viral load [79]. Steroids and angiotensin-converting enzyme (ACE) inhibitors may also be partially effective for treating HIVAN [80, 81]. The efficacy of HAART and other specific interventions for individuals with HIV-related glomerular diseases other than HIVAN have not yet been fully studied. Since adverse effects associated with kidney damage in HIV-infected persons receiving HAART may be due to inappropriate dosing of medications [82], drug dosages should be adjusted according to kidney function.

Specific treatment for comorbidities

Diabetes mellitus and hypertension are increasingly common among contemporary HIV-infected persons with HAART. Therefore, the common and imperative treatment of HIV-infected patients with CKD should involve strict management of blood pressure and serum levels of glucose. Early referral to expert doctors of nephrology, cardiology, and diabetology should be recommended if there is any doubt in regard to optimal treatment.

1. *Hypertension*: Adequate control of blood pressure may play a pivotal role in medical management of kidney disease, as hypertension is both a cause of CKD and a risk factor for progression to ESRD in general population. Prevalence of hypertension in HIV-infected patients is 12–20% in Western countries [83] and 30% in Japan [10]. Current guidelines from the National Kidney Foundation recommend a target blood pressure of 125/75 mmHg or less for patients with diabetes mellitus, proteinuria, or reduced kidney function; alternatively, the recommended blood pressure goal is 135/85 mmHg [54], although this has not been specifically validated in HIV-infected patients with kidney diseases. Salt restriction should be encouraged as a simple nonpharmacologic measure. Angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers for renin–angiotensin system blockade are the drugs of first choice, as they reduce urinary protein and albumin excretion [15] and may slow progression to ESRD. Beta-blockers or nondihydropyridine calcium channel blockers are alternatives, but their metabolism can be blocked by protease inhibitors, which can result in hypotension and in conduction delays.

2. *Diabetes mellitus*: Glycemic control may be critically important in delaying progression of kidney disease in HIV-infected patients with diabetes mellitus. Glycated hemoglobin A_{1c} level (<6.5%), fasting plasma glucose level (90–130 mg/dl), and peak postprandial plasma glucose level (<180 mg/dl) should be strictly controlled, according to the treatment goals for general population, proposed by the Diabetes Association in each individual country.

3. *Other comorbidities*: Treatment of hyperlipidemia is crucial in terms of prevention of cardiovascular disease, which frequently coexists with CKD in general population. Statins are the first-line drugs, but their metabolism is modified by co-use of some antiretroviral drugs including protease inhibitors and by renal dysfunction. Treatment of HCV co-infection should be considered when patients have HCV-related nephropathy proved by renal biopsy. However, as yet, safety and efficacy of interferon treatment for HCV infection in HIV-infected individuals have not been documented.

Summary

Although CKD has been recognized as an important complication of HIV infection since the onset of the HIV epidemic, its epidemiology and management have evolved along with the increasing availability of HAART since the 1990s. CKD likely affects health outcomes with special