Viruses and Kidney Disease: Beyond HIV

Meryl Waldman, MD,* Vickie Marshall, MS,† Denise Whitby, PhD,† and Jeffrey B. Kopp, MD*

Summary: Human immunodeficiency virus (HIV)-infected patients may acquire new viral co-infections; they also may experience the reactivation or worsening of existing viral infections, including active, smoldering, or latent infections. HIV-infected patients may be predisposed to these viral infections owing to immunodeficiency or risk factors common to HIV and other viruses. A number of these affect the kidney, either by direct infection or by deposition of immune complexes. In this review we discuss the renal manifestations and treatment of hepatitis C virus, BK virus, adenovirus, cytomegalovirus, and parvovirus B19 in patients with HIV disease. We also discuss an approach to the identification of new viral renal pathogens, using a viral gene chip to identify viral DNA or RNA.

Semin Nephrol 28:595-607 © 2008 Elsevier Inc. All rights reserved.

Keywords: Hepatitis C, BK virus, adenovirus, cytomegalovirus, parvovirus

The differential diagnosis of kidney injury and urinary abnormalities in a human immunodeficiency virus (HIV)-infected patient is broad. The diagnoses that most commonly are considered include HIV-associated nephropathy (HIVAN), immune complex kidney disease, thrombotic microangiopathy, and drug-related injury. These topics are covered extensively elsewhere in this issue. Less attention is often given to infections with other viruses that can affect the urogenital tract from the urethra to the kidney and that may lead to similar clinical features as the other diagnoses. This review describes the spectrum of renal and urologic syndromes associated with other viral infections in HIV-infected patients. Specifically, we discuss the biologic and epidemiologic features of kidney disease associated with hepatitis C, BK virus, adenovirus, cytomegalovirus, and parvovirus B19.

HEPATITIS C VIRUS

Hepatitis C virus (HCV) co-infection is common among HIV-infected patients. Approximately one third of HIV-infected individuals worldwide also are infected with HCV, with higher rates of co-infection (>75%) observed in patients who were infected parenterally.1,2 Given the high prevalence of co-infection, HCV-related kidney disease is an important consideration in patients with HIV-HCV co-infection who present with renal manifestations. A variety of glomerulonephritides are associated with HCV infection, including membranous glomerulopathy,3,4 focal segmental glomerulosclerosis (FSGS),5,6 and, most commonly, membranoproliferative glomerulonephritis (MPGN) with and without cryoglobulinemia.7,9 A similar spectrum of glomerular diseases has been observed in patients with concurrent HIV and HCV infection.10,11 In addition, post-infectious glomerulonephritis, immunotactoid glomerulopathy,14 and fibrillary glomerulonephritis15 have been reported in this population.9

Two series have reviewed the clinical and renal pathologic features of patients co-infected with HIV and HCV.16,17 Stokes et al16 reported the renal findings in 7 African American and 5
Hispanic co-infected intravenous drug users who presented with proteinuria, hematuria, and renal dysfunction. The majority had hypertension and edema, and 42% had cryoglobulinemia. Renal biopsy findings included MPGN in 5 patients, mesangial proliferation glomerulonephritis in 5 patients, membranous glomerulonephritis in 1 patient, and 1 case of collapsing FSGS with immune complex deposits. Three of 12 patients died and 5 patients (42%) progressed to end-stage renal disease (ESRD) after a mean of 8.4 months. Cheng et al\textsuperscript{17} examined the impact of HIV infection on both renal and patient survival in 14 patients with HCV-associated glomerular disease. All were intravenous drug users with a mean age of 45 years. The majority of patients (93%) were African American. HCV-associated glomerular disease became clinically evident in the setting of moderate to advanced HIV disease; 86% of patients had CD4 cell counts of less than 500/uL and 43% had acquired immune deficiency syndrome (AIDS). The clinical presentations were similar to that of isolated HCV-associated glomerular disease with renal insufficiency and nephrotic range proteinuria in the majority. Renal biopsy findings included 11 cases of MPGN with a relatively high frequency of MPGN type 3 (45%). Three patients had mem branous glomerulonephritis, all of whom had atypical histologic features including diffuse mesangial proliferation with deposits, focal segmental endocapillary proliferative and exudative glomerulonephritis, and 1 of the patients had FSGS with collapsing features suggestive of overlap with HIVAN.

There were several notable differences between the cohort of co-infected patients and those with isolated HCV-associated glomerular disease.\textsuperscript{17} The degree of renal insufficiency at presentation in the HIV co-infected patients was more advanced than reported in HIV-associated MPGN historical controls, although this may reflect delay in renal biopsies. The co-infected patients had a lower prevalence of hypocomplementemia (46%) and cryoglobulinemia (33%) compared with that reported in HCV-associated glomerular disease without HIV.\textsuperscript{7,18} Only 1 patient with cryoglobulinemia had organized deposits. This differs from the high rate of substructure identification in glomerular deposits of HCV-associated glomerular disease in HIV-negative patients.\textsuperscript{7} Renal outcome was worse for co-infected patients compared with patients with isolated HCV-associated glomerular disease and similar creatinine values. A higher percentage had a more rapid progression to ESRD: 71% progressed rapidly to advanced renal failure and 50% required dialysis after a median interval of 2 months after biopsy. A similarly poor course in co-infected patients was reported by Stokes et al.\textsuperscript{16} In addition, mortality was high (57%), and the median combined renal/patient survival was 5.8 months.\textsuperscript{17} The clinical course more closely resembled that of HIVAN rather than HCV-associated glomerular disease.\textsuperscript{19} Although the clinical course of isolated HCV-associated renal disease can vary dramatically, most patients do not progress rapidly to ESRD. Cheng et al speculated that the combined influences of complex glomerular lesions, higher baseline renal insufficiency, greater viral burden, and black race may promote more rapid renal deterioration and higher mortality in HIV\textsuperscript{-}infected patients with HCV-associated glomerular disease.\textsuperscript{17}

Although the co-existence of HIV and HCV infection is common, relatively few cases of HCV-related renal disease in HIV patients have been described in the literature. Several factors may contribute to this observation. The clinical presentation of HCV-associated glomerular disease often is similar to that of HIVAN, and the features that serve as clues to the presence of HCV-associated glomerular disease such as hypocomplementemia and cryoglobulinemia may not be present. Thus, many patients may not undergo renal biopsy to distinguish between the diseases. Also, the renal manifestations typically become clinically apparent in the fifth or sixth decade of life, after long-standing HCV infection. Before the use of highly active antiretroviral therapy (ART), it was unlikely that HIV-infected patients survived long enough to manifest renal disease related to HCV. With improved survival associated with ART, complications related to HCV infection, including glomerular disease, are likely to be observed with greater frequency.

The existence of concomitant HIV infection in patients with HCV-associated glomerular dis-
ease makes the therapeutic approach difficult. The course of renal disease appears to be more aggressive in HIV-infected patients, and there may be greater resistance to interferon-alfa in co-infected patients.\textsuperscript{17} Although interferon has been shown to have anti-HIV activity,\textsuperscript{20} therapy for HCV with pegylated interferon-alfa in combination with ribavirin is associated with adverse effects that may be more pronounced in HIV-infected patients. Anemia can be problematic as a result of ribavirin-related hemolysis and interferon-related suppression of hematopoiesis. Zidovudine may cause severe anemia when used concurrently with anti-HCV therapy. An additional concern is the drug–drug interaction between ribavirin and other nucleoside reverse-transcriptase inhibitors, such as didanosine, which can cause mitochondrial toxicity, pancreatitis, or lactic acidosis.

**BK VIRUS**

BK virus (BKV), is a nonenveloped, icosahedral encapsulated DNA virus that belongs to the Papovaviridae family. JC virus and SV40 are other members of this family. BKV infection is widespread and typically is acquired in childhood.\textsuperscript{21} Approximately 80\% of the population is seropositive for BKV by adulthood. The majority of primary infections with BKV in immunocompetent hosts are asymptomatic. After primary infection, BKV frequently establishes latent infection in renal tubular cells and urinary tract epithelia.\textsuperscript{22,23} The major clinical manifestations appear to result from viral reactivation within the genitourinary tract during conditions of cellular immunosuppression.\textsuperscript{23} Hemorrhagic cystitis is a well-described complication related to BKV reactivation that is common after bone marrow transplantation and also is seen in renal transplant recipients.\textsuperscript{24,25} Ureteral and urethral stenosis leading to hydronephrosis\textsuperscript{26,27} also has been reported. In the renal transplant population, BKV is implicated most frequently in the development of BKV nephropathy, which is associated with a high rate of premature allograft loss.\textsuperscript{28-30}

BKV-related illness is less well characterized in patients with HIV infection. There are 2 reported cases of severe hemorrhagic cystitis caused by BKV in patients with HIV.\textsuperscript{31,32} In both cases, symptoms and viruria persisted despite numerous treatments, including ganciclovir, foscarinet, nalidixic acid,\textsuperscript{32} and cidofovir.\textsuperscript{31} There are 6 published cases of BKV-associated nephropathy in patients with AIDS.\textsuperscript{33-38} All cases occurred in males with CD4 cell counts of 100 cells/\mu L or less. All presented with progressive azotemia and, in some, low-grade proteinuria with bland urine sediment. The diagnosis of BKV nephritis had not been suspected in any of these cases; rather, the kidney dysfunction initially was attributed to alternative diagnoses such as drug-induced interstitial nephritis. Kidney biopsies revealed characteristic findings of tubulointerstitial nephritis with mixed inflammatory infiltrates (lymphocytes and monocytes) and tubular epithelial cells with viral intranuclear inclusions. The presence of BKV was confirmed by immunohistochemistry or in situ hybridization. Three patients progressed to ESRD, all of whom died. The remainder had a progressive decline in creatinine clearance.

It is unclear if the paucity of reports in the literature regarding BKV-related illness reflects true rarity of disease among HIV-infected patients or under-recognition of this viral infection. Support of the latter idea comes from numerous cases of BKV-related tubulointerstitial nephritis in renal biopsy and autopsy specimens from AIDS patients in whom the diagnosis had not been considered.\textsuperscript{33-39} There also are observations that support an interaction between HIV and BKV and suggest that BKV may be an emerging AIDS-associated pathogen. HIV-infected patients have a higher incidence of BKV viruria and also shed BKV at much higher levels than immunocompetent controls.\textsuperscript{22,40,41} Urinary BKV shedding is seen in 20\% to 60\% of HIV-infected patients.\textsuperscript{37,40,42,43} BKV viruria as well as the concentration of BKV in the urine are both related inversely to the CD4 cell count.\textsuperscript{31,43} This may indicate that clinical disease is more common among patients with end-stage AIDS, although this is not a consistent finding.\textsuperscript{42,44} Interestingly, a recent study indicated that the HIV-1 viral protein Tat may enhance BKV transcription,\textsuperscript{45} suggesting that high HIV viral loads may act synergistically with the
immunosuppressed state to enhance BKV viral reactivation.

The dynamics of BKV reactivation and the factors associated with expression of clinically significant disease are not well understood. Several risk factors have been proposed for BKV-associated hemorrhagic cystitis that arises in the setting of hematopoietic stem cell transplant. Some investigators have suggested an immune reconstitution pattern of disease, whereby the disease manifestations are most severe when the immune system is reconstituting and viral antigens in the bladder wall are recognized by emerging, functioning lymphocytes. Interestingly, immune reconstitution syndrome might play a similar role in expression of BKV illnesses in HIV-infected patients. It also has been suggested that mutant BKV strains with altered regulatory regions may be linked to progressive infection and development of renal disease in HIV-infected patients, but further data are needed.

There are limitations with the diagnostic modalities for BKV infection. Cytologic examination of urine to detect decoy cells (polyomavirus-infected cells with an enlarged nucleus containing a basophilic intranuclear inclusion) is a good screening test for the presence of BKV in urothelium, but similar cytopathology can be seen with other viruses, including JC virus and adenovirus. Quantitative urine polymerase chain reaction (PCR) to detect viral DNA is more sensitive than urine cytology and can differentiate BKV from JC virus in urine. However, detection of BKV DNA by PCR does not have high disease specificity because of the high rate of BKV shedding among HIV-infected patients. Demonstration of BKV viremia by plasma PCR is helpful to link BKV replication to presence of disease. Nevertheless, the relationship between BKV viruria and viremia, and the cut-off values and predictive values of BKV viruria and viremia for the occurrence of BKV-related disease, have not been defined in patients with HIV infection.

Definitive diagnosis of BKV-related renal disease is established by renal biopsy showing tubulointerstitial nephritis with characteristic cytopathic changes in the epithelium of the renal tubules and urothelial lining (Fig. 1). The infected cells have an enlarged nucleus with a gelatinous basophilic inclusion resulting from accumulation of newly formed virions. Electron microscopy shows intranuclear viral particles, 45 to 55 nm in diameter. Confirmation of polyomavirus infection usually is performed with immunohistochemical stains, in situ hybridization, or in situ PCR.

Treatment of BKV-related illness remains a major challenge. Currently, there is no antiviral drug with proven efficacy against BKV. Cidofovir and leflunimide and intravenous immunoglobulin have been used to treat BKV nephropathy in renal transplant patients with some success, but randomized control trials have not been performed. Cidofovir, vidarabine, and gamma globulin have been used to treat hemorrhagic cystitis in stem cell transplantation patients. There is also some evidence that fluoroquinolones have potential benefit as prophylactic agents against BKV infection in stem cell transplantation patients. There is little experience treating BKV-related illness in the HIV-infected population. Thus, therapeutic options have to be extrapolated from the aforementioned patient populations.

Reduction of immunosuppression is a major focus of management of renal transplant recipients with BKV nephropathy and often leads to stabilization of renal function and reduction in viremia. Initiating ART would be an analogous approach in HIV-infected patients. Therapeutic relevance of this for BKV infection is unknown, but ART has been shown to be beneficial among HIV patients with JC virus–associated progressive multifocal leukoencephalopathy.

Currently, there are no data to suggest that routine screening for BKV viremia and viruria has benefit in HIV-infected patients. However, as more HIV-infected individuals with ESRD proceed to renal transplantation, BKV infection likely will become particularly relevant because of the combined effects of immunosuppression related to their disease and antirejection medications. An aggressive monitoring protocol may be warranted in this population.
Adenovirus is a nonenveloped, double-stranded DNA virus that is transmitted to human beings through aerosolized droplets and fecal-oral spread. Most infections occur during childhood and cause a self-limited respiratory or gastrointestinal illness in the immunocompetent host. In contrast, adenoviral infection can be lethal in immunocompromised patients, who may develop disease as a result of newly acquired or endogenously reactivated infection. Adenovirus is capable of causing disseminated disease or organ-specific syndromes including enteritis, pneumonitis, hepatitis, and encephalitis. Urinary tract involvement may manifest as hemorrhagic cystitis, which is a well-described complication in bone marrow transplant recipients. Severe acute necrotizing tubulointerstitial nephritis also is associated with adenovirus infection in immunocompromised individuals and is associated with high mortality. It may present with azotemia, gross hematuria that may be attributed incorrectly to cystitis, and, occasionally, hydronephrosis.

The clinical relevance of adenovirus in the HIV-infected population has not been well defined. Adenoviruses have been recovered from HIV-infected patients since the beginning of the AIDS epidemic. Surveillance studies have reported that between 2%-20% of HIV infected patients have symptomatic or asymptomatic adenovirus excretion in the

---

**Figure 1.** Histologic appearance of virally-infected kidney cells. (A and B) Polyoma infection. Renal allograft biopsy showing tubulointerstitial damage. Some tubular epithelial cells show finely granular and markedly enlarged nuclei with a ground-glass appearance (A, arrowhead) which typically is seen in polyoma virus nephropathy. A mononuclear cell infiltrate is present (periodic acid–Schiff stain: magnification, 200×). Immunohistochemical staining for SV40 T antigen shows numerous nuclei of tubular epithelial cells in 1 tubular profile with reaction product (immunoperoxidase: magnification, 200×). Reprinted with permission from Li et al. (C) CMV infection. Kidney tissue showing characteristic large cells with basophilic intranuclear inclusions that have the appearance of an owl’s eye. There also are prominent red cytoplasmic inclusions. (Hematoxylin-eosin stain: magnification, 600×). (D) Adenovirus infection. Kidney tissue from an immunosuppressed patient shows necrosis of tubular epithelial cells. Infected tubular cells have enlarged basophilic nuclei with smudged appearance, which is characteristic of adenovirus. (Hematoxylin-eosin stain: magnification, 400×).
Cells - Tumor tissues - Plasma - Urine - Whole Blood

RNA Extraction

Random Primer PCR
1\textsuperscript{st} Strand Synthesis - primer A

Random Primer PCR
2\textsuperscript{nd} Strand Synthesis - primer B

Template Amplification
40 rounds PCR – primer B

Incorporation of aminoallyl-dUTP
20 PCR cycles – primer B

Purification of aminoallyl-dUTP cDNA and Cy3 labeling

Purification, hybridization on custom Agilent microarray, Wash and Scan
gastrointestinal and urinary tract. It has been proposed that adenovirus infection may reduce the survival of HIV-positive patients with low CD4 cell counts, although death related to adenovirus is difficult to ascertain given the presence of other opportunistic infections.

There are isolated reports of adenovirus-related urologic and renal disease in this population. Mazoyer et al recently described a 34-year-old white man with AIDS and a CD4 count of 0 cells/μL who presented with gross hematuria, mild azotemia, and nonnephrotic proteinuria. Urine culture and urine PCR were positive for adenovirus. Cystitis was suspected but cystoscopy was unremarkable. Renal biopsy was consistent with severe acute tubulointerstitial nephritis, tubular epithelial cell necrosis, and intranuclear viral inclusion bodies. Immunohistochemical staining with anti-adenovirus antibody showed strong intranuclear and cytoplasmic staining in infected tubular epithelial cells. The patient was treated with ribavirin, which decreased urine adenovirus load, but the patient died from a superimposed fungal infection. Two other cases of adenovirus-related interstitial nephritis in patients with AIDS have been reported, and both were diagnosed post mortem. There was also a single case report of severe hemorrhagic cystitis attributed to adenovirus in a patient with AIDS.

The diagnosis of urinary tract involvement by adenovirus typically is made by viral isolation in urine. However, after acute infection, adenovirus may be shed from stool or urine for many months in the immunocompromised host. The diagnosis of urinary tract involvement by adenovirus is typically made by viral isolation in urine. However, after acute infection, adenovirus may be shed from stool or urine for many months in the immunocompromised host. Thus, a positive culture result needs to be interpreted in light of clinical manifestations. Quantitative PCR is a sensitive tool for the detection of adenovirus genome in the blood, but in most institutions it is not performed routinely on urine unless requested to monitor the response to antiviral therapy. Definitive diagnosis of adenovirus nephritis requires a renal biopsy which can show necrotizing tubulointerstitial nephritis, mononuclear infiltrates, smudge cell formations (nuclear enlargement with intranuclear inclusions and cell degeneration) and occasionally hemorrhage (Fig. 1). Electron microscopy shows the crystalline arrays of viral particles. Adenovirus-specific immunohistochemical assays and in situ hybridization help confirm the diagnosis.

There is no standard treatment for adenovirus-associated disease in HIV patients. Although controlled studies are lacking, cidofovir has been associated with clinical improvement in bone marrow and renal transplant recipients. There are anecdotal reports of limited efficacy of other antiviral agents including ribavirin, vidarabine, and ganciclovir.

CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is a double-stranded DNA virus that is a member of the herpes virus family. CMV disease is a life-threatening opportunistic infection in HIV-infected patients with severe immunocompromise. In patients with AIDS, progressive loss of immune function permits CMV reactivation and replication. Before the availability of ART, more than 90% of HIV-infected patients had evidence of disseminated CMV infection at autopsy. Although the incidence of CMV disease in HIV-infected patients declined significantly after the introduction of ART, many patients, particularly those with CD4 cell counts below the critical threshold of less than 100 cells/μL, are still at high risk for CMV disease. In the immunocompromised

Figure 2. Identifying novel or unexpected viruses using a viral gene chip. The starting material typically is RNA obtained from cells, tumor tissue, blood, urine, or other body fluids. After first-strand DNA synthesis with reverse transcriptase, the first and second DNA strands are amplified using a random PCR protocol and standard primers A and B as described. The complementary DNA is used in a subsequent 40-cycle PCR using a specific primer designed to amplify the template. The same primer is used in an additional 20 cycles of PCR that incorporates random primed oligomers in the presence of aminooxy-UTP, thus allowing labeling with the fluorescent molecule Cy3. Once purified, the Cy3-labeled DNA is pre-annealed with human cot-1 DNA and Agilent blocking and hybridization buffers before hybridizing onto the Agilent microarray bearing the sequences from viral open reading frames. A standard custom microarray Agilent protocol is used to wash the microarray before scanning.
host, CMV infects multiple organ systems and may cause a broad array of clinical presentations, including retinitis, encephalitis, pneumonitis, hepatitis, gastrointestinal tract ulceration, hemorrhagic cystitis, and tubulointerstitial nephritis (in renal allografts).

In HIV-infected patients, CMV cystitis has been reported in 2 cases. Disseminated CMV infection has been implicated as the cause of nephritis in an adult and an infant with HIV infection, but renal histologic features were not well described in either of these reports. Mueller et al described a child with AIDS who presented with suprapubic pain, gross hematuria, acute kidney injury, and intermittent urinary tract obstructive symptoms. Retrograde ureterography was consistent with ureteritis. Post mortem examination revealed focal hemorrhagic lesions along the entire length of both ureters. The findings of intranuclear inclusions within submucosal cells and positive immunoperoxidase staining were consistent with CMV infection. Finally, a link between CMV infection and development of thrombotic microangiopathy has been hypothesized based on a case control study by Maslo et al. Endothelial CMV inclusions were observed in 9 of 18 renal biopsy specimens from HIV patients with thrombotic microangiopathy, whereas CMV was not detected in any control specimens.

**PARVOVIRUS B19**

Parvovirus B19 (B19) is a small single-stranded DNA virus. B19 is a common pathogen that infects more than 50% of all individuals by adulthood. Infection often is asymptomatic, but when symptomatic it typically causes erythema infectiosum in children or arthropathy in adults. In individuals with hemolysis or ineffective erythropoiesis, acute B19 infection may lead to transient aplastic crisis. Among immunocompromised individuals, including those receiving immunosuppressive therapy and those infected with HIV, B19 infection can become persistent as a result of the inability to mount an effective humoral and/or cellular response. Pure red cell aplasia is the most common presentation of persistent parvoviral infection in HIV-infected patients.

Whether parvovirus infection has any pathogenic role in renal or urologic disease in HIV-infected patients is unknown. Christensen et al implicated parvoviral infection as the cause of cystitis in a patient with HIV infection. Symptoms of hematuria and pyuria began 8 weeks after the initial diagnosis of acute parvovirus infection and persisted for 2 years. B19 DNA was detected in urine samples during much of that time, and bladder wall biopsy also was weakly positive for B19 DNA. Nevertheless, a strong causal relationship could not be established between the parvoviral infection and symptoms.

There is an association of B19 with a variety of glomerular diseases including post-infectious glomerulonephritis, FSGS, collapsing FSGS, Henoch-Schönlein purpura, and thrombotic microangiopathy in immunocompetent and immunocompromised hosts, but it has been difficult to prove a definitive causal relationship in many cases. Interestingly, Moudgil et al detected B19 DNA in 15% of renal biopsy specimens from patients with HIVAN, although this did not differ significantly compared with controls. In situ hybridization revealed localization of B19 to glomerular parietal and visceral epithelial cells. In HIVAN, HIV has been identified in similar locations. The implications of this are not known. Perhaps an interaction exists between these 2 viruses that may trigger expression of HIVAN or other renal manifestations such as immune complex glomerulonephritis, but this is purely speculation at this point.

**IDENTIFICATION OF NEW VIRAL CAUSES OF RENAL DISEASE**

We have embarked on a program to identify viral causes of unexplained renal disease. In particular, we have focused on idiopathic collapsing glomerulopathy and thrombotic microangiopathy after renal transplant. Although there is strong evidence that HIV-associated kidney disease is a consequence of HIV-1 infection, as reviewed elsewhere in this issue, it is prudent to consider a possible role for other viruses in the etiology of renal manifestations.

The molecular toolkit available for investigators wishing to hunt for new viruses has been
expanded considerably in recent years. In 1994, Yuan Chang and Patrick Moore used representational difference analysis to identify sequences of Kaposi’s sarcoma–associated herpesvirus in a biopsy specimen from an AIDS patient with Kaposi’s sarcoma. The same investigators more recently used deep sequencing to identify a novel polyomavirus in Merkel cell carcinoma. These approaches are technically difficult and labor intensive, have limited sensitivity, and are not applicable to all sample types. Other investigators, notably Don Gannem and Joseph DeRisi, have designed microarrays able to detect sequences of all known viruses. This approach has proven very successful in detecting known and novel viruses in a variety of sample types and disease settings. These approaches are technically difficult and labor intensive, have limited sensitivity, and are not applicable to all sample types. Other investigators, notably Don Gannem and Joseph DeRisi, have designed microarrays able to detect sequences of all known viruses. This approach has proven very successful in detecting known and novel viruses in a variety of sample types and disease settings. We are using a similar approach, but with substantial adaptation, to address the question of whether any known or unknown viruses contribute to the pathogenesis of renal diseases (Fig. 2).

We are using a customized array (Agilent Technologies, Santa Clara, CA), which includes oligonucleotides from 655 viruses from 135 genera. On average, each virus is represented by 10 to 20 individual features distributed across both conserved and unique regions of the viral genome. The grids are printed 8 to a slide, enabling relatively high throughput screening of plasma, peripheral blood mononuclear cells, and urine from patients. An updated version of the array with expanded coverage of virus families such as polyomaviruses, and the inclusion of recently discovered viruses, currently is being designed.

### CONCLUSIONS

This review serves to increase awareness of the renal and urologic manifestations associated with viral co-infections in HIV-infected patients. Table 1 summarizes the clinical spectrum of these syndromes, as well as the approach to diagnosis in this population. The true clinical burden of these 5 viruses, their contribution to renal disease, and their impact on morbidity and mortality in HIV-infected patients have not been well defined. Given the prevalence of these viruses in the general population, the increased susceptibility to viral infections and increased likelihood of reactivation of latent viruses in HIV-infected patients, complications related to these viruses may be more common than currently appreciated. There are challenges in diagnosing these viral infections that may contribute to their under-recognition. A major issue may be a lack of diagnostic suspi-
cian because many renal diseases affecting these patients have similar and overlapping presentations. Also, interpretation of diagnostic tests may not be straightforward because it can be difficult to differentiate viral isolates that are responsible for disease from those that may represent silent reactivation or persistent infection. For many of the viruses, it is not known what level of viremia and viruria is considered normal or abnormal and pathologic in HIV-infected patients. There also is a underutilization of renal biopsies in this patient population, which would help to differentiate renal disease associated with these viruses from other etiologies. Large-scale studies that systematically monitor for these viruses in the blood, urine, and kidney specimens of HIV-infected patients along with CD4 cell count and HIV viral load would be beneficial to understand the relationship between markers of immune function, co-infection, disease manifestations, risk factors, and outcomes.

Acknowledgment
The authors would like to thank Dr. David Kleiner and Dr. Jim Balow for providing the histology images of the cytomegalovirus and adenovirus infection. The authors appreciate the critical review of the manuscript by Dr. Monique Cho.

REFERENCES
Viruses and kidney disease

DNA from autopic samples of HIV-1 positive and negative subjects. Int J Immunopathol Pharmacol. 2003;16:269-76.


Viruses and kidney disease