Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected With HIV: 2014 Update by the HIV Medicine Association of the Infectious Diseases Society of America

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

EXECUTIVE SUMMARY

Background

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health [1]. CKD is common in human immunodeficiency virus (HIV)–infected persons, has many potential underlying etiologies, and is associated with increased morbidity and mortality. These guidelines for the management of CKD in patients infected with HIV are an update of the 2005 version [2], designed to identify clinically

relevant management questions, summarize pertinent data from clinical studies, and offer recommendations for clinical care. The scope of this document is CKD in HIV-infected adults and children in the United States. The guidelines do not address screening, evaluation, or management of HIV-related kidney disease in resource-constrained settings.

Summarized below are the 2014 revised recommendations for the management of CKD in HIV-infected persons. The panel followed a guideline development process that has been adopted by the Infectious Diseases Society of America (IDSA)/HIV Medicine Association (HIVMA), which includes a systematic method of grading both the quality of evidence (very low, low, moderate, and high) and the strength of the recommendation (weak or strong) [3] (Table 1). The guidelines are not intended to replace clinical judgment in the management of individual patients. A detailed description of the methods, background, and evidence summaries that support each recommendation can be found in the full text of the guideline.

Table 1.   Strength of Recommendations and Quality of the Evidence

Strength of Recommendation and Quality of Evidence	Clarity of Balance Between Desirable and Undesirable Effects	Methodological Quality of Supporting Evidence (Examples)	Implications
Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws, or indirect evidence	Recommendation may change when higher-quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Strong recommendation, very-low-quality evidence (very rarely applicable)	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher-quality evidence becomes available; any estimate of effect for at least 1 critical outcome is very uncertain.
Weak recommendation, high-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patients or societal values; further research is unlikely to change our confidence in the estimate of effect
Weak recommendation, moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances; further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, low-quality evidence	Uncertainty in the estimates of desirable effects, harms, and burden; desirable effects, harms, and burden may be closely balanced	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Weak recommendation, very-low-quality evidence	Major uncertainty in the estimates of desirable effects, harms, and burden; desirable effects may or may not be balanced with undesirable effects	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least 1 critical outcome, is very uncertain

Based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [3, 378–382].

Abbreviation: RCT, randomized controlled trial.

RECOMMENDATIONS FOR KIDNEY DISEASE SCREENING

I. How Should HIV-Infected Patients Be Monitored for Kidney Function and Kidney Damage?

Recommendations

1. We recommend monitoring creatinine-based estimated glomerular filtration rate (GFR) when antiretroviral therapy (ART) is initiated or changed, and at least twice yearly in stable HIV-infected patients, using the same estimation method to track trends over time. More frequent monitoring may be appropriate for patients with additional kidney disease risk factors (strong, low).

2. We suggest monitoring kidney damage with urinalysis or a quantitative measure of albuminuria/proteinuria at baseline, when ART is initiated or changed, and at least annually in stable

HIV-infected patients. More frequent monitoring may be appropriate for patients with additional kidney disease risk factors (weak, low).

RECOMMENDATIONS FOR THE EVALUATION OF HIV-RELATED CKD

II. How Should HIV-Related Kidney Disease Be Evaluated and When Is Referral to a Nephrologist Appropriate?
Recommendations

3. We recommend that the evaluation of new-onset or newly discovered kidney disease in HIV-infected persons include serum chemistry panel; complete urinalysis; quantitation of albuminuria (albumin-to-creatinine ratio from spot sample or total albumin from 24-hour collection); assessment of temporal trends in estimated GFR, blood pressure, and blood glucose control (in patients with diabetes); markers of proximal tubular dysfunction (particularly if treated with tenofovir); a renal sonogram; and review of prescription and over-the-counter medications for agents that may cause kidney injury or require dose modification for decreased kidney function (strong, low).

4. We recommend that HIV-infected patients with kidney disease be referred to a nephrologist for diagnostic evaluation when there is a clinically significant decline in GFR (ie, GFR decline by >25% from baseline and to a level <60 mL/minute/ 1.73 m^2) that fails to resolve after potential nephrotoxic drugs are removed, there is albuminuria in excess of 300 mg per day, hematuria is combined with either albuminuria/proteinuria or increasing blood pressure, or for advanced CKD management (GFR < 30 mL/minute/1.73 m^2) (strong, low).

5. When possible, we recommend establishing permanent dialysis access, ideally an arteriovenous fistula or peritoneal catheter, prior to the anticipated start of renal replacement therapy to avoid the use of higher-risk central venous catheters for hemodialysis (strong, moderate).

6. When possible, we recommend avoiding the use of peripherally inserted central catheters and subclavian central venous catheters in patients with HIV who are anticipated to need dialysis in the future because these devices can damage veins and limit options for permanent hemodialysis access (strong, moderate).

RECOMMENDATIONS FOR THE CLINICAL MANAGEMENT OF HIV-INFECTED PATIENTS WITH CKD

III. How Should Antiretroviral Therapy Be Managed in Patients With CKD or End-Stage Renal Disease?
Recommendations

7. We recommend that clinicians prescribe ART and encourage persistence with therapy in HIV-infected patients who have CKD or end-stage renal disease (ESRD), as ART reduces mortality but is underused in this patient population (strong, moderate).

8. We recommend that clinicians use either the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation to estimate GFR or the Cockcroft–Gault equation to estimate creatinine clearance when dosing antiretroviral drugs or other drugs that require reduced doses in patients with reduced kidney function (strong, moderate).

9. We recommend that patients with biopsy-confirmed or clinically suspected HIV-associated nephropathy (HIVAN) receive ART to reduce the risk of progression to ESRD (strong, moderate).

10. In patients infected with HIV who have a GFR <60 mL/ minute/1.73 m^2, we recommend avoiding tenofovir and other potential nephrotoxic drugs (eg, nonsteroidal anti-inflammatory drugs) when feasible (strong, low).

11. In tenofovir-treated patients who experience a confirmed GFR decline by >25% from baseline and to a level <60 mL/minute/1.73 m^2, we recommend substituting alternative antiretroviral drug(s) for tenofovir, particularly in those with evidence of proximal tubular dysfunction (strong, low).

IV. What Are the Roles of Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers, HMG–Coenzyme A Reductase Inhibitors (Statins), and Aspirin in HIV-Infected Patients With CKD to Prevent Kidney Disease Progression and/or Reduce Cardiovascular Disease Risk?
Recommendations

12. We recommend using angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), when clinically feasible, in patients infected with HIV who have confirmed or suspected HIVAN or clinically significant albuminuria (eg, >30 mg/day in diabetic patients; >300 mg/day in nondiabetic patients) (strong, high).

13. We recommend that HIV-infected individuals with pre-ESRD CKD be treated with statins to prevent cardiovascular disease as appropriate for persons in the highest cardiovascular risk group (eg, >7.5% 10-year risk of cardiovascular disease) (strong, high).

14. We suggest that clinicians consider prescribing aspirin (75–100 mg/day) to prevent cardiovascular disease in HIV-infected individuals with CKD; however, the benefit of aspirin should be balanced against the individual's risk of bleeding (weak, high).

V. What Is the Optimal Blood Pressure Goal for HIV-Infected Patients With CKD?
Recommendations

15. We recommend a target blood pressure of <140/90 mm Hg in HIV-infected patients who have CKD with normal to

mildly increased albuminuria (eg, <30 mg/day or equivalent) (strong, moderate).

16. We suggest a target blood pressure of <130/80 mm Hg in HIV-infected patients who have CKD with moderately to severely increased albuminuria (eg, >30–300 mg/day or equivalent) (weak, low).

VI. Should Patients With HIVAN Receive Corticosteroids to Reduce the Risk of ESRD?
Recommendation

17. We suggest that clinicians consider corticosteroids as an adjunct to ART and ACE inhibitors or ARBs in patients with biopsy-confirmed HIVAN (weak, low).

VII. What Is the Role of Kidney Transplantation in Patients Infected With HIV and ESRD or Imminent ESRD?
Recommendations

18. We recommend that HIV providers assess patients with HIV and ESRD or imminent ESRD for the possibility of kidney transplantation, considering history of opportunistic conditions, comorbidities, current immune status, and virologic control of HIV with ART (strong, moderate).

19. We recommend dose adjustment and pharmacologic monitoring of immunosuppressant drugs in patients infected with HIV after kidney transplantation to account for pharmacologic interactions with antiretroviral drugs. When feasible, ART should be selected that minimizes interactions with immunosuppressant drugs (strong, moderate).

RECOMMENDATIONS FOR CKD IN CHILDREN AND ADOLESCENTS WITH HIV

VIII. How Should Children and Adolescents With HIV Be Screened for Kidney Disease and Monitored for Tenofovir-Associated Kidney Toxicity?
Recommendations

20. Similar to adults, we recommend that children and adolescents with HIV who are without evidence of existing kidney disease should be screened for renal function with estimated GFR (using an estimating equation developed for children) when ART is initiated or changed and at least twice yearly. We recommend monitoring for kidney damage with urinalysis or a quantitative measure of proteinuria when ART is initiated or changed, and at least annually in children and adolescents with stable kidney function. More frequent monitoring may be appropriate with additional kidney disease risk factors (strong, low).

21. We suggest avoiding tenofovir as part of first-line therapy in prepubertal children (Tanner stages 1–3) because tenofovir use is associated with increased renal tubular abnormalities and bone mineral density loss in this age group (weak, low).

IX. Should Treatment of HIV-Related Kidney Disease Be Different for Children and Adolescents Than for Adults?
Recommendations

22. We recommend that children and adolescents with HIV who have proteinuric nephropathy (including HIVAN) should be treated with ART and referred to a nephrologist (strong, moderate).

23. We suggest using ACE inhibitors or ARBs to treat proteinuric nephropathy in children with HIV infection and suggest their use as first-line therapy for hypertension in these children. Because HIV-infected children with proteinuria may be at greater risk for salt wasting and prone to dehydration, ACE inhibitors and ARBs should be used with caution in children (weak, very low).

24. We suggest that corticosteroids not be used in children with HIVAN (weak, very low).

The risk of chronic kidney disease (CKD) is increased in individuals infected with human immunodeficiency virus (HIV) compared with the general population [4]. In African Americans, HIV infection imparts a risk for end-stage renal disease (ESRD) that is of similar magnitude to that of diabetes [5]. A constellation of potential factors contributes to excess kidney disease in HIV-infected patients, including direct effects by HIV infection, HIV-associated immune activation, drug toxicity, coinfection with hepatitis C virus, and a high prevalence of traditional kidney disease risk factors. This clinical practice guideline is an update to the 2005 version [2].

In the first section, the panel summarizes background information relevant to the topic. In the second section, the panel poses questions regarding the management of HIV-associated CKD, evaluates applicable clinical trial and observational data, and makes recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [3]. In the third section, we discuss unresolved questions and research priorities for HIV-associated CKD. The following 9 questions were answered:

(I) How should HIV-infected patients be monitored for kidney function and kidney damage?

(II) How should HIV-related kidney disease be evaluated and when is referral to a nephrologist appropriate?

(III) How should antiretroviral therapy be managed in patients with CKD or end-stage renal disease?

(IV) What are the roles of angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, HMG-coenzyme A reductase inhibitors (statins), and aspirin in HIV-infected patients with CKD to prevent kidney disease progression and/ or reduce cardiovascular disease risk?

(V)   What is the optimal blood pressure goal for HIV-infected patients with CKD?

(VI)   Should patients with HIVAN receive corticosteroids to reduce the risk of ESRD?

(VII)   What is the role of kidney transplantation in patients infected with HIV and ESRD or imminent ESRD?

(VIII)   How should children and adolescents with HIV be screened for kidney disease and monitored for tenofovir-associated kidney toxicity?

(IX)   Should treatment of HIV-related kidney disease be different for children and adolescents than for adults?

METHODOLOGY

Panel Composition

The original Infectious Diseases Society of America/HIV Medicine Association (IDSA/HIVMA) guidelines on the management of kidney disease in patients infected with HIV were published in 2005 [2]. For this update, the IDSA Standards and Practice Guidelines Committee convened a multidisciplinary panel of experts in HIV/AIDS, nephrology, internal medicine, pediatric nephrology, kidney pathology, and kidney transplantation.

Evidence Review: The GRADE Method

GRADE is a systematic approach to guideline development that has been described in detail elsewhere [3, 6]. The IDSA/HIVMA adopted GRADE in 2008 [7]. In the GRADE system, the guideline panel assigns each recommendation with separate ratings for the underlying quality of evidence supporting the recommendation and for the strength with which the recommendation is made (Table 1). Data from randomized controlled trials begin as "high" quality, and data from observational studies begin as "low" quality. However, the panel may judge that specific features of the data warrant decreasing or increasing the quality of evidence rating, and GRADE provides guidance on how such factors should be weighed [6]. The strength assigned to a recommendation chiefly reflects the panel's confidence that the benefits of following the recommendation are likely to outweigh potential harms. While the quality of evidence is an important factor in choosing recommendation strength, it is not prescriptive.

Process Overview

The panel first met by teleconference in August 2010, in which an outline of the guideline was discussed and the process of guideline development using the GRADE approach briefly reviewed. The panel subsequently held teleconferences approximately every 3–4 months and then met for face-to-face meetings in February 2011 and in March 2012. Panel subgroups were assigned to specific topic areas and charged with developing clinical questions that were discussed and approved by the full panel.

Panel subgroups generated a list of keywords that were used by an IDSA staff member to carry out literature searches of PubMed, and results were returned to each group for review. Searches were restricted to English-language publications and covered the period of 1990 to September 2013. Abstracts presented at international conferences within the past 2 years were also reviewed for inclusion. Systematic reviews of relevant topics were identified using PubMed and the Cochrane library. Each group was responsible for reviewing the literature relevant to its section, and drafting recommendations and evidence summaries for review and discussion by the full panel.

A Web-based survey was used to allow panel members to indicate agreement or disagreement with the recommendations in each section and to suggest revisions. The groups revised their recommendations based on feedback from the panel. The panel then addressed substantive disagreements and sought consensus through discussion. After the panel discussed and reached consensus on recommendation substance and wording, sections were compiled and the complete guideline draft was circulated to panel members for review and comment.

Conflicts of Interests

Members of the expert panel complied with the IDSA policy regarding conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. IDSA provided a conflicts of interest disclosure statement to panel members and asked them to identify ties to companies manufacturing or developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. Regular updates of information pertaining to conflicts of interest were requested from each panel member following scheduled teleconference meetings. The panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

Review and Approval Process

The panel obtained feedback from 3 external peer reviewers. The guideline was reviewed and approved by the IDSA Standards and Practice Guidelines Committee and the Board of Directors of the IDSA and HIVMA prior to dissemination.

Future Guideline Revisions

At annual intervals, the panel chairs will be asked for their input on the need to update the guideline based on an examination of the current literature. The Standards and Practice Guidelines

Committee of the IDSA will consider this input and determine the necessity and timing of an update. If warranted, the entire panel or a subset thereof will be convened to discuss potential changes.

BACKGROUND

CKD Definition and Classification

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health [1]. Indicators of kidney damage include albuminuria or proteinuria, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, or history of kidney transplantation. Glomerular filtration rate (GFR) that persists below 60 mL/minute/1.73 m^2 for >3 months constitutes CKD, even in the absence of kidney damage markers or other abnormalities. The widely promulgated CKD classification scheme developed by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative in 2002 classified CKD exclusively on the basis of GFR strata (stages 1–5) [8]. Recently published guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) initiative emphasizes identification of CKD etiology and classification of severity according to both GFR level (6 strata) and albuminuria level (3 strata) (Figure 1) [1]. In support of these guidelines, the Chronic Kidney Disease Prognosis Consortium has published a series of meta-analyses showing that GFR and albuminuria are independent and complementary predictors of important clinical outcomes including CKD progression, ESRD, acute kidney injury, cardiovascular mortality, and all-cause mortality [9–12].

Kidney Function and Damage Markers

GFR is the most widely used index of kidney function. GFR may be measured by observing the clearance of exogenous filtration markers (eg, inulin, iohexol, iothalamate) or estimated from serum concentrations of endogenous filtration markers (eg, creatinine, cystatin C) [13]. Methods based on the clearance of exogenous markers are the gold standard for GFR measurement, but are cumbersome and infrequently used in clinical settings.

In clinical practice, serum creatinine is most commonly used to estimate GFR. The generation of creatinine, which is principally determined by muscle mass and nutritional intake, varies by sex, race, and age, requiring adjustment for these factors in GFR estimating equations. Diseases that lead to muscle wasting can reduce creatinine generation, which may lead to overestimation of the GFR. To minimize variability in serum creatinine measurements, virtually all clinical laboratories report calibrated serum creatinine values that are traceable to an isotope dilution mass spectrometry reference measure [1].

Cystatin C, which is produced by all nucleated cells [14], varies less by race, sex, or body composition than creatinine, and has been proposed to be a clinically relevant alternative or complementary GFR marker to creatinine [15, 16]. However, cystatin C concentration may be affected by thyroid disease and corticosteroid use [17, 18], has been found to be correlated with
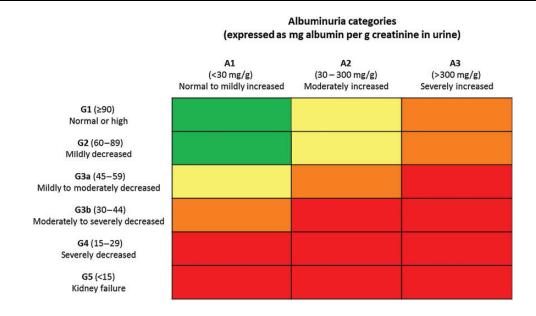
Figure 1. Chronic kidney disease classification according to glomerular filtration rate and albuminuria strata, adapted from the Kidney Disease: Improving Global Outcomes Guidelines [1]. The colors in the table reflect degree of risk for clinical outcomes including end-stage renal disease, cardiovascular events and related mortality, and all-cause mortality. Green represents low risk, yellow is moderately increased risk, orange is high risk, and red is very high risk.

inflammatory markers in the general population [19, 20], and has been reported to be correlated with HIV RNA levels, hepatitis C coinfection, and T-cell activation indices in HIV-infected persons [21–23]. In both the general population and in HIV-infected persons, cystatin C is a stronger predictor of mortality and cardiovascular events than creatinine or creatinine-based GFR estimates [24–27]. Table 2 shows commonly used equations to estimate GFR. Additionally, online GFR calculators are available to assist clinicians whose clinical laboratories do not report estimated GFR with serum creatinine measurements (https://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm).

Although GFR estimating equations have not been well validated in diverse HIV-infected populations, several published studies have compared GFR estimating equations to a direct measure of GFR in HIV-infected adults, most of whom were taking antiretroviral therapy (ART) and had normal or near-normal kidney function [23, 28, 29]. Consistent with findings from the general population [30], these studies found the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation to be more accurate than the older Modification of Diet in Renal Disease (MDRD) equation in HIV-infected individuals. Available data suggest that the cystatin C–based CKD-EPI equation is not more accurate or precise than the creatinine-based CKD-EPI equation in the general population [15] or in HIV-infected persons [28, 29]. However, the CKD-EPI equation that uses both creatinine and cystatin C (Table 2) has been found to be somewhat more accurate and precise than equations based on a single biomarker in both the general population and in HIV-infected persons [15, 23, 28].

Detection of albuminuria or proteinuria is the most common method of detecting kidney damage. Detectable kidney damage typically precedes loss of kidney function by years, as in the case of diabetic nephropathy. Proteinuria includes both albumin and low-molecular-weight proteins (eg, β-2 microglobulin, immunoglobulin light chains, retinol binding protein). Low-molecular-weight proteins are filtered at the glomerulus, but are mostly reabsorbed by the proximal tubule. Increased amounts of low-molecular-weight proteins in the urine may indicate proximal tubular dysfunction, whereas substantial levels of albuminuria usually indicate glomerular disease. Traditionally, very low levels of albuminuria have been considered normal, although even within the normal range of albumin excretion, higher levels of albuminuria are associated with increased cardiovascular risk and all-cause mortality [31]. KDIGO guidelines recommend albuminuria as the preferred marker for staging CKD [1].

Urinalysis (urine dipstick) provides a semiquantitative measure of protein concentration in the urine (eg, trace, 1+, etc) in addition to detecting other pathologic indicators, including hematuria and glycosuria. Although dipstick measures of proteinuria are useful for screening, they detect predominantly albumin (ie, do not detect low-molecular-weight proteins) and

can substantially underestimate or overestimate true protein excretion depending on hydration status [32].

Quantitative measures of albuminuria or proteinuria include absolute measures in a 24-hour collection or ratios of albumin or protein concentrations to creatinine concentration in a urine sample (Table 3). Twenty-four-hour urine collections are the reference standard for measuring urinary excretion of albumin or protein, although collection errors are common. The adequacy of a 24-hour urine collection can be assessed by comparing the total creatinine in the sample with that expected (ie, 20–25 and 15–20 mg/kg/day of creatinine in men and women, respectively). The most clinically useful methods for quantifying albumin or protein excretion rates are the albumin-to-creatinine and the protein-to-creatinine ratios, respectively, which may be performed on random urine samples. On average, humans excrete approximately 1 g of creatinine in the urine each day, so the ratios of albumin or protein to creatinine correspond to the total daily excretion (eg, milligrams of albumin or protein per gram of creatinine approximates milligrams of albumin or protein per day). Albumin-to-creatinine ratios from random urine samples (ideally using the first morning sample) correlate closely with 24-hour urine collections, are simpler to obtain, and are less prone to collection errors [33]. A random albumin-to-creatinine ratio is often referred to as a urine "microalbumin" test. Although this term is widely used, it is misleading and KDIGO discourages its use in favor of the more descriptive term albumin-to-creatinine ratio [1].
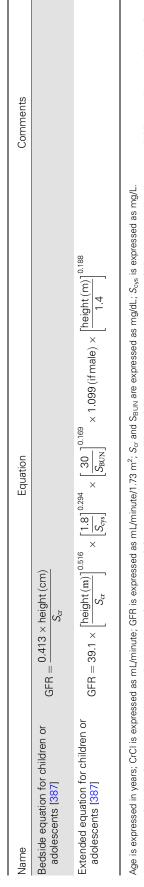
Epidemiology

HIV infection is a well-established risk factor for CKD and ESRD in industrialized countries. The reported prevalence of CKD (defined by GFR <60 mL/minute/1.73 m^2) among patients infected with HIV in North America and Europe ranges from 4.7% to 9.7%, and higher rates have been reported when CKD was defined by either reduced GFR or proteinuria [5, 34–43]. Compared with HIV-negative persons, the prevalence of albuminuria >30 g/day has been reported to be 2- to 5-fold higher in HIV-infected individuals [39, 43]. The incidence of kidney function decline or the development of CKD among HIV-infected persons followed in longitudinal studies has been reported to be between 3.9 and 11.2 per 1000 person-years [5, 44–46].

Factors associated with an increased risk of CKD in HIV-infected individuals include older age, female sex, diabetes, hypertension, injection drug use, lower CD4 cell count, specific antiretroviral drugs, history of acute kidney injury, and higher HIV RNA levels [40, 42, 44, 46–49]. Additionally, coinfection with hepatitis C has been identified as a risk factor for kidney disease in a number of studies and in a recent meta-analysis [40, 42, 46, 50–52]. Some studies have linked improvements in kidney function or proteinuria to use of ART and suppressed HIV RNA levels [40, 42, 53, 54] (Table 4).

Table 2. Commonly Used Glomerular Filtration Rate Estimating Equations Based on Serum Concentration of Creatinine or Cystatin C

Name	Equation	Comments
Cockcroft–Gault [383]	$\mathrm{CrCl} = \dfrac{[140 - \text{age}] \times \text{weight (kg)}}{72 \times S_{\text{cr}}} \times 0.85 \text{ (if female)}$	• Least accurate or precise of available equations [205, 384] • May be useful for older, cachectic patients • FDA has traditionally required this equation be used for recommended drug dose modifications in kidney disease
MDRD, 4-variable, using standardized[a] serum creatinine concentration [205]	$\mathrm{GFR} = 175 \times S_{\text{cr}}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$	• Widely used by clinical laboratories to estimate GFR • Accurate GFR estimates at GFR <60 mL/min/1.73 m^2 • Underestimates GFR in patients with GFR >60 mL/min/1.73 m^2 [385]
CKD-EPI creatinine equation, using standardized[a] serum creatinine concentration [15, 30]	Female, $S_{\text{cr}} \leq 0.7$: $\mathrm{GFR} = 144 \times \left(\dfrac{S_{\text{cr}}}{0.7}\right)^{-0.329} \times (0.993)^{\text{age}} \times 1.159 \text{ (if black)}$ Female, $S_{\text{cr}} > 0.7$: $\mathrm{GFR} = 144 \times \left(\dfrac{S_{\text{cr}}}{0.7}\right)^{-1.209} \times (0.993)^{\text{age}} \times 1.159 \text{ (if black)}$ Male, $S_{\text{cr}} \leq 0.9$: $\mathrm{GFR} = 141 \times \left(\dfrac{S_{\text{cr}}}{0.9}\right)^{-0.411} \times (0.993)^{\text{age}} \times 1.159 \text{ (if black)}$ Male, $S_{\text{cr}} > 0.9$: $\mathrm{GFR} = 141 \times \left(\dfrac{S_{\text{cr}}}{0.9}\right)^{-1.209} \times (0.993)^{\text{age}} \times 1.159 \text{ (if black)}$	More accurate than MDRD equation, particularly at GFR >60 mL/min/1.73 m^2 [30, 386]
CKD-EPI cystatin C equation, using standardized[a] serum cystatin C concentration [15]	$S_{\text{cys}} \leq 0.8$: $\mathrm{GFR} = 133 \times \left(\dfrac{S_{\text{cys}}}{0.8}\right)^{-0.499} \times 0.996^{\text{age}} \times 0.932 \text{ (if female)}$ $S_{\text{cys}} > 0.8$: $\mathrm{GFR} = 133 \times \left(\dfrac{S_{\text{cys}}}{0.8}\right)^{-1.328} \times 0.996^{\text{age}} \times 0.932 \text{ (if female)}$	• Race not required for estimate • Similar accuracy and precision to CKD-EPI creatinine equation [15]
CKD-EPI creatinine-cystatin C equation, using standardized[a] serum creatinine and cystatin C concentrations [15]	Female, $S_{\text{cr}} \leq 0.7$, $S_{\text{cys}} \leq 0.8$: $\mathrm{GFR} = 130 \times \left(\dfrac{S_{\text{cr}}}{0.7}\right)^{-0.248} \times \left(\dfrac{S_{\text{cys}}}{0.8}\right)^{-0.375} (0.995)^{\text{age}} \times 1.08 \text{ (if black)}$ Female, $S_{\text{cr}} \leq 0.7$, $S_{\text{cys}} > 0.8$: $\mathrm{GFR} = 130 \times \left(\dfrac{S_{\text{cr}}}{0.7}\right)^{-0.248} \times \left(\dfrac{S_{\text{cys}}}{0.8}\right)^{-0.711} (0.995)^{\text{age}} \times 1.08 \text{ (if black)}$ Female, $S_{\text{cr}} > 0.7$, $S_{\text{cys}} \leq 0.8$: $\mathrm{GFR} = 130 \times \left(\dfrac{S_{\text{cr}}}{0.7}\right)^{-0.601} \times \left(\dfrac{S_{\text{cys}}}{0.8}\right)^{-0.375} (0.995)^{\text{age}} \times 1.08 \text{ (if black)}$ Female, $S_{\text{cr}} > 0.7$, $S_{\text{cys}} > 0.8$: $\mathrm{GFR} = 130 \times \left(\dfrac{S_{\text{cr}}}{0.7}\right)^{-0.601} \times \left(\dfrac{S_{\text{cys}}}{0.8}\right)^{-0.711} (0.995)^{\text{age}} \times 1.08 \text{ (if black)}$ Male, $S_{\text{cr}} \leq 0.9$, $S_{\text{cys}} \leq 0.8$: $\mathrm{GFR} = 135 \times \left(\dfrac{S_{\text{cr}}}{0.9}\right)^{-0.207} \times \left(\dfrac{S_{\text{cys}}}{0.8}\right)^{-0.375} (0.995)^{\text{age}} \times 1.08 \text{ (if black)}$ Male, $S_{\text{cr}} \leq 0.9$, $S_{\text{cys}} > 0.8$: $\mathrm{GFR} = 135 \times \left(\dfrac{S_{\text{cr}}}{0.9}\right)^{-0.207} \times \left(\dfrac{S_{\text{cys}}}{0.8}\right)^{-0.711} (0.995)^{\text{age}} \times 1.08 \text{ (if black)}$ Male, $S_{\text{cr}} > 0.9$, $S_{\text{cys}} \leq 0.8$: $\mathit{GFR} = 135 \times \left(\dfrac{S_{\text{cr}}}{0.9}\right)^{-0.601} \times \left(\dfrac{S_{\text{cys}}}{0.8}\right)^{-0.375} (0.995)^{\text{age}} \times 1.08 \text{ (if black)}.$ Male, $S_{\text{cr}} > 0.9$, $S_{\text{cys}} > 0.8$: $\mathrm{GFR} = 135 \times \left(\dfrac{S_{\text{cr}}}{0.9}\right)^{-0.601} \times \left(\dfrac{S_{\text{cys}}}{0.8}\right)^{-0.711} (0.995)^{\text{age}} \times 1.08 \text{ (if black)}$	• Currently the most accurate method to estimate GFR • Requires measurement of both serum creatinine and cystatin C

Table 2 continued.

Name	Equation	Comments
Bedside equation for children or adolescents [387]	$GFR = \dfrac{0.413 \times height\,(cm)}{S_{cr}}$	
Extended equation for children or adolescents [387]	$GFR = 39.1 \times \left[\dfrac{height\,(m)}{S_{cr}}\right]^{0.516} \times \left[\dfrac{1.8}{S_{cys}}\right]^{0.294} \times \left[\dfrac{30}{S_{BUN}}\right]^{0.169} \times 1.099\ (if\ male) \times \left[\dfrac{height\,(m)}{1.4}\right]^{0.188}$	

Age is expressed in years; CrCl is expressed as mL/minute; GFR is expressed as mL/minute/1.73 m²; S_{cr} and S_{BUN} are expressed as mg/dL; S_{cys} is expressed as mg/L.

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CrCl, creatinine clearance; FDA, US Food and Drug Administration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; S_{BUN}, serum blood urea nitrogen concentration; S_{cr}, serum creatinine concentration; S_{cys}, serum cystatin C concentration.

[a] Standardized serum creatinine and cystatin C refers to values that have been calibrated in clinical laboratories to track a universal standard [206, 388].

Among HIV-infected individuals with CKD, notable risk factors for progression to ESRD include HIV-associated nephropathy (HIVAN) diagnosis [55], African American lineage, family history of ESRD [56], magnitude of proteinuria [44], and advanced immunosuppression [45, 57, 58]. In the HIV-infected population, racial differences in early-stage CKD (eg, albuminuria or GFR between 45 and 59 mL/minute/1.73 m²) are modest, but individuals of African descent are at much greater risk for progression to ESRD than white persons [5, 44, 59]. In a large cohort of American veterans, HIV infection conferred no increased risk for ESRD in whites, but conferred a 3-fold higher risk in blacks [5].

Pathogenesis and Clinical Correlations

HIVAN and HIV immune complex kidney disease comprise the 2 major categories of HIV-related kidney disease. HIVAN predominantly occurs in individuals of African descent [60, 61], and emerging data indicate that the racial differences in HIVAN (and other nondiabetic nephropathies) are strongly associated with risk alleles on chromosome 22q12 involving the genes that encode apolipoprotein L1 and non–myosin IIA heavy chain [62–66]. HIVAN is most common in the setting of untreated HIV infection with advanced immunosuppression, and is characterized clinically by heavy proteinuria without hematuria or red blood cell casts on urinalysis, rapid GFR decline, and echogenic kidneys on renal ultrasound [55, 60, 61, 67–69]. Histologically, HIVAN is characterized by collapsing focal segmental glomerulosclerosis, microcystic tubular dilatation, and tubulointerstitial inflammation by macrophages and T lymphocytes [67, 70–74]. Transgenic mouse models and in vitro human studies implicate direct effects by HIV infection on renal epithelial cells, particularly glomerular epithelial cells, with cellular proliferation that results in collapse of the glomerular capillary tuft and accompanying foot process effacement, pseudocrescent formation, and glomerular basement membrane thickening [75–86].

HIV immune complex kidney disease comprises a diverse group of immune-mediated glomerulonephritides including immune complex glomerulonephritis, immunoglobulin A nephropathy, and lupus-like glomerulonephritis [87–90], and is present in up to 30% of cases in biopsy series [55, 61, 91–93]. These diseases are characterized by immune complexes, comprised of antibody bound to HIV antigens that are deposited on capillary loops and in the mesangium. Complement activation may result in a lupus-like pathology in the kidney without other systemic or serologic features of lupus [88]. In contrast to HIVAN, the renal cell proliferation with immune complex disease predominately affects mesangial cells, leading to mesangial expansion [87, 89]. Tubulointerstitial inflammation is also common with immune complex disease, but this involves a mixture of macrophages, eosinophils, and B cells.

Table 3. Classification of Albuminuria and Proteinuria

Measurement	Normal to Mildly Increased (A1)	Moderately Increased (A2)	Severely Increased (A3)
AER, mg/24 h	<30	30–300	>300
PER, mg/24 h	<150	150–500	>500
ACR			
mg/mmol	<3	3–30	>30
mg/g	<30	30–300	>300
PCR			
mg/mmol	<15	15–50	>50
mg/g	<150	150–500	>500
Protein reagent strip	Negative or trace	Trace to 1+	1+ or greater

Adapted from the Kidney Disease Outcomes Quality Initiative Clinical Guidelines for Chronic Kidney Disease, 2013 [1].

Abbreviations: ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; PCR, protein-to-creatinine ratio; PER, protein excretion rate.

Other diseases reported in HIV kidney biopsy series—which may or may not occur at increased frequency compared with HIV-uninfected individuals—include thrombotic thrombocytopenic purpura [93–95], membranous nephropathy or membranoproliferative glomerulonephritis (associated with hepatitis B or C coinfection and syphilis) [90, 95–99], diabetic nephropathy, hypertensive glomerulosclerosis, acute tubular necrosis, interstitial nephritis, postinfectious glomerulonephritis, chronic pyelonephritis, and amyloid [55, 61, 91, 93, 100].

Table 4. Risk Factors for Chronic Kidney Disease and End-Stage Renal Disease: Data From Studies of HIV-Infected Persons and the General Population

	CKD (GFR <60 mL/min/1.73 m^2 or Proteinuria)		ESRD or (GFR <15 mL/min/1.73 m^2)	
Factor	Relative Risk Range	Reference(s)	Relative Risk Range	Reference(s)
African descent	1.7–2.4	[36, 42, 44, 54, 122]	4.5–31	[5, 45, 54, 389]
Female sex	1.5–1.7	[44, 46]	NR	
Family history of ESRD	NR		5.4–8.0	[56, 390]
Age	1.2–5.5 per 10 y older	[35, 36, 38, 44, 46, 391]	2.0 for age >50 vs <30 y	[45]
Diabetes	1.5–2.6	[38, 42, 46, 54, 121, 122]	4.8–9.0	[5, 392]
Hypertension	1.4–3.5	[35, 38, 42, 46, 54, 121, 122, 156]	4.9	[393]
CD4 cell count	1.1–1.25 per 100 cells/μL lower 1.4–2.2 for CD4 <200 vs ≥200 cells/μL	[42, 46, 54, 121, 122, 156, 394]	1.7 per 100 cells/μL lower 1.4–2.7 for CD4 <200 vs ≥200 cells/μL	[45, 54, 57, 58]
HIV RNA	1.3–2.2 for detectable or higher vs undetectable or lower HIV RNA	[36, 38, 54, 122]	2.0 per 1 log$_{10}$ increase in HIV RNA	[54]
Hepatitis C coinfection or history of injection drug use	1.3–2.2	[36, 38, 42, 44, 46, 51, 54, 121, 122, 394]	2.8–5.0	[54, 395]
Tenofovir	1.2–1.3 per year of exposure 1.6–2.2 for any or recent exposure vs no or remote exposure	[35, 46, 156, 157]	NR	
Tenofovir plus a ritonavir-boosted protease inhibitor	3.4 vs an NNRTI-based regimen without tenofovir	[54]	NR	
Indinavir	2.0–2.5 for any or recent exposure vs no or remote exposure	[35, 156]	NR	
Atazanavir	1.2 per year of exposure	[46]	NR	
Lopinavir	1.1 per year of exposure	[46]	NR	

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; NR, not reported.

Implications of CKD in HIV-Infected Persons

As in the general population, CKD has important implications for clinical outcomes in HIV-infected persons: ESRD, cardiovascular disease, and all-cause mortality. The risk of ESRD in HIV-infected patients is strongly influenced by race, with incidences of 0.9 and 7.3 per 1000 person-years in HIV-infected whites and blacks, respectively [5, 45]. Among HIV-infected individuals with ESRD, the introduction of combination ART has been accompanied by improved survival on dialysis [101–105], leading to increased consideration of kidney transplantation in this population [101, 106].

CKD also predisposes individuals infected with HIV to acute kidney injury, which occurs at an estimated incidence of between 2.8 and 5.9 cases per 100 person-years [107, 108]. Among hospitalized patients, acute kidney injury is 3- to 4-fold more common in HIV-infected patients than in other hospitalized patients, and acute kidney injury is strongly associated with greater in-hospital mortality [109]. In a recent study that examined the long-term consequences of acute kidney injury and included >17 000 hospitalized veterans with HIV who survived at least 90 days after an initial hospitalization, the occurrence and severity of acute kidney injury was associated with greater incidences of heart failure, cardiovascular events, ESRD, and mortality, in dose-response relationships [49].

In the general population, decreased GFR and albuminuria are strongly associated with increased risks of cardiovascular events and cardiovascular-related mortality [12, 31, 110–114]; the same also appears to be true in patients infected with HIV [41, 115–117]. In a large cohort of US veterans with HIV, those with albuminuria and a GFR <30 mL/minute/1.73 m² had a 6-fold greater risk of cardiovascular events compared with those without albuminuria and a normal GFR [41].

Decreased GFR and albuminuria have consistently been found to be associated with higher mortality in HIV-infected individuals [4, 118–122]. In the prospective Women's Interagency HIV Study, albuminuria >30 mg/day in HIV-infected women conferred a 2-fold increased mortality risk after adjusting for other factors [123]—a notable finding given that low-grade albuminuria is several-fold more prevalent in HIV-infected than HIV-negative persons [39, 87, 123]. Part of the excess mortality in HIV-related CKD may be due to underuse of ART. One study found that, compared with those with normal kidney function, ART use decreased monotonically in patients with lower GFR, which accounted for up to one-third of the excess mortality in HIV-related CKD in this study [124].

Kidney Toxicity of Antiretroviral Therapy

Antiretroviral agents have the potential to be nephrotoxic. Among current drugs, most attention has focused on tenofovir, which (in combination with emtricitabine) is a recommended nucleoside reverse transcriptase inhibitor in HIV treatment guidelines from the US Department of Health and Human Services (DHHS) and the International Antiviral Society–USA [125, 126], although a tenofovir-sparing regimen of dolutegravir plus abacavir/lamivudine has recently been endorsed as a recommended regimen for first-line therapy by the DHHS guidelines [125].

Nephrotoxicity from tenofovir encompasses several patterns of kidney injury including proximal tubular dysfunction, acute kidney injury, CKD, and nephrogenic diabetes insipidus [127–129]. The proximal tubular dysfunction is principal among these, resulting from drug-induced mitochondrial DNA depletion that is mediated by accumulation of drug within the proximal renal tubules [127]. Excessive drug accumulation may be facilitated by genetic polymorphisms in the drug transport proteins that are associated with increased drug uptake, via organic anion transporter type 1 and 3 proteins, or reduced drug egress, via multidrug-resistant protein type 4 within proximal tubule cells [130–133]. Proximal tubular dysfunction rarely may progress to Fanconi syndrome, a complete tubulopathy that includes metabolic acidosis and bone disorders [128, 134] (Table 5).

Two randomized trials assessed the associations between tenofovir and markers of proximal tubular dysfunction. One study found abnormalities in 2 of 3 such markers (β-2 microglobulin and retinol binding protein, but not N-acetyl-β-D-glucosaminidase), but there was no difference in albumin-to-creatinine ratios or estimated GFR in subjects who were randomized to tenofovir compared with abacavir [135]. A second randomized study reported higher urinary excretion of α-1 microglobulin but similar estimated and measured GFR in subjects who were randomized to switch from zidovudine to tenofovir [136]. Several small to moderately sized observational studies have assessed serum phosphorous, fractional excretion of phosphorous, fractional excretion of uric acid, the ratio of urine albumin to protein, glycosuria with normal serum glucose, and other markers of proximal tubular dysfunction or damage [137–151]. Most but not all of these studies reported statistically significantly higher levels of at least one biomarker in subjects taking tenofovir compared with subjects not taking tenofovir. Estimated GFR was often normal in these studies, but in one study, increased urinary excretion of β-2 microglobulin was associated with declines in estimated GFR in patients who received tenofovir [137].

Although many randomized trials have reported modest estimated GFR declines (of 5–10 mL/minute/1.73 m²) in patients who received tenofovir, compared with other nucleoside analogues, treatment-limiting renal adverse events were unusual, and generally similar to those of subjects who did not receive tenofovir in these studies [135, 152, 153]. For example, a pooled analysis of data from 1111 antiretroviral-naive participants in the Gilead 903 and 934 studies reported that GFR change

Table 5. Laboratory Indicators of Proximal Tubular Dysfunction

Abnormality	Definition of Abnormality	Comment	Calculations
Serum abnormalities			
Hypokalemia	Serum potassium concentration below laboratory reference range	• Trend is of more clinical relevance than single abnormal value • Neither sensitive nor specific	
Low serum bicarbonate	Serum bicarbonate concentration below laboratory reference range	• Trend is of more clinical relevance than single abnormal value • Nonspecific in the setting of reduced glomerular filtration rate	
Hypophosphatemia	Serum phosphorous concentration below laboratory reference range	• Normal value does not exclude urinary phosphorous wasting. However, hypophosphatemia combined with urinary wasting is diagnostic of renal tubular injury	
Urine abnormalities			
Urine glucose on dipstick	Glycosuria in the absence of diabetes, or in diabetics with well-controlled blood glucose	• Diagnostic of renal tubular injury	
Fractional excretion of phosphate [396]	<10% is normal and >20% is abnormal	• Increased FE_{phos} in the setting of normal kidney function is of more clinical relevance than when kidney function is impaired • Upward trend in urinary phosphate wasting is suggestive of tubular injury • Loss of phosphate may lead to osteomalacia	$FE_{phos} = \dfrac{[U_{phos}] \times [P_{creat}]}{[P_{phos}] \times [U_{creat}]} \times 100$ Tubular reabsorption of phosphate (%) = $100 - FE_{phos}$
Tubular maximum for phosphate corrected for GFR [396]	Lower than reference value (normal, 2.8–4.4 mg/dL)	• Assess renal phosphate handling independent of plasma phosphate and renal function	$\dfrac{TmP}{GFR} = [P_{phos}] - \dfrac{[U_{creat}] \times [P_{creat}]}{[U_{phos}]}$
Fractional excretion of uric acid	<15% is normal and >20% is abnormal	• Increased FE uric acid in the setting of normal kidney function is of more clinical relevance than when kidney function is impaired • Upward trend in urinary uric acid wasting is strongly suggestive of proximal tubular dysfunction	$FE_{UA} = \dfrac{[U_{UA}] \times [P_{creat}]}{[P_{UA}] \times [U_{creat}]} \times 100$
Urine albumin-to-protein ratio [151]	uAPR <0.4 suggests predominantly tubulointerstitial disease, whereas uAPR >0.4 suggests predominantly glomerular disease	• Based on theory that albumin accounts for a lower proportion of protein in urine when loss is from tubular as opposed to glomerular disease • Only evaluated in individuals with urine protein-to-creatinine ratio >200 mg/g	$uAPR = \dfrac{[U_{alb}]}{[U_{prot}]}$
Other laboratory indicators of proximal tubular dysfunction			
Nonspecific indicators • Proteinuria/albuminuria • Hematuria		Investigational markers or markers with limited clinical availability • Aminoaciduria • Urinary α-1 microglobulin • Urinary β-2 microglobulin • Urinary retinol binding protein • Urinary cytochrome C • Urinary cystatin C	

Abbreviations: FE_{phos}, fractional excretion of phosphate; FE_{UA}, fractional excretion of uric acid; P_{creat}, plasma concentration of creatinine; P_{phos}, plasma concentration of phosphorus; P_{UA}, plasma concentration of uric acid; TmP/GFR, tubular maximum for phosphate corrected for glomerular filtration rate; U_{alb}, urine concentration of albumin; uAPR, urine albumin-to-protein ratio; U_{creat}, urine concentration of creatinine; U_{phos}, urine concentration of phosphorus; U_{prot}, urine concentration of protein; U_{UA}, urine concentration of uric acid.

from baseline to week 144 was −6 mL/minute/1.73 m^2 and 5 mL/minute/1.73 m^2 in subjects assigned to tenofovir and the comparator nucleoside analogue, respectively [152]. However, only 3 subjects in each group developed a serum creatinine level >1.5 mg/dL during follow-up, and the changes in serum phosphorous concentrations were not significantly different between study arms. The median age of subjects in these trials was 36 years and exclusion criteria included serum creatinine ≥1.5 mg/dL, serum phosphorus <2.2 mg/dL, and calculated creatinine clearance by Cockcroft–Gault equation <60 mL/minute (in study 903) or <50 mL/minute (in study 934). In AIDS Clinical Trials Group (ACTG) study 5202, clinical diagnoses of Fanconi syndrome, toxic nephropathy, proteinuria, or renal failure were reported in similar numbers of subjects who were randomly assigned to tenofovir or abacavir (5 and 4 in each arm, respectively), representing 1% of the total subjects in this study [154]. The median age of subjects in ACTG 5202 was 39 years and individuals with creatinine clearance by Cockcroft–Gault equation <60 mL/minute were ineligible.

In a systematic review and meta-analysis of 17 studies that included 9 randomized controlled trials (3 in ART-naive and 6 in ART-experienced subjects, respectively), 7 prospective observational cohorts of ART-naive or -experienced patients, and one drug registry study from high- or middle-income countries, tenofovir was associated with lower creatinine clearance (by an average of −3.9 mL/minute) compared with tenofovir-sparing regimens [155]. Studies in this meta-analysis had an overall median follow-up duration of 48 weeks, and subjects with GFR <50 or <60 mL/minute/1.73 m^2 were excluded in 11 of them. Tenofovir was associated with greater GFR reductions in observational studies compared with clinical trials, and when it was included within second-line or greater ART regimens, compared with first-line regimens. Tenofovir was associated with a 16%–55% relative increase in the incidence of CKD in 3 large observational studies (sample sizes ranging from 6843 to 10 841) [46, 156, 157], corresponding to 2–5 excess CKD cases per 1000 patient-years. In one case series of tenofovir-associated acute kidney injury, the average duration of tenofovir exposure was 11 months, with a range of 1–29 months [129]. Tenofovir also was associated with greater GFR declines when combined with atazanavir, amprenavir, or a ritonavir-boosted protease inhibitor in some studies [54, 129, 154, 158–161], suggesting increased risk for nephrotoxicity with these combinations. In studies where tenofovir was discontinued because of kidney damage, GFR and proximal tubule dysfunction tended to improve during follow-up, but they did not always return to baseline [46, 157, 162].

Indinavir has consistently been linked to increased risks of nephrolithiasis and CKD [35, 46, 163–166], and is infrequently used in clinical practice because of these concerns. Atazanavir has been associated with increased risks of reduced GFR, nephrolithiasis, proximal tubular dysfunction, interstitial nephritis, and acute kidney injury, independent of concurrent tenofovir use [46, 139, 154, 167–169]. Studies from the D:A:D and the EuroSIDA cohorts found an increased risk of CKD in association with the use of either ritonavir-boosted atazanavir or lopinavir or unboosted atazanavir that was independent of tenofovir use in multivariate models [46, 170]. However, 2 other large cohort studies did not find statistically significant associations with atazanavir or lopinavir/ritonavir and CKD [156, 157]. It is therefore not known whether boosted protease inhibitors in general or specific protease inhibitors should be avoided in patients with CKD, even when tenofovir is not being used concurrently.

Cobicistat is a potent cytochrome P450 3A (CYP3A) inhibitor that is used as a pharmacologic boosting agent, which is currently available in a coformulated preparation with elvitegravir, emtricitabine, and tenofovir, but is expected be marketed as a monodrug product. In healthy volunteers, cobicistat was associated with small, nonprogressive increases in serum creatinine that corresponded with an estimated GFR decline of approximately 10 mL/minute/1.73 m^2 [171]. However, these creatinine increases may have been mediated by reduced tubular secretion of creatinine, rather than decreased glomerular filtration, as GFR did not change when measured by iohexol clearance, and serum creatinine concentrations returned to baseline upon discontinuation of cobicistat. Cobicistat inhibits several renal transport proteins in tubular epithelial cells, including multidrug and toxin extrusion efflux proteins, of which creatinine is a substrate [172]. In a phase 3 randomized trial of ART-naive, HIV-infected participants, elvitegravir/cobicistat/emtricitabine/tenofovir was associated with larger declines in creatinine-based estimated GFR compared to atazanavir in combination with ritonavir and emtricitabine/tenofovir (median changes at week 48: −14.1 mL/minute/1.73 m^2; interquartile range {IQR}, −21.0 to −7.1] and −9.6 mL/minute/1.73 m^2 [IQR, −17.0 to −1.7], respectively) [173]. Elvitegravir/cobicistat/emtricitabine/tenofovir is not recommended in patients with estimated creatinine clearance <70 mL/minute and should be discontinued if estimated creatinine clearance falls below 50 mL/min.

Small, stable increases in serum creatinine also were seen within the first 2–4 weeks after initiating rilpivirine (by 5.69–9.07 µmol/L, or 0.06–0.10 mg/dL), a nonnucleoside reverse transcriptase inhibitor [174], and dolutegravir (by 10.2–13.4 µmol/L, or 0.12–0.15 mg/dL), an integrase inhibitor [175]. As with cobicistat and trimethoprim [176], these drugs inhibit creatinine secretion by renal transport proteins within tubular epithelial cells without reducing glomerular filtration [177].

Progress With Kidney Transplantation in HIV-Infected Persons

Experience with kidney transplantation in HIV-infected persons has expanded considerably since these guidelines were

last published in 2005 [2]. Kidney transplantation was rarely attempted in HIV-infected individuals prior to the advent of combination ART, and was associated with poorer outcomes than in HIV-uninfected transplant patients [178]. As the virologic and clinical durability of ART improved, interest was rekindled in solid organ transplantation for the HIV-infected patient population given the strong survival advantages that are associated with kidney transplantation in the general population, wherein one study estimated a 68% lower risk of mortality for kidney transplant recipients, compared with patients receiving renal replacement therapy who remained on the transplant waiting list (relative risk, 0.32 [95% confidence interval {CI}, .30–.35]) [179].

Initial findings from a multicenter, prospective, nonrandomized trial of kidney transplantation in HIV-infected candidates in the United States were published in 2010 [106]. The study included 150 transplant recipients and median follow-up of 1.7 years posttransplant, which is the largest clinical experience to date in HIV-infected subjects. Subjects with ESRD were eligible for the trial if they had a CD4 cell count of at least 200 cells/μL and undetectable plasma HIV RNA levels while being treated with a stable antiretroviral regimen. Patients with adequately treated opportunistic infections were eligible, except those with a history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, primary central nervous system lymphoma, or visceral Kaposi sarcoma.

The HIV-infected participant survival rates at 1 and 3 years were 94.6% and 88.2%, with corresponding graft survival rates of 90.4% and 73.7%, respectively [106]. These survival rates were similar to rates in the US Scientific Registry of Transplant Recipients during the same time period [106]. In a multivariate model, use of antithymocyte globulin induction, treated rejection, and receipt of a transplant from a deceased donor were significantly associated with graft failure.

Although patient and graft survival rates in this trial were similar to those in the general transplant registry population, rates of acute graft rejection were substantially higher in HIV-infected study participants. The cumulative acute rejection rate was 31% in the HIV-infected cohort at 1 year, compared with 12.3% in the general transplant registry population [106]. In a multivariate model, increased risk of acute graft rejection was significantly associated with use of a kidney from a deceased donor and cyclosporine use. A higher posttransplant CD4 cell count was associated with a trend toward reduced risk of acute rejection ($P = .07$). Data from earlier studies have also suggested that HIV-infected transplant recipients are at increased risk of acute rejection, with rejection rates ranging from 13% to 67% [180–195]. The reasons for increased risk of organ rejection in HIV-infected recipients have not been clarified, although immune system dysregulation and interactions between antiretroviral and immunosuppressant drugs are potential mechanisms.

Long-term follow-up will be needed to determine if HIV-infected transplant recipients are at higher risk of opportunistic infections or malignancies than non-HIV-infected transplant recipients.

RECOMMENDATIONS FOR KIDNEY DISEASE SCREENING

I. How Should HIV-Infected Patients Be Monitored for Kidney Function and Kidney Damage?

Recommendations

1. We recommend monitoring creatinine-based estimated GFR when ART is initiated or changed, and at least twice yearly in stable HIV-infected patients, using the same estimation method to track trends over time. More frequent monitoring may be appropriate for patients with additional kidney disease risk factors (strong, low).

2. We suggest monitoring kidney damage with urinalysis or a quantitative measure of albuminuria/proteinuria at baseline, when ART is initiated or changed, and at least annually in stable HIV-infected patients. More frequent monitoring may be appropriate for patients with additional kidney disease risk factors (weak, low).

Evidence Summary

The goals of monitoring kidney function and damage in patients infected with HIV are to (1) identify conditions for which effective treatments are available, (2) detect drug nephrotoxicity, and (3) estimate GFR for proper dose adjustments of renally cleared drugs in individuals with reduced kidney function. As with routine laboratory monitoring of most medical conditions, there are few data that directly address the clinical benefits of monitoring kidney function or damage in patients infected with HIV or in other patient populations. The panel recommends that clinicians monitor GFR a minimum of twice yearly, and a urinalysis a minimum of once yearly in stable patients on ART. More frequent monitoring may be considered in patients with additional risk factors for kidney disease (Table 4).

One African randomized trial compared clinical monitoring alone with clinical plus routine laboratory monitoring— chemistry panel (including serum creatinine), complete blood count, and CD4 cell count—in 3321 HIV-infected patients initiating ART (the majority with tenofovir) [196]. Compared with participants assigned to the laboratory monitoring arm, individuals assigned to the clinical monitoring arm experienced statistically higher rates of HIV disease progression or death, but similar rates of serious adverse events. These data suggest that routine chemistry, hematologic, and CD4 cell monitoring are beneficial, but the independent contribution of kidney function monitoring cannot be determined.

A major rationale for monitoring GFR and albuminuria/ proteinuria is the timely identification of HIVAN, an aggressive

kidney disease for which effective treatment is available [55, 60, 61, 197–202]. US and international HIV treatment guidelines consider HIVAN an indication for ART, independent of CD4 cell count [125, 126, 203, 204]. Although HIVAN is rare in HIV-infected patients on suppressive ART, clinically important reductions in GFR due to drug toxicity and other kidney diseases are common in this population [44, 46, 107, 108, 157].

Monitoring Kidney Function. A number of GFR estimation equations are available (Table 2). The CKD-EPI creatinine equation, which includes data on race, sex, and age, has been shown to be more accurate and precise than the older MDRD equation in both the general population [30] and in HIV-infected persons [28, 29], and is the preferred creatinine-based GFR estimation method [1]. The MDRD equation underestimates exogenously measured GFR in individuals with normal or near-normal kidney function. The Cockcroft–Gault equation estimates creatinine clearance rather than GFR and is less accurate and precise than the MDRD and CKD-EPI equations [205]. However, the Cockcroft–Gault equation has historically been used for recommendations regarding the dosing of renally cleared drugs in patients with kidney dysfunction. Most clinical laboratories report creatinine-based GFR estimated by either the CKD-EPI or MDRD equations, and online calculators are available to assist clinicians (https://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm).

Studies from the general population and HIV-infected persons in which GFR was measured exogenously have reported similar overall performance between the CKD-EPI equations based on either creatinine alone or cystatin C alone, whereas the CKD-EPI equation that uses both creatinine and cystatin C has been reported to be more precise and accurate than either of the single-biomarker equations [15, 23, 28, 29]. The CKD-EPI equations are based on measures of creatinine and cystatin C that are calibrated to standard reference materials. Reporting of calibrated creatinine values is nearly universal, but clinicians should be aware that, at present, many clinical laboratories do not report cystatin C values that are calibrated to an international standard [206]. Use of the CKD-EPI combined biomarker equation or an exogenous measure of GFR (eg, iohexol clearance) may be helpful when estimated GFR–creatinine is near 60 mL/minute/1.73 m^2, and a more accurate or precise GFR estimate would directly affect clinical management, such as with dose adjustment of a medication with a narrow therapeutic index [1, 207].

Monitoring Albuminuria/Proteinuria. A large body of observational data, both from the general population and from cohorts of HIV-infected persons, shows strong and consistent associations between albuminuria/proteinuria and clinical outcomes (mortality, cardiovascular disease, and ESRD) that are independent of GFR [10–12, 27, 41, 52, 115]. Additionally, data from the general population also indicate that use of

angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) has clinical benefits in individuals with albuminuria/proteinuria, particularly in patients with diabetes and or hypertension (refer to Recommendation 12) [208–211], which provides a rationale for periodic urine monitoring in high-risk populations.

Urinalysis, which provides a semiquantitative measure of protein concentration in the urine, is an acceptable screen for albuminuria/proteinuria and has the advantage of detecting other abnormalities. For example, glycosuria in the absence of elevated blood glucose is considered a specific marker of proximal tubular dysfunction (Table 5) and may identify early tenofovir nephrotoxicity [143]. Proteinuria ≥1+ on urinalysis should be quantified with either albumin-to-creatinine ratio (often called a urine "microalbumin" test) or a protein-to-creatinine ratio (Table 3) [1]. Diabetes management guidelines recommend monitoring albuminuria annually, and it is appropriate to apply these recommendations to HIV-infected diabetics [212].

Benefits: Routine monitoring of kidney function (GFR) and kidney damage (albuminuria/proteinuria or other urine abnormalities) may lead to earlier diagnosis of underlying conditions, removal of nephrotoxic agents, dose adjustment of renally cleared medications with reduced kidney function, or interventions that ameliorate the progression of kidney disease and reduce the risk of cardiovascular events.

Harms: Routine monitoring may lead to patient anxiety, diagnostic evaluations that have risks, and interventions of uncertain benefit.

RECOMMENDATIONS FOR THE EVALUATION OF HIV-RELATED CKD

II. How Should HIV-Related Kidney Disease Be Evaluated and When Is Referral to a Nephrologist Appropriate?
Recommendations

3. We recommend that the evaluation of new-onset or newly discovered kidney disease in HIV-infected persons include serum chemistry panel; complete urinalysis; quantitation of albuminuria (albumin-to-creatinine ratio from spot sample or total albumin from 24-hour collection); assessment of temporal trends in estimated GFR, blood pressure, and blood glucose control (in diabetic patients); markers of proximal tubular dysfunction (particularly if treated with tenofovir); a renal sonogram; and review of prescription and over-the-counter medications for agents that may cause kidney injury or require dose modification for decreased kidney function (strong, low).

4. We recommend that HIV-infected patients with kidney disease be referred to a nephrologist for diagnostic evaluation when there is a clinically significant decline in GFR (ie, GFR decline by >25% from baseline and to a level <60 mL/minute/1.73 m^2) that fails to resolve after potential nephrotoxic drugs

are removed, there is albuminuria in excess of 300 mg per day, hematuria is combined with either albuminuria/proteinuria or increasing blood pressure, or for advanced CKD management (GFR <30 mL/minute/1.73 m^2) (strong, low).

5. When possible, we recommend establishing permanent dialysis access, ideally an arteriovenous fistula or peritoneal catheter, prior to the anticipated start of renal replacement therapy to avoid the use of higher-risk central venous catheters for hemodialysis (strong, moderate).

6. When possible, we recommend avoiding the use of peripherally inserted central catheters and subclavian central venous catheters in patients with HIV who are anticipated to need dialysis in the future because these devices can damage veins and limit options for permanent hemodialysis access (strong, moderate).

Evidence Summary

Diagnostic Considerations and Initial Evaluation. The diagnostic evaluation of kidney disease in an HIV-infected individual is similar to that in HIV-negative individuals, although the differential diagnosis should be expanded to include HIV-related diagnoses including HIVAN, HIV immune complex kidney disease, and HIV-related thrombotic microangiopathy [55, 61, 88, 91, 93, 213]; nephrotoxic effects of antiretroviral agents and other medications; and kidney disease related to hepatitis B or C coinfection [90, 98, 214–217]. Measuring markers of proximal tubular dysfunction (Table 5) may be useful in patients with worsening kidney function while receiving tenofovir. Two indicators—glycosuria with normal serum glucose and urinary phosphorous wasting (as determined by fractional excretion of phosphorous) with low serum phosphorous—are highly specific markers of proximal tubular dysfunction. However, these manifestations are uncommon in clinical practice and their absence should not be used to exclude tenofovir as a cause of GFR decline [143].

In addition to blood and urine studies, existing guidelines for CKD management in the general population recommend renal ultrasound as part of the routine evaluation, noting that ultrasound can identify evidence of obstruction, chronic infection or reflux, and polycystic kidney disease, as well as providing information on kidney size and echogenicity [8].

Nephrology Referral. Referral to a nephrologist, when feasible, is appropriate to establish a diagnosis by kidney biopsy, to guide the use of renoprotective therapy, to identify and manage complications of CKD, and to prepare patients with progressive CKD for renal replacement therapy. Nephrology referral should be considered in patients with markers of severe disease, including clinically significant GFR decline, albuminuria >300 mg per day, or hematuria of kidney origin [8, 218–220].

As a result of the broad differential diagnosis and the limited sensitivity and specificity of noninvasive testing, kidney biopsy should be considered in HIV-infected patients in whom a definitive diagnosis may affect management or inform prognosis. Although HIVAN classically presents with heavy proteinuria in the setting of advanced HIV disease, data from retrospective biopsy series suggest that noninvasive diagnostic testing lacks sufficient sensitivity and specificity to distinguish HIVAN from non-HIVAN diagnoses [55, 197, 221–223]. Biopsy confirmation of HIVAN is helpful to guide decisions about adjunctive use of corticosteroids, which have evidence for benefit in HIVAN but have risks (discussed in Section VI) and may not be indicated for alternative diagnoses (eg, HIV immune complex kidney disease).

Kidney biopsy involves a <10% risk of complications, and deaths are rare [224–227]. In a single-center review of 1116 kidney biopsies (performed under ultrasound guidance) in HIV-infected and HIV-negative patients, the rates of any complication (8.6% vs 7.2%) and major complications (treatment-emergent bleeding or hypotension) (3.3% vs 2.6%) were similar in the 2 groups, respectively [224]. Retrospective data support a 24-hour postbiopsy observation period to identify and manage any resulting complications [226].

Two important objectives of nephrology referral in advanced CKD are management of complications and preparation for renal replacement therapy. Complications in advanced CKD are common and include hypertension, anemia [228–230], metabolic acidosis, and disorders of bone mineral metabolism. Clinical practice guidelines are available that address the medical management of advanced CKD including anemia [231] and disorder of bone mineral metabolism and metabolic acidosis [232, 233].

Nephrologists also educate and prepare patients with advanced CKD for renal replacement therapy, including hemodialysis, peritoneal dialysis, and kidney transplantation. Although data specific to HIV-infected individuals are lacking, data from the general CKD population suggest that earlier (as opposed to later) referral to a nephrologist is associated with improved outcomes among patients nearing ESRD. A recent systematic review of the literature concluded that nephrology referral at least 1 year prior to the initiation of dialysis was associated with improved survival [234]. This conclusion is consistent with current recommendations from the National Kidney Foundation's Kidney Disease Outcome Quality Initiative to refer all patients with estimated GFR <30 mL/minute/1.73 m^2 and to consider referral in patients with GFR 30–59 mL/minute/1.73 m^2 and ESRD risk factors [8].

Dialysis Modality. The choice of dialysis modality should consider patient preference, comorbid conditions, and the ability to establish optimal dialysis access. In particular, patients with a history of intravenous drug use or peripherally inserted central venous catheters may have inadequate veins for the creation of an arteriovenous fistula, whereas patients with

prior abdominal surgery or trauma may have adhesions that could interfere with the placement or function of a peritoneal catheter. Although small studies have suggested an increased risk of peritonitis and hospitalization among HIV-infected patients undergoing peritoneal dialysis [102], mortality data from the US Renal Data System demonstrate no difference in the survival of HIV-infected ESRD patients treated with peritoneal dialysis vs hemodialysis in the antiretroviral era [235].

Because of the high risk of bacteremia associated with the use of central venous catheters [236], permanent dialysis access should be planned and established prior to the anticipated initiation of dialysis, consistent with recommendations from the National Kidney Foundation [8]. Although data are limited, small studies suggest improved patency and decreased infection rates with arteriovenous fistulae compared with arteriovenous grafts in HIV-infected patients [237, 238], similar to the benefit observed in the general ESRD population [102, 239, 240]. It may be reasonable to defer permanent dialysis access in individuals with a potentially reversible etiology such as HIVAN or medication toxicity, if recovery is anticipated with initiation of ART or removal of the offending agent.

Benefits: Definitive diagnosis of kidney disease may guide therapy and allow more accurate prognostication. A nephrologist may facilitate care and improve outcomes in HIV-infected patients with CKD.

Harms: Invasive tests, such as kidney biopsy, have risks of complications and may fail to yield information that improves management.

RECOMMENDATIONS FOR THE CLINICAL MANAGEMENT OF HIV-INFECTED PATIENTS WITH CKD

III. How Should Antiretroviral Therapy Be Managed in Patients With CKD or End-Stage Renal Disease?
Recommendations
7. We recommend that clinicians prescribe ART and encourage persistence with therapy in HIV-infected patients who have CKD or ESRD, as ART reduces mortality but is underused in this patient population (strong, moderate).

8. We recommend that clinicians use either the CKD-EPI creatinine equation to estimate GFR or the Cockcroft–Gault equation to estimate creatinine clearance when dosing antiretroviral drugs or other drugs that require reduced doses in patients with reduced kidney function (strong, moderate).

9. We recommend that patients with biopsy-confirmed or clinically suspected HIVAN receive ART to reduce the risk of progression to ESRD (strong, moderate).

10. In patients infected with HIV who have a GFR <60 mL/minute/1.73 m^2, we recommend avoiding tenofovir and other potential nephrotoxic drugs (eg, nonsteroidal anti-inflammatory drugs) when feasible (strong, low).

11. In tenofovir-treated patients who experience a confirmed GFR decline by >25% from baseline and to a level <60 mL/minute/1.73 m^2, we recommend substituting alternative antiretroviral drug(s) for tenofovir, particularly in those with evidence of proximal tubular dysfunction (strong, low).

Evidence Summary
Benefits of ART in Patients Infected With HIV and CKD or ESRD.
Observational data demonstrate that the survival benefits of ART extend to patients with ESRD who are receiving renal replacement therapy [101, 105]. However, studies have consistently shown underuse of ART in HIV-infected individuals with CKD or ESRD [101, 103, 105, 124, 201, 241–243].

Antiretroviral Drug Dose Adjustments With Reduced Kidney Function.
Incorrect dosing of antiretroviral drugs at reduced levels of kidney function is common in both inpatient and outpatient settings, and is a major source of ART-associated medication errors [124, 244–246]. Higher mortality was associated with ART underexposure or incorrect ART dosing in 2 studies among HIV-infected patients with CKD [124, 244]. With the exception of abacavir, dose reductions are required for nucleoside and nucleotide reverse transcriptase inhibitors when kidney function is reduced (Table 6). The necessity for differential dose adjustments of one or more components usually precludes the use of fixed-dose combinations in patients with moderately to severely impaired kidney function.

Clinicians should use estimated creatinine clearance or GFR to modify the dose of renally cleared drugs in the setting of kidney insufficiency (Table 6 and Table 7 summarize recommended dose modifications for antiretroviral drugs and other commonly used agents, respectively). The US Food and Drug Administration has historically required that creatinine clearance estimated by the Cockcroft–Gault equation be used for pharmacokinetic studies of drugs in adults with decreased kidney function [1]. However, KDIGO guidelines recommend that clinicians use the method that provides the most accurate assessment of GFR, which, at present, is the CKD-EPI equation based on creatinine alone, cystatin C alone, or both biomarkers together [1].

The C-C chemokine receptor type 5 inhibitor, maraviroc, is contraindicated in patients with creatinine clearance <30 mL/minute when combined with a potent CYP3A inhibitor (eg, ritonavir), and should be used with caution (and potentially at reduced dose) in all other patients with creatinine clearance <30 mL/minute because of increased risk of postural hypotension. No dose adjustments are needed for protease inhibitors, nonnucleoside reverse transcriptase inhibitors (NNRTIs), or the integrase inhibitors raltegravir and dolutegravir in patients with CKD. Atazanavir concentrations are decreased by 25%–43%

Table 6. Dosing of Antiretroviral Drugs for HIV-Infected Adults With Chronic Kidney Disease or End-Stage Renal Disease

Antiretroviral Drug and Dosing Category	Dosage	Comments
Nucleoside reverse transcriptase inhibitors		
Zidovudine		[397–404]
Usual dosage	300 mg po bid	
Dosage for patients with CKD or ESRD		
CrCl ≥15 mL/min	No adjustment	
CrCl <15 mL/min, hemodialysis, or peritoneal dialysis	100 mg po q6–8h or 300 mg qd	Based on longer intracellular half-life [405]
Lamivudine		[406–408]
Usual dosage	150 mg po bid/300 mg po qd	
Dosage for patients with CKD or ESRD		
CrCl ≥50 mL/min	No adjustment	
CrCl 30–49 mL/min	150 mg po qd	
CrCl 15–29 mL/min	150 mg po first dose, then 100 mg po qd	
CrCl 5–14 mL/min	150 mg po first dose, then 50 mg po qd	To avoid using the liquid formulation and because of the favorable safety profile, some recommend the of use lowest available tablet dose of 100 mg (lamivudine hepatitis B formulation) or 150 mg (lamivudine) daily in advanced renal disease.
CrCl <5 mL/min, hemodialysis, or peritoneal dialysis	50 mg po first dose, then 25 mg po qd	
Abacavir		[409]
Usual dosage	300 mg po bid/600 mg po qd	
Dosage for patients with CKD or ESRD		
All CrCl	No adjustment	
Receiving hemodialysis	No adjustment[a]	
Receiving peritoneal dialysis	Unknown, use with caution	
Stavudine		[410]
Body weight ≥60 kg		
Usual dosage	40 mg po bid (WHO recommends 30 mg po bid)	
Dosage for patients with CKD or ESRD		
CrCl >50 mL/min	No adjustment	
CrCl 26–50 mL/min	20 mg po bid	
CrCl ≤25 mL/min	20 mg po qd	
Receiving hemodialysis	20 mg po qd[a]	Give post-HD, on days of HD
Receiving peritoneal dialysis	Unknown, use with caution (dose reduction needed)	
Body weight <60 kg		
Usual dosage	30 mg po bid	
Dosage for patients with CKD or ESRD		
CrCl >50 mL/min	No adjustment	
CrCl 26–50 mL/min	15 mg po bid	
CrCl ≤25 mL/min	15 mg po qd	
Receiving hemodialysis	15 mg po qd[a]	
Receiving peritoneal dialysis	Unknown, use with caution (dose reduction needed)	
Didanosine delayed-release capsules		[411–413]
Body weight ≥60 kg		
Usual dosage	400 mg po qd	

Table 6 continued.

Antiretroviral Drug and Dosing Category	Dosage	Comments
Dosage for patients with CKD or ESRD		
CrCl ≥60 mL/min	No adjustment	
CrCl 30–59 mL/min	200 mg po qd	
CrCl 10–29 mL/min	125 mg po qd	
CrCl <10 mL/min	125 mg po qd	
Receiving hemodialysis	125 mg po qd[a]	
Receiving peritoneal dialysis	125 mg po qd	
Body weight <60 kg		
Usual dosage	250 mg po qd	
Dosage for patients with CKD or ESRD		
CrCl ≥60 mL/min	No adjustment	
CrCl 30–59 mL/min	125 mg po qd	
CrCl 10–29 mL/min	125 mg po qd	
CrCl <10 mL/min, hemodialysis, or peritoneal dialysis	Do not use didanosine delayed-release capsules; use 75 mg (pediatric powder for suspension) qd	
Emtricitabine		[414]
Usual dosage	200 mg po qd	
Dosage for patients with CKD or ESRD		
CrCl ≥50 mL/min	No adjustment	
CrCl 30–49 mL/min	200 mg po q48h	
CrCl 15–29 mL/min	200 mg po q72h	
CrCl <15 mL/min	200 mg po q96h	
Receiving hemodialysis	200 mg po q96h[a]	
Receiving peritoneal dialysis	Unknown, use with caution (dose reduction needed)	
Tenofovir disoproxil fumarate		[415]
Usual dosage	300 mg po qd	
Dosage for patients with CKD or ESRD		
CrCl ≥50 mL/min	No adjustment	
CrCl 30–49 mL/min	300 mg po q48h	This guideline recommends avoiding tenofovir in patients with CrCl <50 mL/min who are not on hemodialysis
CrCl 10–29 mL/min	300 mg po q72–96h	
Receiving hemodialysis	300 mg po every 7 d[a] (an additional dose may be needed if >12 h HD per week)	
Receiving peritoneal dialysis	Unknown, use with caution (dose reduction needed)	
Emtricitabine/tenofovir disoproxil fumarate		[416]
Usual dosage	200 mg/300 mg po qd	
Dosage for patients with CKD or ESRD		
CrCl ≥50 mL/min	No adjustment	
CrCl 30–49 mL/min	One tablet po q48h	
CrCl <30 mL/min	Should not use combination tablet	
Non-nucleoside reverse transcriptase inhibitors	No dose adjustment needed with CKD or ESRD for all NNRTIs	
Nevirapine		[417–421]
Usual dosage	200 mg po bid (after 2 wks of 200 mg po qd)	

Table 6 continued.

Antiretroviral Drug and Dosing Category	Dosage	Comments
Efavirenz		[422–424]
Usual dosage	600 mg po qhs	
Delavirdine		[425]
Usual dosage	400 mg po tid	
Etravirine		
Usual dosage	200 mg po bid	
Rilpivirine		
Usual dosage	25 mg po qd	
Protease inhibitors	No dose adjustment needed with CKD or ESRD for all PIs	[426]
Indinavir		[427, 428]
Usual dosage	800 mg po bid (in combination with ritonavir 100 mg bid)	
Saquinavir		[418, 429, 430]
Usual dosage	1000 mg po bid (in combination with ritonavir 100 mg bid)	
Nelfinavir		[419, 431, 432]
Usual dosage	1250 mg po bid or 750 mg tid	
Fosamprenavir		[433]
Usual dosage	1400 mg po qd (in combination with ritonavir 100–200 mg qd) OR 700 mg po bid (in combination with ritonavir 100 mg bid)	
Ritonavir (used in combination with a second protease inhibitor as a pharmacokinetic enhancer)	100–400 mg per day	[421, 429, 434]
Lopinavir/ritonavir		[435, 436]
Usual dosage	400 mg/100 mg po bid OR 800 mg/200 mg po qd. LPV trough lower in HD; use with caution in PI-experienced patients [247]	
Atazanavir		[437]
Usual dosage	400 mg po qd OR 300 mg po qd (in combination with ritonavir 100 mg po qd) Avoid unboosted ATV in HD. Avoid boosted ATV in treatment-experienced patients on HD	
Darunavir		
Usual dosage	800 mg po qd (in combination with ritonavir 100 mg po qd) OR 600 mg po bid (in combination with ritonavir 100 mg bid)	
Entry/fusion inhibitors	No dose adjustment needed with CKD or ESRD	
Enfuvirtide		[438]
Usual dosage	90 mg subcutaneous bid	
Integrase strand transfer inhibitors		
Raltegravir	No dose adjustment needed with CKD or ESRD	
Usual dosage	400 mg po bid	
Elvitegravir, cobicistat, tenofovir disoproxil fumarate, emtricitabine (Stribild)		
Usual dosage if CrCl ≥70 mL/min	1 tablet (150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine, 300 mg tenofovir disoproxil fumarate) po qd with food	
CrCl <50 mL/min	Discontinue	
Dolutegravir		
Usual dose	50 mg once daily (ARV- or INSTI-naive patients) 50 mg twice daily (INSTI-experienced with certain INSTI mutations)	
CrCl >30 mL/min	Usual dose	

Table 6 continued.

Antiretroviral Drug and Dosing Category	Dosage	Comments
CrCl <30 mL/min	Use with close monitoring	Dolutegravir concentrations decreased by 40%. Clinical significance unknown, but INSTI-experienced patients with INSTI mutations may be at increased risk for virologic breakthrough.
CCR5 antagonist		
Maraviroc		
Usual dosage	300 mg po bid (adjustment needed with most PI and NNRTI coadministration)	
Dosage for patients with CKD or ESRD		
CrCl >30 mL/min	No dose adjustment	
CrCl <30 mL/min	300 mg po bid. Reduce dose to 150 mg po bid if orthostatic hypotension occurs. Avoid maraviroc with CYP3A4 inhibitor (eg, macrolides, protease inhibitors)	

Abbreviations: ARV, antiretroviral; ATV, atazanavir; bid, twice daily; CKD, chronic kidney disease; CrCl, creatinine clearance; CYP3A4, cytochrome P450 isoenzyme 3A4; ESRD, end-stage renal disease; HD, hemodialysis; INSTI, integrase strand transfer inhibitor; LPV, lopinavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; po, by mouth; qd, every day; qhs, every night at bedtime; tid, 3 times daily; WHO, World Health Organization.

[a] Administer dose after hemodialysis on days when hemodialysis performed.

in patients on hemodialysis. The manufacturer recommends that clinicians should avoid non-ritonavir-boosted atazanavir in hemodialysis patients and that ritonavir-boosted atazanavir should not be initiated in hemodialysis patients who are ART experienced. Similarly, one study reported that trough concentrations of ritonavir-boosted lopinavir were reduced in hemodialysis patients [247]; although the clinical significance of this is unknown, clinicians should monitor antiviral efficacy closely in protease inhibitor treatment–experienced patients.

Benefits of ART in HIVAN. ART has been associated with a lower incidence of HIVAN, and with improved kidney function and lower ESRD risk in observational studies of patients with biopsy-confirmed or clinically suspected HIVAN. Six observational studies examined the impact of ART on the risk of developing HIVAN, or the risk of progressive kidney disease among patients with established HIVAN [60, 197–199, 201, 248]. Patients who received ART, compared with those who did not, had a significantly a longer time to ESRD (18.4 months vs 3.9 months) and a higher overall renal survival (18.1% vs 12.5%) in a retrospective series of 36 patients with biopsy-confirmed HIVAN [201]. In a retrospective case series of 11 patients with clinically suspected HIVAN, zero of 5 patients who received ART had a doubling of the serum creatinine, compared with 6 of 6 patients who did not, all of whom also progressed to ESRD [198]. In a second retrospective series of 19 patients with HIVAN (biopsy confirmed or clinically defined), ART use was associated with a slower rate of GFR decline (0.08 vs 4.3 mL/minute/month, respectively; $P = .04$) [199]; and only one case of HIVAN was identified among 23 patients who had a plasma HIV RNA level <400 copies/mL, compared with 23 cases of

HIVAN among 63 patients with a plasma HIV RNA $\geq$ 400 copies/mL ($P < .01$) in a single-center, retrospective case series of patients who underwent kidney biopsy for clinical indications [197]. However, progression to ESRD within 3 months of HIVAN diagnosis did not differ between those who did and those who did not achieve HIV RNA suppression to <200 copies/mL with ART in a retrospective cohort study that included 61 patients with HIVAN (45 biopsy confirmed/16 clinically defined) [248]. On the basis of these studies, guidelines from DHHS and the International Antiviral Society include HIVAN among the indications to initiate ART [125, 126, 203].

Benefits of ART in Non-HIVAN CKD. HIV-associated thrombotic microangiopathy (TMA) appears to benefit from ART, wherein ART initiation was associated with clinical remissions in patients with TMA, and marked declines in the incidence of TMA were documented to be concurrent with widespread ART use [94, 249, 250]. It is not known whether ART prevents or modifies the course of other HIV-related kidney diseases, including HIV immune complex kidney disease.

In large observational studies, either ART use, or ART-associated increases in CD4 cell counts or decreases in plasma HIV RNA, were associated with a reduced CKD risk, GFR improvements, or slower rates of GFR decline [40, 46, 53, 54, 57, 58, 251–254]. The causes of kidney disease in these patients were not known and may have included HIVAN in some, particularly in studies from sub-Saharan Africa [253, 254]. In the Strategies for Management of Antiretroviral Therapy (SMART) study, participants who were randomized to episodic ART had a trend toward fewer fatal and nonfatal ESRD events than did those assigned to continuous ART, but there was no difference in ESRD events

Table 7. Dosing of Antimicrobial Agents for HIV-Infected Patients With Chronic Kidney Disease or End-Stage Renal Disease

Drug and Dosing Category	Dosage
Acyclovir	
Usual dosage (high dose for zoster)	200–800 mg po 3–5 times per day; 5–10 mg/kg of ideal body weight IV q8h
Dosage for patients with CKD or ESRD	
CrCl 25–50 mL/min	200–800 mg po 3–5 times per day; 5–10 mg/kg of ideal body weight IV q12h
CrCl 10–24 mL/min	200–800 mg po q8h; 5–10 mg/kg of ideal body weight IV q24h
CrCl <10 mL/min	200–800 mg q12h; 2.5–5 mg/kg of ideal body weight IV q24h
CrCl <10 mL/min receiving hemodialysis	2.5–5 mg/kg of ideal body weight IV q24h; on days of HD, dose post-HD
Adefovir	
Usual dosage	10 mg po q24h
Dosage for patients with CKD or ESRD	
CrCl 30–49 mL/min	10 mg q48h
CrCl 10–29 mL/min	10 mg q72h
Receiving hemodialysis	10 mg every 7 d following dialysis
Amphotericin B deoxycholate	
Usual dosage	0.7–1.0 mg/kg IV q24h
Dosage for patients with CKD or ESRD	No dose adjustment (but consider lipid amphotericin formulations, azoles, or echinocandins)
Amphotericin B colloidal dispersion	
Usual dosage	3.0–6.0 mg/kg of actual body weight IV q24h
Dosage for patients with CKD or ESRD	No dose adjustment
Amphotericin B lipid complex	
Usual dosage	5 mg/kg of actual body weight IV q24h
Dosage for patients with CKD or ESRD	No dose adjustment
Amphotericin B liposomal	
Usual dosage	4.0–6.0 mg/kg of actual body weight IV q24h
Dosage for patients with CKD or ESRD	No dose adjustment
Cidofovir	
Usual dosage	5 mg/kg IV q week × 2 wk, then every other week (with probenecid and hydration)
Dosage for patients with CKD or ESRD	
Increase in serum creatinine level to 0.3–0.4 above baseline	3 mg/kg of body weight IV every other week (with probenecid and hydration)
Increase in serum creatinine level to ≥0.5 above baseline or development of grade 3+ proteinuria	Discontinue
Baseline serum creatinine level >1.5, CrCl ≤55 mL/min, or grade ≥2+ proteinuria	Not recommended
Ciprofloxacin	
Usual dosage	500–750 mg po q12h OR 400 IV q8h-12h
Dosage for patients with CKD or ESRD	
CrCl 30–50 mL/min	500–750 mg q12h OR 400 IV q12h
CrCl <30 mL/min	250–500 mg q18–24h OR 400 IV q24h
Receiving hemodialysis	250–500 mg q24h OR 200–400 IV q24h (days of HD dose post-HD)
Clarithromycin	
Usual dosage	500 mg po q12h
Dosage for patients with CKD or ESRD	Reduce dose by one-half if CrCl <30 mL/min. With PI coadministration, dose reduction by 50% with CrCl 30–60 mL/min and 75% reduction with CrCl <30 mL/min
Ethambutol	
Usual dosage	15–25 mg/kg of body weight po q24h
Dosage for patients with CKD or ESRD	
CrCl 10–50 mL/min	15–25 mg/kg of body weight po q24–36h
CrCl <10 mL/min	15–25 mg/kg of body weight po q48h
Famciclovir	
Usual dosage	500 mg po q12h (HSV) or 500 q8h (VZV)
Dosage for patients with CKD or ESRD	
CrCl 20–39 mL/min	500 mg q24h
CrCl <20 mL/min	250 mg q24h
Receiving hemodialysis	250 mg after each dialysis

Table 7   continued.

Drug and Dosing Category		Dosage
Fluconazole		
Usual dosage		200–1200 mg po q24h
Dosage for patients with CKD or ESRD		
CrCl ≤50 mL/min		Half-dose
Receiving hemodialysis		Full dose after dialysis
Flucytosine		Monitor levels: target 30–80 µg/mL (2 h postdose)
Usual dosage		25 mg/kg q6h
20–40 mL/min		25 mg/kg q12h
10–20 mL/min		25 mg/kg q24h
<10 mL/min		25 mg/kg q48h
Foscarnet		
CrCl (mL/min/kg)	CMV induction treatment	CMV maintenance treatment
>1.4	90 mg/kg q12h	90 mg/kg q24h
1.0–1.4	70 mg/kg q12h	70 mg/kg q24h
0.8–1.0	50 mg/kg q12h	50 mg/kg q24h
0.6–0.8	80 mg/kg q24h	80 mg/kg q48h
0.5–0.6	60 mg/kg q24h	60 mg/kg q48h
0.4–0.5	50 mg/kg q24h	50 mg/kg q48h
<0.4	Not recommended	Not recommended
Ganciclovir		
Usual dosage		5 mg/kg q12h (I); 5 mg/kg q24h (M)
50–69 mL/min		2.5 mg/kg q12h (I); 2.5 mg/kg q24h (M)
25–49 mL/min		2.5 mg/kg q24h (I); 1.25 mg/kg q24h (M)
10–24 mL/min		1.25 mg/kg q24h (I); 0.625 mg/kg q24h (M)
<10 mL/min; HD		1.25 mg/kg TIW (I) post-HD; 0.625 mg/kg TIW (M) post-HD
Isoniazid		
Usual dosage		300 mg po q24h
Dosage for patients with CKD or ESRD		300 mg q24h (on days of HD, dose post-HD)
Levofloxacin		
Usual dosage		250–750 mg po q24h
Dosage for patients with CKD or ESRD (receiving 500 mg po q24h)		
CrCl 20–49 mL/min		500 mg loading dose, then 250 mg q24h
CrCl 10–19 mL/min		500 mg loading dose, then 250 mg q48h
Receiving hemodialysis or PD		750–500 mg loading dose, then 250–500 mg q48h (dose post-HD on days of dialysis)
Pentamidine		
Usual dosage		4.0 mg/kg of body weight IV q24h
Dosage for patients with CKD or ESRD		
CrCl 10–50 mL/min		3.0 mg/kg of body weight IV q24h (use with caution)
CrCl <10 mL/min		4.0 mg/kg of body weight IV q-48h
Pyrazinamide		
Usual dosage		20–25 mg/kg of body weight q24h
Dosage for patients with CKD or ESRD		
CrCl <10 mL/min		15–20 mg/kg q24h
Receiving hemodialysis		20 mg/kg q24h (dose post-HD on days of dialysis)
Peginterferon alfa-2a		
Usual dosage		180 µg/kg weekly
<30 mL/min; HD		135 µg/kg weekly
Peginterferon alfa-2b		
Usual dosage		1.5 µg/kg q wk
30–50 mL/min		Decrease dose by 25%
10–29 mL/min; HD		Decrease dose by 50%

Table 7 continued.

Drug and Dosing Category	Dosage
Ribavirin	
Usual dosage	800–1200 mg/day (based on weight) in 2 divided doses.
Dosage for patients with CKD or ESRD	
CrCl 30–50 mL/min	Alternate 200 mg and 400 mg qod
CrCl <30 mL/min	200 mg qd
CrCl <10 mL/min on HD	200 mg/d (limited data w/ high dropout rates)
Rifabutin	
Usual dosage	300 mg po q24h (dose adjustment needed with PI/r coadministration)
<30 mL/min	Consider 50% dose reduction
Rifampin	
Usual dosage	600 mg po q24h
Dosage for patients with CKD or ESRD	
CrCl 10–50 mL/min	100% of full dose
CrCl <10 mL/min	50%–100% of full dose
Receiving hemodialysis	50%–100% of full dose; no supplement
Receiving peritoneal dialysis	50%–100% of full dose; extra 50%–100% of full dose after receipt of peritoneal dialysis. Therapeutic drug monitoring recommended
Sulfadiazine	
Usual dosage	1–1.5 g po q6h (1.5 g for >60 kg)
10–50 mL/min	1–1.5 g po q12h
<10 mL/min; HD	1–1.5 g po q24h
Trimethoprim-sulfamethoxazole	
Usual dosage (*Pneumocystis jirovecii* pneumonia prophylaxis)	1 double-strength dose po q24h; 1 double-strength dose po 3 times per week; 1 single-strength dose po q24h
Dosage for patients with CKD or ESRD	
CrCl 15–30 mL/min	Half-dose
CrCl <15 mL/min	Half-dose or use alternative agent
Dosage for treatment of *Pneumocystis jirovecii* pneumonia	
Usual dosage	5 mg/kg (as trimethoprim component) IV or po q6–8h
In patients with CKD or ESRD	
CrCl 10–30 mL/min	5 mg per kg (as trimethoprim component) q12h
CrCl <10 mL/min	5 mg per kg (as trimethoprim component) q24h
Valacyclovir	
Usual dosage	500 mg–1 g po q8h
Dosage for patients with CKD or ESRD	
CrCl 30–49 mL/min	500 mg–1 g po q12h
CrCl 10–20 mL/min	500-1 g mg po q24h
CrCl <10 mL/min	500 mg po q24h
Valganciclovir	
Usual dosage	900 mg po q12h (I); 900 mg po q24h (M)
Dosage for patients with CKD or ESRD	
CrCl 40–59 mL/min	450 mg q12h (I); 450 mg qd (M)
CrCl 25–39 mL/min	450 mg qd (I); 450 mg qod (M)
CrCl 10–24 mL/min	450 mg qod I); 450 mg twice per wk (M)
CrCl <10 mL/min	Not recommended by US manufacturer. Use IV ganciclovir or consider 200 mg suspension tiw (I)/100 mg suspension tiw (M)
Receiving hemodialysis	Consider 200 mg oral powder formulation tiw (I); 100 mg tiw (M)

Abbreviations: CKD, chronic kidney disease; CMV, cytomegalovirus; CrCl, creatinine clearance; ESRD, end-stage renal disease; HD, hemodialysis; HIV, human immunodeficiency virus; HSV, herpes simplex virus; I, induction; IV, intravenous; M, maintenance; PD, peritoneal dialysis; PI, protease inhibitor; po, by mouth; q, every; qd, every day; qh, every hour; qod, every other day; tiw, three times a week; VZV, varicella zoster virus.

between the original treatment groups after all subjects were assigned to continuous ART upon study modification [252, 255], possibly indicating that ART may delay, but might not prevent, progression to ESRD. Available evidence, including epidemiological data showing a decline in the incidence of kidney disease since the availability of ART, consistently supports salutary effects

of ART on kidney function that are not limited to patients with HIVAN, particularly in those with low CD4 cell counts and poorly controlled HIV replication [122].

Tenofovir Use in Patients With Preexisting Kidney Disease. Given consistent data from observational studies suggesting an increased risk of CKD with tenofovir use and putative mechanisms for proximal tubular dysfunction or toxicity, it is prudent to avoid tenofovir in HIV-infected individuals with preexisting kidney disease when other effective HIV treatment options exist. Data are limited and conflicting on the safety and efficacy of tenofovir in adults with preexisting kidney disease and GFR <60 mL/minute/1.73 m^2. An increased risk of tenofovir-associated nephrotoxicity was observed in patients with baseline renal insufficiency in some, but not all, studies from North America and Europe [46, 54, 134, 157, 256]. Nevertheless, in the small numbers of patients with preexisting CKD and a GFR <60 mL/minute/1.73 m^2 who received tenofovir within 3 large US observational cohorts, worsening kidney function was not uniformly observed [54, 157, 256], although the power to detect differences between ART regimens in this small subset of patients was limited. Furthermore, in observational studies of patients who initiated ART in sub-Saharan Africa, tenofovir was well tolerated and often was associated with GFR improvements in individuals with baseline CKD, although some of these improvements may have reflected HIVAN improving with ART as many participants in these studies had advanced HIV at the time of enrollment [118, 196, 253, 257–261]. These data suggest that tenofovir may be considered with close kidney function monitoring in patients with preexisting renal insufficiency who have limited ART options or who need tenofovir for the treatment of hepatitis B infection. In such cases, the dose of tenofovir should be reduced as appropriate for the estimated creatinine clearance or GFR (Table 6), and concurrent use of other potentially nephrotoxic drugs should be avoided, including atazanavir and other boosted protease inhibitors (which have been implicated in increasing the risk of tenofovir-associated nephrotoxicity) when possible [54, 129, 154, 158, 161].

Worsening Kidney Function in Patients Receiving Tenofovir. Despite consistent evidence of proximal tubular dysfunction in association with tenofovir use, no studies have specifically examined the safety of continued tenofovir use in patients with evidence of proximal tubular dysfunction but preserved GFR. We recommend that tenofovir should be discontinued in patients who develop reduced GFR (ie, by >25% from baseline and to a level <60 mL/minute/1.73 m^2), particularly when there is evidence of proximal tubular dysfunction, such as euglycemic glycosuria or increased urinary phosphorus excretion and hypophosphatemia, or new-onset or worsening proteinuria (Table 5). Although proteinuria is not specific for proximal tubular dysfunction, some data suggest that a lower ratio of albumin-to-protein concentrations in urine (urinary albumin–total protein ratio <0.4) may be useful in distinguishing proteinuria that is predominantly due to proximal tubular disease vs glomerular disease [151, 262].

Tenofovir-Sparing ART Regimens. Existing data on the balance of kidney safety, plasma HIV RNA suppression efficacy, and cardiovascular risk are inadequate to recommend specific antiretroviral drugs or strategies for HIV-infected patients with GFR <60 mL/minute/1.73 m^2. Abacavir is the only nucleoside analogue that does not require dose modifications for renal insufficiency, making it an attractive option for patients with CKD. Abacavir has a risk of hypersensitivity reactions early in treatment, although the risk can be greatly reduced by screening for the HLA-B*57:01 allele prior to treatment [263]. Additionally, a higher risk for virologic failure was observed in participants with baseline HIV RNA >100 000 copies/mL with abacavir/lamivudine compared with tenofovir/emtricitabine in a trial in which these agents were combined with either efavirenz or ritonavir-boosted atazanavir [264]. However, the combination of abacavir/lamivudine plus dolutegravir was superior to tenofovir/emtricitabine plus efavirenz, with no differences by baseline HIV RNA level [175]. Abacavir has been associated with an increased risk of cardiovascular events in some observational studies [265–268], although other studies did not find such an association [269–271] and mechanisms for increased cardiovascular risk have not been established. Because CKD is associated with significantly increased risk of cardiovascular disease [41, 115], a causal association between abacavir and cardiovascular risk would decrease the attractiveness of this drug.

Nucleoside-sparing regimens, although attractive to eliminate the risk of nephrotoxicity that may result from tenofovir and the need to reduce doses of other nucleoside reverse transcriptase inhibitors (NRTIs), have not been prospectively studied in patients with CKD. Nucleoside-sparing regimens that have been evaluated to date in patients without CKD include protease inhibitor monotherapy [272, 273], or protease inhibitors in combination with either NNRTIs [274, 275], C-C chemokine receptor type 5 antagonists [276, 277], or integrase inhibitors [278–281]. Compared with established nucleoside analogue–based regimens, nucleoside-sparing regimens have generally been associated with more laboratory abnormalities, higher rates of virologic failure, or higher rates of emergent drug-resistant mutations. For example, in a single-arm, multicenter study of darunavir/ritonavir plus raltegravir in ART-naive subjects that was conducted through the ACTG, the rate of virologic failure (defined by a confirmed HIV RNA level >50 copies/mL) was 26% by week 48, and failure was significantly associated with a higher baseline HIV RNA (hazard ratio for failure, 3.76 [95% CI, 1.52–9.31] with baseline HIV RNA >100 000 copies/mL) [280]. All 5 subjects with integrase mutations that were identified during virologic failure in this study

had baseline HIV RNA above this threshold. Furthermore, in a recent large multicenter, randomized, noninferiority study comparing darunavir/ritonavir plus either raltegravir or tenofovir/emtricitabine in ART-naive subjects, although the nucleoside-sparing arm was noninferior in terms of virologic efficacy and safety overall, in prespecified sensitivity analyses subjects randomized to raltegravir had a higher risk of virologic failure when baseline CD4 counts were <200 cells/µL (39% vs 21%; $P = .02$), and had a trend towards higher risk of virologic failure with baseline HIV RNA >100 000 copies/mL (36% vs 27%; $P = .09$); treatment-emergent resistance during failure was detected in 5 of 28 vs 0 of 13 patients in the raltegravir vs the nucleoside arm, respectively [281]. In summary, although the use of a nucleoside-sparing regimen is a reasonable approach in HIV-infected patients who have CKD, the data supporting these regimens are currently inadequate to recommend such regimens as a general strategy.

Benefits: Available data that suggest patients infected with HIV and CKD receive significant benefit from ART. Use of a tenofovir-sparing regimen in these patients removes a potentially exacerbating factor from the management strategy.

Harms: Some studies raise concern that abacavir may increase cardiovascular risk, although data are mixed. Nucleoside-sparing regimens are options for treating HIV patients with CKD, but none of these regimens has sufficient data to establish virologic noninferiority compared with standard regimens, particularly in patients with low CD4 cell counts or high HIV RNA concentrations.

IV. What Are the Roles of Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers, HMG–Coenzyme A Reductase Inhibitors (Statins), and Aspirin in HIV-Infected Patients With CKD to Prevent Kidney Disease Progression and/or Reduce Cardiovascular Disease Risk?

Recommendations

12. We recommend using ACE inhibitors or ARBs, when clinically feasible, in patients infected with HIV who have confirmed or suspected HIVAN or clinically significant albuminuria (eg, >30 mg/day in diabetic patients; >300 mg/day in nondiabetic patients) (strong, high).

13. We recommend that HIV-infected individuals with pre-ESRD CKD be treated with statins to prevent cardiovascular disease as appropriate for persons in the highest cardiovascular risk group (eg >7.5% 10-year risk of cardiovascular disease) (strong, high).

14. We suggest that clinicians consider prescribing aspirin (75–100 mg/day) to prevent cardiovascular disease in HIV-infected individuals with CKD; however, the benefit of aspirin should be balanced against the individual's risk of bleeding (weak, high).

Evidence Summary

ACE Inhibitors and ARBs in CKD. There are few studies regarding the use of ACE inhibitors or ARBs in HIV-infected persons with CKD, and those that are available focused on HIVAN during the era prior to the availability of potent combination ART, wherein ACE inhibitor use was associated with a significantly lower risk of ESRD or with a longer time to ESRD in 3 observational studies [61, 200, 202].

Several large randomized trials in the general population have demonstrated that ACE inhibitors and ARBs can reduce proteinuria and slow the loss of kidney function in patients with proteinuria, particularly in those with diabetic or hypertensive nephropathy. The National Kidney Foundation endorses ACE inhibitors or ARBs as the preferred antihypertensive agents in patients with diabetes mellitus and stage 1–4 CKD [212]. In patients with diabetes and albuminuria >30 mg/day, treatment with ACE inhibitors or ARBs reduced the rate of progression to overt proteinuria [282, 283] and slowed progression to ESRD in diabetic patients with higher levels of albuminuria [208, 210, 284–286].

ACE inhibitors and ARBs also reduced the risk of ESRD in patients with nondiabetic CKD, mainly due to hypertension [287–290], but this benefit appears to be restricted to patients with severely increased proteinuria (eg, albuminuria >300 mg/day or equivalent (Table 3) and not with lower levels of albuminuria or reduced GFR alone [211, 291]. Although patients with proteinuric kidney disease who did not have either diabetes or hypertension were included in some of these studies [287, 289, 292], the low number of renal events limited the ability to detect benefits by ACE inhibitors or ARBs in such patients [211]. In addition to these renal benefits, ACE inhibitor use was associated with a reduced risk of nonfatal cardiovascular events in a systematic review of randomized trials among patients with albuminuria >30 mg/day and at least one cardiovascular risk factor [211].

Combination therapy with an ACE inhibitor and an ARB was found to reduce proteinuria and systolic blood pressure to a greater degree than either drug class alone in a meta-analysis [293]. However, large trials failed to show clinical benefits to a strategy of combining an ACE inhibitor with an ARB, including within the subset of subjects with low GFR and albuminuria [209]. Additionally, some studies found greater risks for harm with combination therapy including increased hypotension, syncope, renal dysfunction, and hyperkalemic events [211, 294–296].

Statin Therapy to Reduce Cardiovascular Risk in CKD. There are no studies to date assessing the efficacy of statins in HIV-infected persons with CKD. In studies of subjects from the general population, there is consistent evidence of benefit with statin use in subjects with non-ESRD CKD; however, there is conflicting evidence of benefit in subjects with ESRD. Recently revised guidelines on the treatment of blood

cholesterol to reduce the risk of cardiovascular disease by the American College of Cardiology and the American Heart Association recommend statin use for secondary and primary prevention in individuals whose 10-year risk of cardiovascular disease exceeds 7.5%, with the exception of individuals with ESRD receiving maintenance hemodialysis or those with New York Heart Association class II–IV heart failure [297]. Although the Framingham risk score does not include renal indices, individuals with CKD (defined by a GFR between 15 and 60 mL/minute/1.73 m^2) had a >7.5% 10-year risk of incident cardiovascular disease in one large population-based study [298].

Statin use was associated with consistently lower risks of cardiovascular-associated mortality in individuals with CKD (relative risks, 0.80 [95% CI, .71–.94], 0.81 [95% CI, .74–.88], and 0.82 [95% CI, .74–.91]) in 3 recent systematic reviews and meta-analyses involving 6–80 randomized controlled trials, when studied as primary or secondary cardiovascular disease prophylaxis [211, 299, 300], wherein these benefits did not differ significantly between participants with or without CKD. Of note, cardiovascular benefits of statins also were evident in 3 trials that included participants with CKD and mean baseline low-density lipoprotein (LDL) cholesterol levels <130 mg/dL [301–303], and there were no significant associations between cardiovascular events and baseline LDL cholesterol levels ($P = .95$), or net LDL changes ($P = .72$) in one meta-regression analysis [299].

However, among patients with ESRD, data regarding statin efficacy are mixed. Although simvastatin plus ezetimibe was associated with a significant reduction in primary cardiovascular events among the subset of 3023 participants with ESRD on dialysis in the Study of Heart and Renal Protection study [302], statins did not reduce the risk of fatal or nonfatal cardiovascular events in 2 large randomized controlled trials of ESRD participants on hemodialysis [304, 305], and one meta-analysis determined that statins were not associated with reduced cardiovascular mortality or cardiovascular events among persons with ESRD [300]. The reasons for the discrepancy between these studies are not known.

Aspirin Therapy to Reduce Cardiovascular Risk in CKD.
Aspirin use is associated with reduced risk of cardiovascular disease in individuals with and without a history of cardiovascular disease, but also with increased risk of major bleeding complications [306]. The US Preventive Services Task Force (USPSTF) recommends aspirin to prevent cardiovascular disease in men aged 45–79, and in women aged 55–79, whose risk of cardiovascular disease exceeds their age-adjusted risk of a major bleeding event [307]. Although there are no studies on the efficacy of aspirin use to prevent cardiovascular disease in HIV-infected individuals, <20% of HIV-infected patients meeting the 2009 USPSTF criteria for aspirin use as primary prevention of cardiovascular events were prescribed aspirin in one recent study [308].

In a post hoc analysis of the Hypertension Optimal Treatment study among 3619 subjects with a GFR <60 mL/minute/1.73 m^2, aspirin 75 mg/day was associated with significantly fewer cardiovascular events and lower all-cause mortality, and this survival benefit increased in association with lower GFR categories. For every 1000 persons with a GFR <45 mL/minute/1.73 m^2, aspirin use was estimated to prevent 76 major cardiovascular events and 54 all-cause deaths while contributing to 27 excess major bleeds [309]; however, there was also a trend toward an increased risk of bleeding in association with lower GFR ($P = .08$). In another randomized placebo-controlled study of aspirin and simvastatin in participants with CKD, including patients with ESRD or a functioning kidney transplant and predialysis patients with a creatinine level ≥1.7 mg/dL, aspirin 100 mg/day was associated with a 3-fold higher risk of minor, but not major, bleeding episodes [310]. The 2013 KDIGO guidelines suggest that adults with CKD who are at risk for atherosclerotic events be offered treatment with antiplatelet agents unless there is an increased bleeding risk that needs to be balanced against the possible cardiovascular benefits [1]. The optimal dose of aspirin is not known. In a meta-analysis by the Antithrombotic Trialists' Collaboration of 6 large trials of aspirin for primary prevention in the general population, the risk reductions achieved with low doses (75–162 mg/day) were as large as those obtained with higher doses (500–1500 mg/day) and larger than those that used doses <75 mg/day [311]; therefore, the American Diabetes Association and the American Heart Association jointly recommended 75–162 mg/day of aspirin as a primary prevention strategy [312]. Doses of 75–100 mg/day were effective in trials of patients with CKD.

Benefits: In randomized trials, ACE inhibitors and ARBs have consistently shown renal and cardiovascular benefits in proteinuric kidney disease, and they remain renoprotective in those with GFR <30 mL/minute/1.73 m^2. Trial data from the general CKD population show that statins and aspirin reduce the risk of cardiovascular disease in patients with non-ESRD CKD.

Harms: Adverse effects of ACE inhibitors and ARBs include acute kidney injury, hyperkalemia, peripheral edema, hypotension, angioedema, cough, headache, and nausea, and they are associated with teratogenicity [296, 313, 314]. KDIGO guidelines recommend that the initial dose should be lower for individuals with GFR <45 mL/minute/1.73 m^2, in whom GFR and potassium should be measured within 1 week of starting, or following any dose escalation, and regularly thereafter. ACE inhibitors or ARBs may be temporarily discontinued during intercurrent illness, planned intravenous radiocontrast administration, bowel preparation prior to colonoscopy, or before major surgery [1]. Contraindications for ACE inhibitors and ARBs include a history of allergy or angioedema and bilateral renal artery stenosis [315]. Although not contraindicated in women

of reproductive age, ACE inhibitors or ARBs should be immediately discontinued as soon as pregnancy is anticipated or suspected.

Statins have important drug–drug interactions with protease inhibitors and other drugs that are metabolized by the CYP3A system and pose an increased risk of myopathy.

Among the currently available statins, atorvastatin, fluvastatin (except with nelfinavir), pitavastatin, pravastatin (except with darunavir), and rosuvastatin are acceptable options in ART-treated patients with appropriate dosing and monitoring [316]. It is not clear that statins are beneficial in patients with ESRD. Kidney disease may increase the risk of bleeding with aspirin.

V. What Is the Optimal Blood Pressure Goal for HIV-Infected Patients With CKD?

Recommendations

15. We recommend a target blood pressure of <140/90 mm Hg in HIV-infected patients who have CKD with normal or mildly increased albuminuria (eg, <30 mg/day or equivalent) (strong, moderate).

16. We suggest a target blood pressure of <130/80 mm Hg in HIV-infected patients who have CKD with moderately to severely increased albuminuria (eg, >30–300 mg/day or equivalent) (weak, low).

Evidence Summary

There are no studies directly evaluating blood pressure targets in HIV-infected persons with CKD. A systematic review [317] of 3 randomized controlled trials comparing standard (<140/90 mm Hg) and strict (<125–130/75–80 mm Hg) blood pressure targets in nondiabetic subjects with CKD from the general population (the MDRD study [318], the African American Study of Kidney Disease and Hypertension [AASK] Trial [290], and the Ramipril Efficacy in Nephropathy [REIN-2] trial [292]) reported that low blood pressure targets were not associated with statistically significant improvements in primary or secondary clinical outcomes. Similarly, a recent systematic review from the USPSTF found no evidence that stricter blood pressure control reduced mortality or ESRD risk in patients with stage 1–3 CKD [211]. However, subgroup analyses by baseline proteinuria levels in the AASK and MDRD trials, but not the REIN-2 trial, suggested benefit for the lower blood pressure target in patients with proteinuria (>300 mg/day and >1000 mg/day, respectively) [317]. The 2012 KDIGO guidelines recommend a target blood pressure ≤140/90 mm Hg for both diabetic and nondiabetic patients with CKD and albuminuria ≤30 mg/day, and suggest a target blood pressure ≤130/80 mm Hg for patients with CKD and moderately or severely increased albuminuria [1].

Benefits: A blood pressure goal of <130/80 mm Hg may reduce the risk of kidney disease progression and cardiovascular events in patients infected with HIV and CKD with higher levels of proteinuria.

Harms: A lower blood pressure target may increase pill burden and the risk of adverse events, including syncope. At lower levels of proteinuria, there is no evidence that a lower blood pressure target is beneficial in reducing the risk of clinical events.

VI. Should Patients With HIVAN Receive Corticosteroids to Reduce the Risk of ESRD?

Recommendation

17. We suggest that clinicians consider corticosteroids as an adjunct to ART and ACE inhibitors or ARBs in patients with biopsy-confirmed HIVAN (weak, low).

Evidence Summary

During the pre–combination ART era, corticosteroids were associated with a lower risk of progression to ESRD in patients infected with HIVAN and with improvement in serum creatinine and reductions in proteinuria [199, 319–321]. Studies of HIVAN used prednisone 60 mg/day or the equivalent of 1 mg/kg of prednisone per day. Renal improvement was typically observed after 1–4 weeks of initiating corticosteroids, and responders were continued at that dose for 2–11 weeks then tapered off over 2–26 weeks. We recommend that patients who do not respond after 1–4 weeks of prednisone should be rapidly tapered [322, 323]. Corticosteroids for the treatment of HIVAN were not associated with increased risk of opportunistic infections in the only study in which this risk was assessed [319], but other studies in HIV-infected persons have reported a 4- to 7-fold increased risk of avascular necrosis in association with prior corticosteroid use [324–326].

Corticosteroids are effective for treatment of other complications of HIV that may be immune mediated, but there is no published experience of corticosteroid use in patients with kidney diseases other than HIVAN, including HIV immune complex kidney disease. Therefore, the use of corticosteroids for HIV-related kidney diseases other than HIVAN cannot be recommended.

Benefits: Corticosteroids may reduce kidney disease progression in HIV-infected patients with HIVAN.

Harms: Corticosteroids are associated with an increased risk of avascular necrosis in patients with HIV, and they have potential to increase the risk of infections. Most data supporting corticosteroid benefit came prior to the availability of combination ART, so the additive benefit of corticosteroids to combination ART in patients with HIVAN is not known.

VII. What Is the Role of Kidney Transplantation in Patients Infected With HIV and ESRD or Imminent ESRD?

Recommendations

18. We recommend that HIV providers assess patients with HIV and ESRD or imminent ESRD for the possibility of kidney

transplantation, considering history of opportunistic conditions, comorbidities, current immune status, and virologic control of HIV with ART (strong, moderate).

19. We recommend dose adjustment and pharmacologic monitoring of immunosuppressant drugs in patients infected with HIV after kidney transplantation to account for pharmacologic interactions with antiretroviral drugs. When feasible, ART should be selected that minimizes interactions with immunosuppressant drugs (strong, moderate).

Evidence Summary

In the previous version of these guidelines [2], kidney transplantation in patients infected with HIV and ESRD was considered experimental. However, data over the past 8 years indicate that high rates of patient and graft survival can be achieved in selected patients, although the risk of acute graft rejection has consistently been found to be higher in HIV-infected compared with HIV-uninfected recipients of kidney transplant [106]. The panel's strong recommendation to consider transplant in all HIV-infected persons with ESRD or imminent ESRD is based on data that kidney transplantation is associated with reduced mortality compared with remaining on dialysis from studies of the general ESRD population [179].

Eligibility Factors. Broadly similar eligibility criteria for kidney transplantation in HIV-infected individuals have been adopted in North America and Western Europe. Based on the historic CD4 cell count threshold where the risk of opportunistic infections increases sharply in HIV-infected persons [327], a CD4 count >200 cells/μL has been used as an eligibility criterion in almost all published experience with kidney transplantation in this population [106, 180–194, 328–332]. Additionally, guidelines from Europe and the United States require transplantation candidates to have an undetectable plasma HIV RNA on a stable ART regimen [106, 328, 330, 331, 333]. The inability to achieve an undetectable viral load, either because of antiretroviral drug resistance or inadequate adherence, remains a contraindication to transplant at most centers because virologic failure is a harbinger of clinical disease progression in HIV infection [334, 335].

In early experience with kidney transplantation in HIV-infected persons, any prior opportunistic condition was considered a contraindication to organ transplantation. With experience, these restrictions have been liberalized [328, 330, 333]. The US multicenter trial included patients with a history of treated opportunistic conditions, but excluded those with a history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, primary central nervous system lymphoma, or visceral Kaposi sarcoma [106].

Coinfection With Hepatitis C or B Virus. Approximately 30% of HIV-infected patients have hepatitis C virus (HCV) coinfection, and 5%–10% are coinfected with hepatitis B [336].

In the general kidney transplant population, hepatitis C infection is associated with poorer transplantation outcomes than in uninfected persons, and part of this excess risk has been attributed to progressive liver disease after transplantation [337]. This concern is magnified in HIV/HCV-coinfected patients, as HIV infection is also associated with more rapid progression of HCV-associated liver disease [338–340]. Patients with decompensated liver disease are poor candidates for transplantation, unless a combined liver/kidney transplant is possible. Patients with compensated liver disease but with significant fibrosis are at higher risk for progressive liver disease after transplant than those with significant fibrosis [337].

At present, pharmacologic treatment of hepatitis C with interferon/ribavirin-based therapy is problematic both in the setting of ESRD and after kidney transplantation because of challenges using these drugs in these clinical contexts. However, a number of direct-acting agents for hepatitis C infection are in development that offer the promise of hepatitis C cure for a large proportion of infected persons without the need to use interferon or ribavirin [341–343], although data about the safety and efficacy of new treatments in the setting of ESRD are incomplete.

Antiretroviral Drug–Drug Interactions With Immunosuppressant Drugs. Because many immunosuppressants and antiretroviral drugs are CYP substrates, inhibitors, or inducers, there is potential for clinically significant drug–drug interactions and pharmacokinetic variability (Table 8). One possible reason for higher rates of graft rejection in HIV-infected compared with HIV-uninfected transplant patients is the difficulty in achieving optimal immunosuppression because of complex pharmacological interactions between antiretroviral drugs and immunosuppressive drugs. Close therapeutic drug monitoring of tacrolimus, cyclosporine, and sirolimus with dose adjustments are needed to achieve the target trough concentrations. Significant increases in immunosuppressant exposure with the coadministration of protease inhibitors have been documented [344–349], and dramatic dose reductions of immunosuppressant drugs are often required to maintain target trough concentrations, such that some patients require only 1%–2% of a typical dose of the immunosuppressive drug. In contrast, NNRTIs (eg, efavirenz) can modestly decrease tacrolimus concentrations [346, 350], and require compensatory dose increases in immunosuppressant drugs.

Maraviroc, raltegravir, and NRTIs are not inhibitors or inducers of CYP. No significant drug–drug interactions were observed when raltegravir and tenofovir were coadministered with cyclosporine and tacrolimus [351–353]. If feasible, clinicians should consider switching a transplantation candidate who is receiving a protease inhibitor or a NNRTI to a raltegravir-based regimen to minimize the likelihood of drug–drug interactions with cyclosporine, tacrolimus, or sirolimus. However,

switching to a raltegravir-based regimen should be done cautiously. In a randomized clinical trial, higher rates of virologic failure occurred when subjects on stable lopinavir/ritonavir therapy switched to raltegravir compared with remaining on lopinavir/ritonavir, particularly in participants with a past history of virologic failure [354]. The availability of specialists who are experienced with pharmacologic monitoring and interactions between immunosuppressant and ART drugs is important in kidney transplantation to HIV-infected individuals.

Benefits: Kidney transplantation is associated with improved survival in the general ESRD population compared with remaining on dialysis. Kidney transplantation offers HIV-infected patients with ESRD freedom from dialysis and the potential for an improved quality of life.

Harms: The rate of acute graft rejection is higher in HIV-infected than in HIV-negative transplant recipients, and these early rejections are likely to adversely affect long-term allograft function. There are many pharmacologic interactions between immunosuppressant and antiretroviral drugs.

RECOMMENDATIONS FOR CKD IN CHILDREN AND ADOLESCENTS WITH HIV

VIII. How Should Children and Adolescents With HIV Be Screened for Kidney Disease and Monitored for Tenofovir-Associated Kidney Toxicity?
Recommendations

20. Similar to adults, we recommend that children and adolescents with HIV who are without evidence of existing kidney disease should be screened for renal function with estimated GFR (using an estimating equation developed for children) when ART is initiated or changed and at least twice yearly. We recommend monitoring for kidney damage with urinalysis or a quantitative measure of proteinuria when ART is initiated or changed, and at least annually in children and adolescents with stable kidney function. More frequent monitoring may be appropriate with additional kidney disease risk factors (strong, low).

21. We suggest avoiding tenofovir as part of first-line therapy in prepubertal children (Tanner stages 1–3) because tenofovir use is associated with increased renal tubular abnormalities and bone mineral density loss in this age group (weak, low).

IX. Should Treatment of HIV-Related Kidney Disease Be Different for Children and Adolescents Than for Adults?
Recommendations

22. We recommend that children and adolescents with HIV who have proteinuric nephropathy (including HIVAN) should be treated with ART and referred to a nephrologist (strong, moderate).

23. We suggest using ACE inhibitors or ARBs to treat proteinuric nephropathy in children with HIV infection and suggest their use as first-line therapy for hypertension in these children. Because HIV-infected children with proteinuria may be at greater risk for salt wasting and prone to dehydration, ACE inhibitors and ARBs should be used with caution in children (weak, very low).

24. We suggest that corticosteroids not be used in children with HIVAN (weak, very low).

Evidence Summary

Similar to adults, kidney disease was common in children and adolescents with AIDS before the availability of combination ART, particularly among those of African descent [355–360]. Kidney function often improved with ART, including reduced proteinuria in association with HIV RNA suppression [361]. Improved survival with ART was also observed in children and adolescents with ESRD, and approximately 2% of deaths were attributable to kidney disease during the era of combination ART in both children and adults [204, 362–366]. Glomerular collapse may be a less common feature of HIVAN in children, who also may be more likely to exhibit tubulointerstitial changes alone or in combination with mesangial hyperplasia, but who are without other glomerular pathology [357, 360, 365, 367]. HIV-infected children appear to be at higher risk for an atypical and often fatal form of hemolytic uremic syndrome than adults [365, 368].

Because of higher bone turnover rates in young children (<10 years old), tenofovir may have a greater adverse effect on bone mineral density compared with adolescents or adults [204, 369]. Consequently, tenofovir is not recommended for children <2 years of age, nor is it recommended as part of first-line treatment in children with Tanner stages 1–3, but the US Food and Drug Administration recently approved tenofovir for use in children aged ≥2 years [203].

Several studies have examined the renal safety of tenofovir in children and adolescents aged 2–18 years [142, 144, 369–375]. Serious renal adverse events resulting in tenofovir discontinuation were observed at a rate of 2.2 per 100 child-years in one study [371]. Renal tubular abnormalities may be more common in children than adults. In one prospective study, abnormal urine osmolality was detected in 8 of 37 (22%) children on tenofovir, and decreased tubular phosphate reabsorption was found in 74% [372]. In a second study of 456 children on ART, of whom 131 received tenofovir, 20 (4.4%) children developed serum phosphate concentrations <2.5 mg/dL, which occurred at a significantly higher rate in association with tenofovir use (4.3 vs 0.9 per 100 child-years, with and without tenofovir, respectively) [142].

Although ACE inhibitors or ARBs should be considered for the treatment of proteinuric CKD and hypertension in children

Table 8. Immunosuppressant and Antiretroviral Drug–Drug Interactions

Immunosuppressant Drug	ATV, NFV, FPV, IDV, ELV/c	DRV/r, LPV/r, FPV/r, ATV/r, IDV/r, Cobicistat	TPV/r	EFV, NPV, ETR	RAL, DTG, MVC, Enfuvirtide, RPV, and all NRTIs	Comments
Tacrolimus (CYP3A4 and P-gp substrate)	Tacrolimus concentrations may be increased	Tacrolimus concentrations may be significantly increased	May increase tacrolimus concentrations initially, but at steady-state may decrease tacrolimus concentration	Tacrolimus concentrations may be decreased	Drug interaction unlikely	Target trough: 5–15 ng/mL. Higher tacrolimus trough associated with 10% lower rates of allograft rejection
Cyclosporine (CYP3A4 and P-gp substrate)	Cyclosporine concentrations may be increased	Cyclosporine concentrations may be significantly increased	Cyclosporine concentrations may be increased initially, but at steady-state concentrations may be decreased	Cyclosporine concentrations may be decreased	Drug interaction unlikely	Target trough: 150–450 ng/mL. Significantly higher rejection rates observed with cyclosporine. Consider tacrolimus or sirolimus
Prednisone (CYP3A4 substrate)	RTV increases prednisolone AUC. With unboosted PIs and ELV/c, prednisolone AUC may also be increased	RTV increased prednisolone AUC 30%–41%	RTV increased prednisolone AUC 30%–41%	Prednisolone AUC may be decreased	Drug interaction unlikely	Standard dose recommended
Mycophenolate (glucuronosyltransferase, renal)	Drug interaction unlikely with NFV, FPV IDV, ATV, or ELV/c may increase mycophenolic acid (active drug) serum concentrations	Drug interaction unlikely with DRV/r, IDV/r, and FPV/r LPR/r may decrease mycophenolic acid ATV/r may increase mycophenolic acid (active drug) serum concentrations Interactions with ELV/c unknown	TPV/r may decrease mycophenolic acid	NVP concentrations may be decreased	Drug interaction unlikely	With ATV coadministration, monitor for potential mycophenolate-associated toxicities
Sirolimus (CYP3A4 and P-gp substrate)	Sirolimus concentrations may be increased	Sirolimus concentrations may be significantly increased	Sirolimus concentrations may be increased initially, but at steady-state, concentrations may be decreased	Sirolimus concentrations may be decreased	Drug interaction unlikely	Target trough: 3–12 ng/mL; sirolimus recommended for patients with calcineurin-associated nephrotoxicity

Abbreviations: ATV, atazanavir; AUC, area under the curve; CYP3A4, cytochrome P450 isoenzyne 3A4; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ELV/c, elvitegravir/cobicistat; ETR, etravirine; FPV, fosamprenavir; IDV, indinavir; LPV, lopinavir; MVC, maraviroc; NFV, nelfinavir; NRTI, nucleoside reverse transcriptase; NVP, nevirapine; P-gp, P-glycoprotein; PI, protease inhibitor; /r, boosted with ritonavir; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; TPV, tipranavir.

Urine abnormalities are generally more sensitive and specific than serum abnormalities in the diagnosis of renal proximal tubular dysfunction. For example, the presence of glycosuria alone (in the absence of clinical diabetes) is diagnostic of proximal tubular dysfunction. Conversely, the presence of any of the plasma abnormalities alone cannot be used as diagnostic criterion.

[1], the risk of acute kidney injury due to dehydration from diarrhea or vomiting is substantially higher in young children than in adults receiving these agents [376]. In contrast to adults, corticosteroids did not appear to confer benefit in case series of children (aged <10 years) with HIVAN [358, 360].

FUTURE DIRECTIONS

Strong associations between markers of kidney function and important clinical outcomes, including cardiovascular events and all-cause mortality in ART-treated persons living with HIV, provide a compelling rationale to identify interventions that preserve or improve kidney function while also reducing the incidence of these clinical outcomes. First, changing age demographics as a result of dramatic improvements in survival among persons living with HIV, combined with increased risks of age-related comorbidities including CKD, highlight an emerging research focus on HIV in aging populations. Second, the recent identification of risk alleles of the genes that encode apolipoprotein L1 and nonmuscle myosin IIA heavy chain that are associated with HIVAN and other CKDs in African-Americans presents a major opportunity to advance the understanding of HIVAN and other CKDs that disproportionately affect African Americans. Third, a growing appreciation of the importance of hepatitis C coinfection with kidney disease in these patients also represents an important area of future inquiry. As a number of highly effective direct-acting agents are in late-stage development for the treatment of hepatitis C, it will be of interest to assess the role of hepatitis C treatment/cure in managing hepatitis C–associated glomerular disease and to prevent CKD in HIV/HCV-coinfected persons. Fourth, additional research is needed to identify markers of antiretroviral-associated tubular damage that are predictive of clinically significant adverse outcomes, and to determine the efficacy of monitoring for tubular toxicity in patients taking antiretroviral drugs that may cause proximal tubule dysfunction in randomized controlled trials.

Among clinical trials that are currently enrolling, CKD is included among the clinical endpoints in the Strategic Timing of Antiretroviral Therapy Trial that is being conducted by the International Network for Strategic Initiative in Global HIV. This study will assess the benefits and risks of initiating ART at a CD4 count >500 cells/μL, compared with deferring until the CD4 count is <350 cells/μL, and may provide important insights into ART effects on kidney function preservation [377].

Notes

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