KIDNEY DISEASE IN HIV-INFECTED PATIENTS

KEY RECOMMENDATIONS
Clinicians should: • **Inform and educate HIV-infected patients about the associations between HIV and kidney disease** (BIII) • **Routinely assess kidney function in HIV-infected patients** (AIII) • **Counsel patients with HIV-associated nephropathy about the increased urgency of initiating ART** (AII) • **Assess whether dose adjustments or discontinuation of renally cleared ART medications are necessary when a patient's glomerular filtration rate reaches ≤50 mL/min** (Table 2) (AIII)

KEY TO ABBREVIATED TERMS	
ACE	Angiotensin-converting enzyme
ARB	Angiotensin receptor blocker
ARF	Acute renal failure
ART	Antiretroviral therapy
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Consortium
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HCV	Hepatitis C virus
HIVAN	HIV-associated nephropathy
MDRD	Modification of diet in renal disease
MPGN	Membranoproliferative glomerulonephritis
NSAID	Nonsteroidal anti-inflammatory drug

I. INTRODUCTION

Kidney disease in the setting of HIV can pose a significant challenge to patients and clinicians by increasing the risk for AIDS-defining illness, hospitalization, and death.[1-3] The importance of routine screening, even for patients not receiving antiretroviral therapy (ART),[4] is underscored by the following:

- Risk for HIV-associated nephropathy, a kidney disease that is caused directly by HIV infection
- Use of potentially nephrotoxic agents, such as some ART medications, as well as nonsteroidal anti-inflammatory drugs (NSAIDs)
- Increased prevalence of recognized causes of kidney disease in the HIV-infected population compared with the non-HIV-infected population, including diabetes,[5] hypertension,[5] and liver disease[6]

Key Point:
HIV-infected black patients with chronic kidney disease (CKD) have a significantly higher risk for end-stage renal disease (ESRD) compared with HIV-infected white patients with CKD.[7]

II. PATIENT EDUCATION ABOUT KIDNEY DISEASE

RECOMMENDATION:
Clinicians should educate patients about the following (BIII)**:**

- **The association between HIV and kidney disease**
- **The role of ART in prevention of HIVAN**
- **Importance of routine monitoring appointments to assess for other causes of kidney disease**

Patient education about preserving kidney function, even for those who are asymptomatic for kidney disease, should emphasize the importance of ART to prevent HIVAN,[8,9] as well as the importance of keeping routine monitoring appointments to assess for other causes of kidney disease, including medication-related nephrotoxicity, hypertension, and diabetes.

III. Renal Syndromes and Risk Factors for Kidney Disease

A. Acute Renal Failure

Acute renal failure (ARF), also known as acute kidney injury, is characterized by a rapid loss of kidney function,[10] including the capacity to excrete waste and maintain fluid balance. In HIV-infected patients, immunodeficiency may be the greatest risk factor for ARF.[6] However, many of the common risk factors for ARF are similar in both the HIV-infected and non-HIV-infected populations, such as older age, diabetes, and exposure to nephrotoxic agents. Many agents used to treat opportunistic infections, as well as certain antiretroviral medications used in the primary treatment of HIV, have nephrotoxic potential.[11] ARF in HIV-infected patients in ambulatory care settings is most frequently due to pre-renal azotemia or acute tubular necrosis, possibly caused by exposure to nephrotoxic agents.[11] Unlike CKD, race has not been clearly established as a risk factor for ARF.

Appendix A provides information about the reported prevalence of ARF among HIV-infected patients.

B. Chronic Kidney Disease

CKD is defined as either proteinuria, a marker of kidney damage, or glomerular filtration rate (GFR) <60 mL/min for ≥3 months. Hypertension and diabetes are important causes of CKD in HIV. In one cross-sectional analysis, 55% of patients with HIV and CKD had hypertension and 20% had diabetes.[12]

There is a higher prevalence of both HIV and CKD among blacks compared with whites. CKD in the setting of HIV is more likely to progress to ESRD in black patients. Genetic factors unique to individuals of African descent, and not to whites, are associated with focal segmental glomerulosclerosis and non-diabetic ESRD.[13-17] An allele that confers protection against infection by *Trypanosoma brucei*, a parasite commonly found in Africa, has been linked to greater susceptibility to non-diabetic kidney disease among blacks.[17] The presence of this allele among blacks in the United States may contribute to the higher incidence of advanced kidney disease in this population.[17]

Other known risk factors include hepatitis C virus (HCV) co-infection, family history, increased viral load levels (>4000 copies/mL), reduced CD4 cell count (<350 cells/mm^3), and older age, although GFR does naturally decline with age.[11] It is estimated that as many as 40% of individuals older than 70 years meet criteria for CKD based on GFR levels <60 mL/min. These cases may be misclassified because the distinction between physiologic aging and CKD at or near a GFR of 60 mL/min is unclear. CKD risk factors, including arteriosclerosis, hypertension, and diabetes, increase with age, and development and/or progression of kidney disease may occur when these risk factors increase in elderly patients.

Appendix B provides information about the reported prevalence of CKD among HIV-infected patients.

IV. Routine Kidney Disease Screening: Laboratory Assessment

Recommendations:

Clinicians should routinely assess kidney function in all HIV-infected patients. A renal assessment should include:

- **Glomerular filtration rate estimated from serum creatinine (baseline and at least every 6 months)** (AII)
- **Blood urea nitrogen (baseline and at least every 6 months)** (AIII)
- **Urinalysis (baseline and at least annually)** (AIII)
- **For patients with diabetes and no known proteinuria: calculation of urine albumin-to-creatinine ratio to detect microalbuminuria (baseline and at least annually)** (AI)

For patients receiving a tenofovir-containing regimen, clinicians should estimate glomerular filtration rate at initiation of therapy, 1 month after initiation of therapy, and at least every 4 months thereafter.

Routine tests for kidney disease screening in HIV-infected patients should be performed according to the recommendations above.

A. Glomerular Filtration Rate

A glomerular filtration rate (GFR) of <60 mL/min meets criteria for CKD; this threshold is supported by epidemiologic data linking low GFR to an increased frequency of hospitalization, cardiovascular events, or death.[18] GFR can be calculated in the clinical setting using one of the following three equations:

- *Chronic Kidney Disease Epidemiology Consortium (CKD-EPI):* Estimates GFR based on age, race, and serum creatinine. A CKD-EPI calculator can be found at http://mdrd.com
- *Modification of diet in renal disease (MDRD)*: Estimates GFR based on age, race, sex, and serum creatinine. An MDRD calculator can be accessed at http://mdrd.com
- *Cockcroft-Gault*: Calculates creatinine clearance based on serum creatinine, age, weight, and sex. A Cockcroft-Gault calculator can be accessed at http://nephron.com/cgi-bin/CGSI.cgi

Any of these equations may be used to follow trends in creatinine as part of determining GFR. If creatinine is rising, GFR will be falling by any of these equations; if creatinine is stable, then GFR is stable by any of these equations.

These equations remain the most highly validated formulas for screening and ongoing assessment of kidney disease; however, they have not been validated in large numbers of patients with HIV infection.

Important Limitations to Calculating GFR

- Unlike the CKD-EPI, the MDRD and Cockcroft-Gault have not been validated in people with normal kidney function and do not accurately estimate GFR in the normal range; therefore, when GFR is >60 mL/min, small but possibly meaningful changes in GFR that may indicate early kidney disease cannot be reliably measured with the MDRD and Cockcroft-Gault equations.
- All of these equations have diminished accuracy in patients with extremes of body weight, such as body builders, amputees, and frail individuals; for these patients, a 24-hour creatinine clearance may be a better test because serum creatinine within the normal range may not correlate with a normal GFR.

Key Points:

- The MDRD or CKD-EPI, not the Cockcroft-Gault, equations are used by clinical laboratories when reporting estimated GFR from serum creatinine; however, drug manufacturers' recommended dose adjustments for kidney function are based on the Cockcroft-Gault equation, not the MDRD.
  - For MDRD and CKD-EPI calculators, refer to http://mdrd.com
  - For Cockcroft-Gault, refer to http://nephron.com/cgi-bin/CGSI.cgi
- The CKD-EPI equation has begun to replace the MDRD equation when clinical laboratories report GFR. Unlike the other equations, the CKD-EPI equation has been validated in individuals with normal kidney function of >60 mL/min, although this has not been studied in the setting of HIV infection.

Other markers that reliably measure GFR are needed. Cystatin C, a member of the cysteine protease family, may be more closely correlated with changes in GFR. Evidence suggests that a proposed equation combining creatinine and cystatin C performs better than creatinine alone.[19] However, no standardized measurement is currently available.

B. Urine Protein Excretion

The most sensitive indicator of kidney damage is an elevated urinary protein excretion, measured qualitatively using urine dipstick or quantitatively using a spot urine protein-to-creatinine ratio or a 24-hour urine collection. A protein-to-creatinine ratio is measured from a random sample of urine, as opposed to the timed collection (e.g., a 24-hour calculation).

For patients with ≥1+ by urinary dipstick, urinary protein excretion should be quantified using the protein-to-creatinine ratio from a random sample of urine or a 24-hour urine collection. Patients with heavy proteinuria and apparently normal GFR may have worse clinical outcomes than those with moderately reduced GFR and normal proteinuria.[20]

The laboratory may report urinary protein and creatinine concentrations (both in milligrams per deciliter) and provide the ratio, or the laboratory may report milligrams of protein per gram of creatinine. With these results, kidney function can be assessed as follows:

- ***150 to <200 mg protein/gram creatinine***: the upper limit of normal (ratio, 0.15 to <0.2) and approximately 150 to 200 mg protein excretion per 24 hours

- ***200 to <1500 mg protein/gram creatinine***: mild proteinuria (ratio, 0.2 to <1.5) that is generally asymptomatic but may indicate tubulointerstitial disease or a focal glomerular abnormality

- ***1500 to ≤2000 mg protein/gram creatinine:*** moderate proteinuria (ratio, 1.5 to ≤0.2) suggesting glomerular disease

- ***>2000 mg protein/gram creatinine***: nephrotic-range proteinuria with glomerular disease

Key Point:
Microscopic hematuria and mild proteinuria (urinary protein excretion <1500 mg/day) are generally asymptomatic. They have little clinical impact alone but can indicate an early stage of a serious disease, such as acute or chronic glomerular disease. A kidney biopsy is often deferred in such circumstances until the renal disease progresses, as manifested by increasing proteinuria, decreasing GFR, or the development of hypertension.

C. Microalbuminuria Screening in Diabetic Patients

The standard dipstick is not sufficient for urinary screening in individuals with diabetes because the dipstick will not detect microalbuminuria, which predicts the subsequent development of clinically important kidney disease in patients with diabetes. In diabetic patients without gross proteinuria, the albumin-to-creatinine ratio should be used annually to detect microalbuminuria, according to American Diabetes Association Guidelines.[21] A urinary albumin excretion between 30 and 299 µg/mg creatinine indicates microalbuminuria. Isolated microalbuminuria in patients without diabetes has not been clearly linked to the subsequent development of kidney failure, and screening for microalbuminuria in all patients is not currently recommended.

V. DIAGNOSIS AND EVALUATION OF KIDNEY DISEASE

RECOMMENDATIONS:

All patients with borderline glomerular filtration rate, regardless of age, should undergo the following diagnostic evaluation of kidney function (AII)**:**

- **Urinalysis to screen for cells and cellular casts**
- **Quantification of urinary protein excretion**
- **Renal sonogram**
- **Careful physical examination**

Primary care clinicians should refer patients to a nephrologist when (AII)**:**

- **The diagnosis is uncertain**
- **Kidney disease is progressing rapidly**
- **Stage 4 to 5 chronic kidney disease is present** (see Table 1)
- **Kidney biopsy is being considered**

Although most aspects of the diagnosis and evaluation of kidney disease can be performed by the primary care clinician, consultation with a nephrologist, including patient referral, may benefit the patient's care during any stage of his/her disease.

Diagnosis of CKD is often delayed because it may be asymptomatic. CKD is often detectable only by laboratory testing. The distinction between CKD and ARF frequently requires a careful physical examination and review of the patient's medical record, including prior laboratory tests, as well as follow-up visits and repeat laboratory testing.

CKD is categorized in five stages (see Table 1). Patients with normal GFRs but have evidence of kidney damage are classified as having stage 1 or 2 CKD.

TABLE 1
STAGES OF CHRONIC KIDNEY DISEASE

Stage	Description[a]	GFR[b] (mL/min)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	<15 (or dialysis)

Adapted from *K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification*[22] by permission of Elsevier.

[a]CKD is defined as either kidney damage or GFR <60 mL/min for≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in urine tests or imaging studies.

[b]GFR can be calculated in the clinical setting using one of the following equations:

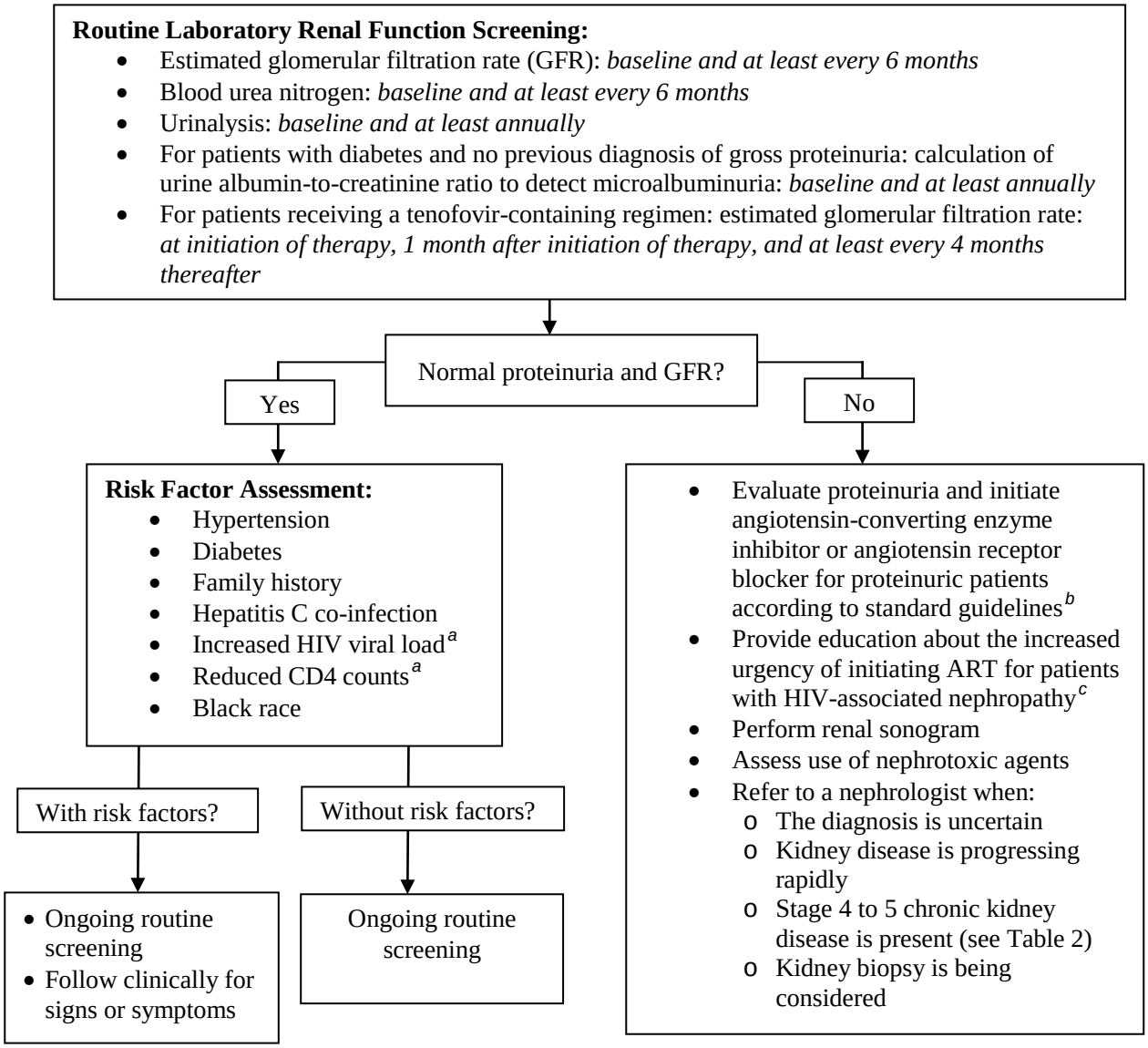
1) Chronic Kidney Disease Epidemiology Consortium (CKD-EPI). A CKD-EPI calculator can be found at http://mdrd.com
2) Modification of diet in renal disease (MDRD). An MDRD calculator can be accessed at http://mdrd.com
3) Cockcroft-Gault. A Cockcroft-Gault calculator can be accessed at http://nephron.com/cgi-bin/CGSI.cgi

Key Point:
As CKD progresses, more pronounced signs or symptoms may appear, including increased blood pressure, anemia, or edema (mild to severe). All forms of CKD have the potential to progress to ESRD.

Once the presence of kidney disease has been confirmed, the history and physical examination will likely provide important information about the duration of disease and predisposing risk factors, such as hypertension, diabetes, liver disease, or exposure to potential nephrotoxins. In addition, urinalysis to detect red cells, white cells, and cellular casts can provide information about the cause of kidney disease.

Steps for screening and initial management of kidney disease are provided in Figure 1.

Figure 1. Steps for screening and initial management of kidney disease.



[a]The Infectious Disease Society of America indicates viral load levels of >4000 copies/mL and CD4 counts of <350 cells/mm^3 as risk factors for kidney disease.[11]
[b]See Section VI. B. *Management of Comorbid Hyperglycemia, Dyslipidemia, Anemia, and Hypertension.*
[c]See *Antiretroviral Therapy:* Section III. *Deciding When to Initiate ART*.

A. Renal Sonogram

A renal sonogram provides information about kidney size and structure and can demonstrate obstructive uropathy or small, echogenic kidneys diagnostic of chronic disease. The test is readily available, noninvasive, and inexpensive and should be performed in all patients with ARF or CKD.

B. Kidney Biopsy

The indications for performing a kidney biopsy in HIV-infected patients are difficult to generalize and should not be different from those of non-HIV-infected patients. Biopsies have the greatest clinical utility in patients with acute glomerulonephritis or unexplained CKD, especially in the setting of heavy proteinuria (defined as 24-hour urinary protein excretion of >2000 mg or protein-to-creatinine ratio >2000 mg/g creatinine) or in patients with relatively rapid decreases in GFR, because they are at high risk for progression to ESRD.

Most nephrologists would treat a proteinuric patient (e.g., 24-hour urinary protein excretion of >300 mg/g or protein-to-creatinine ratio of >200 mg/g creatinine) with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), regardless of whether or not a biopsy is obtained (see Section VI. B. *Management of Comorbid Hyperglycemia, Dyslipidemia, Anemia, and Hypertension*).

C. Diagnosis of HIV Associated Nephropathy

RECOMMENDATIONS:

In circumstances when a kidney biopsy is not performed for an HIV-infected patient with kidney dysfunction, because of contraindication, clinician judgment, or patient preference, the following diagnostic criteria for HIV-associated nephropathy are reasonable (BIII)**:**

- **No other explainable cause(s) of kidney disease *and***
- **Proteinuria of >2000 mg *and***
- **Normal to large echogenic kidneys on sonogram *and***
- **Black race**

For patients with empirically diagnosed HIV-associated nephropathy whose kidney disease worsens after initiation of ART, a biopsy should be performed to determine the underlying cause. (AIII)

The first reports of AIDS-related kidney disease appeared in the mid-1980s and described immunosuppressed patients with nephrotic-range proteinuria who progressed to renal failure and required dialysis within several weeks after presentation.[23] These were cases of what is now recognized as HIV-associated nephropathy (HIVAN), a kidney disease with a pathogenesis that is directly related to the expression of HIV mRNA or DNA in glomerular and tubule epithelial cells, leading to renal damage through pro-inflammatory cytokines.[24,25] HIVAN is a combined glomerular and tubule disorder, with collapsing glomerulopathy, focal glomerulosclerosis, microcystic tubule damage, varying degrees of interstitial inflammation, and tubular atrophy.[23,26,27] The disease has been described in black patients at much higher rates than other racial populations and occurs primarily in patients with advanced HIV disease. A genetic polymorphism on chromosome 22 may explain this racial predilection.

In the era of ART, HIVAN has become more indolent, which makes it difficult to distinguish from other forms of kidney disease with clinical assessment alone. HIVAN is a pathologic entity that is distinct from other kidney diseases. Black race, high viral load level, low CD4 cell count, and heavy proteinuria (24-hour urinary protein excretion of >2000 mg or protein-to-creatinine ratio >2000 mg/g creatinine) predict the presence of HIVAN. However, no guidelines currently exist for diagnosing HIVAN in the absence of biopsy. According to biopsy studies, the predictive value of clinical signs alone are not very specific.[28,29]

VI. Management of Kidney Disease

Recommendations:

Patients with low-grade proteinuria and/or slightly decreased glomerular filtration rate should receive ART if not already receiving it, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and careful monitoring of kidney function.

Clinicians should consult with a nephrologist when managing patients who are approaching end-stage renal disease due to stage 4 to 5 chronic kidney disease (see Table 1) **and require special interventions for hyperparathyroidism, anemia, hemodialysis vascular access, peritoneal dialysis, and/or kidney transplant options.** (AII)

A. Use of ART to Prevent Progression of Kidney Disease

Recommendation:

Clinicians should educate patients with HIV-associated nephropathy about the increased urgency of initiating ART (see *Antiretroviral Therapy:* Section III: *Deciding When to Initiate ART*)**.** (AII)

The incidence and spectrum of kidney diseases in HIV have been dramatically altered by ART. The risk for ESRD has been reduced, survival on dialysis among HIV-infected patients approaches survival for non-HIV-infected patients, and kidney transplantation is a viable option.[30-33] One multicenter study demonstrated a 3-year survival rate of 83% among HIV-infected patients.[34] Survival on dialysis is expected to continue to improve with newer antiretroviral drug therapies.[31]

Several case reports provide evidence that ART reverses the structural and functional abnormalities associated with HIVAN.[35-37] Patients with HIVAN who are receiving effective ART have a slower decrease in GFR[3,38,39] and experience fewer incidents of fulminant renal failure.[33] ART is responsible for at least a 30% reduction in new ESRD cases from HIVAN.[32]

ART-naïve patients should be educated about the increased importance of initiating ART in the presence of HIVAN, and patients with low-grade proteinuria and/or slightly decreased GFR should initiate ART if not already receiving it. However, initiation of ART may not have a beneficial effect on the natural history of other forms of CKD, such as IgA nephropathy and diabetes, which could be mistaken for HIVAN when a biopsy is not obtained. If kidney disease worsens after initiating ART, a biopsy should be performed to determine the underlying cause.

B. Management of Comorbid Hyperglycemia, Dyslipidemia, Anemia, and Hypertension

RECOMMENDATIONS:
Clinicians should treat hyperglycemia, dyslipidemia, anemia, and hypertension in HIV-infected patients with kidney disease according to standard guidelines[22,40-42] for non-HIV-infected patients. (AI)

HIV-infected normotensive patients with kidney disease should receive angiotensin-converting enzyme inhibitors or angiotensin receptor blockers according to standard guidelines for non-HIV-infected patients. (AI)

For most patients, the most effective approach to CKD treatment is effective medical management of two major risk factors: diabetes and hypertension.

HIV-infected patients with low-grade proteinuria and/or slightly decreased GFR should receive ART if not already receiving it, an ACE inhibitor or ARB, and careful monitoring of kidney function. HIV-infected patients with kidney disease who have hyperglycemia, dyslipidemia, anemia, or hypertension should receive management and treatment according to standard guidelines[22,40-42] for the non-HIV-infected population. Guidelines for treating hypertension in HIV-infected patients with kidney disease, including antihypertensive therapy for normotensive patients with proteinuria, are the same as those for non-HIV-infected patients. Standard ACE inhibitor or ARB therapy should also be considered for normotensive patients with HIVAN.[11]

C. Management Considerations Requiring Referral to a Nephrologist

RECOMMENDATION:
Clinicians should refer HIV-infected patients with kidney disease to a nephrologist when:

- **Considering management with steroids, immunosuppression, hemodialysis, or transplantation** (AIII)
- **A diagnosis of membranoproliferative glomerulonephritis has been made for HIV/HCV co-infected patients** (AIII)

Consultation with a nephrologist can be useful at any stage of a patient's kidney disease to guide clinical examination and interpret findings. Referral to a nephrologist is recommended when treatment for a patient's kidney disease becomes complex, such as when steroids, immunosuppression, hemodialysis, transplantation, or treatment for membranoproliferative glomerulonephritis (MPGN) may be required.

Steroids and Immunosuppression
Steroids have been used in HIVAN because they can reduce urinary protein excretion and/or improve GFR in other kidney diseases, such as idiopathic focal segmental glomerulosclerosis and interstitial nephritis. In nonrandomized trials, kidney function can stabilize or improve in steroid-treated patients.[43]

Hemodialysis and Transplantation

Proper planning for hemodialysis, peritoneal dialysis, or kidney transplantation should be managed by a nephrologist, well in advance of uremic symptoms. In patients who are likely to begin hemodialysis, an arteriovenous fistula should be created months before an anticipated start date. Dose adjustments for ART in patients on hemodialysis have been well established[44] and are available in *Antiretroviral Therapy:* Appendix A.

Successful results have been demonstrated in HIV-infected renal transplant patients receiving ART. The rates of both acute rejection and infection among HIV-infected patients were comparable to non-HIV-infected transplant recipients.[45,46] More recently, prospective data from the Solid Organ Transplantation in HIV: Multi-Site Study demonstrated excellent patient and graft survival, despite an increased rate of acute rejection in HIV-infected kidney transplant recipients.[47] Clinicians should be aware of the potential for significant drug-drug interactions between ART and immunosuppressive agents.

Membranoproliferative Glomerulonephritis in HIV/HCV Co-infected Patients

HIV/HCV co-infection increases the risk for CKD.[48,49] Antibodies to HCV can induce immune complex glomerular disease and MPGN. However, relatively few cases of MPGN have been reported in HIV-infected patients, suggesting other associations between HCV and CKD.

The decision to initiate anti-HCV therapy for HCV and MPGN is often simplified by the fact that therapy is indicated for the liver disease, irrespective of cryoglobulinemia, and a kidney biopsy is not necessary to confirm the clinical suspicion of MPGN. A more difficult decision arises when anti-HCV therapy is ineffective and the kidney disease remains active. In this setting, a kidney biopsy should be obtained to confirm the diagnosis. If MPGN is present, the patient should be referred to a nephrologist for treatment.

VII. HIV-Related Medication Adjustments in the Setting of Renal Complications

Recommendation:

Clinicians should determine whether dose adjustments are required for certain antiretroviral agents or whether patients should avoid use of certain agents when glomerular filtration rate reaches ≤50 mL/min; recommendations for such considerations are provided in Table 2. (AIII)

When GFR approaches levels that suggest the need for ART dose adjustments, the decision to make adjustments should be based on trends in serum creatinine levels over time and on clinical judgment. Dose modification of antiretroviral agents may be necessary when GFR is chronically reduced. Nucleoside/nucleotide agents that are cleared renally (i.e., zidovudine, stavudine, didanosine, lamivudine, emtricitabine, and tenofovir) require dose modification when GFR is reduced. Combination pills that contain these nucleosides/nucleotides should not be used in patients with reduced GFR because the individual components require separate dosing regimens (see Table 2).

TABLE 2 RECOMMENDED ART DOSE ADJUSTMENTS AT GFR ≤50 mL/min[a]	
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors	
• Zidovudine	- Adjust dose if creatinine clearance reaches ≤15 mL/min
• Didanosine[b] • Emtricitabine • Lamivudine • Stavudine • Tenofovir[c]	- Adjust dose if creatinine clearance reaches ≤50 mL/min - Avoid or use with caution when didanosine is co-administered with tenofovir in renal failure
CCR5 Co-Receptor Agonists	
• Maraviroc	- Adjust dose if creatinine clearance reaches <30 mL/min and patient experiences postural hypotension
Co-Formulated Agents	
• Combivir (zidovudine + lamivudine) • Epzicom (abacavir + lamivudine) • Trizivir (abacavir + lamivudine + zidovudine) • Atripla (tenofovir[c] + emtricitabine + efavirenz) • Stribild (emtricitabine + tenofovir[c] + elvitegravir + cobicistat)	- Do not use if creatinine clearance reaches <50 mL/min - Individual components should be administered with appropriate dose adjustments
• Truvada (tenofovir[c] + emtricitabine)	- Do not use if creatinine clearance reaches <30 mL/min

[a] Clinicians should refer to prescribing information for individual agents when a patient has reduced GFR (see *Antiretroviral Therapy*).
[b] The manufacturer recommends adjustment at ≤60 mL/min for didanosine; however, adjustment at ≤50 mL/min is a reasonable approach.
[c] Alternative antiretroviral agents should be considered in patients with renal insufficiency.

A. Tenofovir

RECOMMENDATION:
For patients receiving tenofovir-containing regimens, clinicians should:

- **Estimate glomerular filtration rate at initiation of therapy, 1 month after initiation of therapy, and at least every 4 months thereafter** (BII)
- **Adjust tenofovir dosing when glomerular filtration rate approaches 50 mL/min or discontinue tenofovir according to clinical status** (AII)
- **Withhold tenofovir until all potential causes have been determined in patients who develop acute renal failure** (BII)

Tenofovir-associated kidney disease is characterized either by a decrease in GFR or by tubule dysfunction, such as Fanconi syndrome (tubular injury with hypophosphatemia, euglycemic glycosuria, tubule proteinuria, uric acid wasting, and aminoaciduria). For prescribing information, see the package insert.

For patients receiving a tenofovir-containing ART regimen, GFR should be assessed at initiation of therapy, 1 month after initiation of therapy, and at least every 4 months thereafter. Product labeling recommends routine monitoring of serum phosphate levels, but there is little evidence to suggest that serum phosphate is a sensitive or specific marker of tubule dysfunction, nor is it a more sensitive indicator for tenofovir-associated renal dysfunction than measuring GFR (serum creatinine) alone. There are insufficient data to support tenofovir dose adjustment or discontinuation based on low serum phosphate alone. However, the combination of reduced GFR and hypophosphatemia is highly suggestive of tenofovir-associated renal dysfunction, and tenofovir should be dose-adjusted according to GFR or discontinued according to clinical status. Concomitant use of nephrotoxic agents should be avoided in these circumstances.

As an initial regimen, tenofovir is relatively contraindicated in patients with preexisting kidney disease and GFR levels near 50 to 60 mL/min. Tenofovir should be dose-adjusted when GFR approaches 50 mL/min. Both the renal and nonrenal safety profiles, as well as the efficacy, of alternative regimens play an important role in the decision to switch regimens. The decision to continue treatment in patients with gradually decreasing GFR and CKD, such as in patients with hypertension or diabetes, is more complex and should be individualized. The underlying cause of kidney disease should be considered, as should the likelihood that kidney function may stabilize or improve after stopping tenofovir. When patients develop ARF while receiving tenofovir, the drug should be withheld until all potential causes have been determined.

For additional ART dosing information, see *Antiretroviral Therapy:* Appendix A.

B. Nonsteroidal Anti-inflammatory Drugs

RECOMMENDATION:
Clinicians should assess for use of nonsteroidal anti-inflammatory drugs in HIV-infected patients with declining renal function. Decisions about the use of such agents for these patients should be individualized and patients should be educated about the importance of using these drugs with caution. (BII)

Use of nonsteroidal anti-inflammatory drugs (NSAIDs), which is common among HIV-infected patients with pain syndromes, may exacerbate kidney disease. NSAID use should be assessed, and these agents should be used with caution, in the setting of declining renal function.

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APPENDIX A. PREVALENCE AND COMPLICATIONS OF ACUTE RENAL FAILURE IN HIV-INFECTED PATIENTS

APPENDIX A PREVALENCE AND COMPLICATIONS OF ACUTE RENAL FAILURE IN HIV-INFECTED PATIENTS	
Cohort	**Characteristics**
HIV-infected patients in ambulatory care (2005)[1]	• Among 754 HIV-infected patients in ambulatory care, 10% experienced at least one episode of ARF over 2 years • More than half of the ARF episodes were attributed to underlying infections, 76% of which were AIDS-defining illnesses • Complications of drug therapy accounted for nearly one-third of ARF cases; conventional antibiotics and antifungal agents were the primary agents that caused the complications • Liver disease accounted for approximately 10% of cases, and HCV co-infection and lower CD4 cell counts were identified as independent risk factors
Hospital discharges in New York State (2006)[2]	• In an analysis of administrative data from more than 2 million hospital discharges in New York State, HIV infection was associated with a 2.8-fold increase in documented ARF • ARF was associated with a nearly 6-fold increase in in-hospital mortality

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APPENDIX B. PREVALENCE REPORTS OF CHRONIC KIDNEY DISEASE IN HIV-INFECTED PATIENTS

APPENDIX B PREVALENCE REPORTS OF CHRONIC KIDNEY DISEASE IN HIV-INFECTED PATIENTS	
Study	**Characteristics of Cohort**
EuroSIDA	• A total of 3.5% of patients with HIV-1 infection had a GFR <60 mL/min • The low prevalence might be explained by: 1) the predominantly white study population, in whom risk for kidney disease is lower than in blacks; and 2) lack of information about proteinuria
HERS	• Kidney disease was present in 7.2% of HIV-infected women at baseline and developed in an additional 14% over a mean follow-up period of 21 months[1] • This study defined kidney disease as serum creatinine >1.4 mg/dL or urine dipstick >2+ protein on any research visit; such criteria omitted patients with a low GFR and a serum creatinine <1.4 mg/dL and likely underestimated CKD prevalence
National Sample of US Veterans Affairs Patients	• A total of 7.1% of HIV-infected individuals had a GFR <60 mL/min,[2] whereas an analysis of HIV-infected patients in an urban AIDS center found 15.5% had low GFR or proteinuria[3]
Fat Redistribution and Metabolic Change in HIV Infection (FRAM)	• Microalbuminuria, which is predictive of kidney disease in diabetic patients, was detected in 11% of HIV-infected participants

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