Published in final edited form as:

Semin Nephrol. 2008 November ; 28(6): 556–562. doi:10.1016/j.semnephrol.2008.08.008.

Acute Kidney Injury in HIV- Infected Patients

Sahir Kalim, MD,

Department of Medicine Mount Sinai School of Medicine, New York, NY

Lynda A. Szczech, MD [Associate Professor], and

Department of Medicine, Division of Nephrology Duke University School of Medicine, Durham, NC

Christina M. Wyatt, MD [Associate Professor]

Department of Medicine, Division of Nephrology Mount Sinai School of Medicine, New York, NY

Abstract

Acute kidney injury is common in HIV-infected patients, and has been associated with increased morbidity and mortality. Prior to the introduction of effective antiretroviral therapy, acute kidney injury in HIV-positive patients was most commonly the result of volume depletion, septicemia, or nephrotoxic medications. Acute kidney injury remains a significant problem in the antiretroviral era, and is still commonly attributed to infection or nephrotoxic medications. Less common causes such as direct infectious insults, immune restoration inflammatory syndrome, rhabdomyolysis, and obstruction should be considered when the underlying process is not obvious. In addition to advanced HIV disease, several other patient characteristics have emerged as potential risk factors for acute kidney injury in the antiretroviral era, including older age, diabetes, pre-existing chronic kidney disease, and hepatitis co-infection or liver disease.

Keywords

Acute kidney injury; acute tubular necrosis; HIV

Kidney disease in HIV-infected individuals was initially described more than two decades ago.¹ Advances in HIV care, most notably the introduction of effective antiretroviral therapy (ART) at the end of 1995, have resulted in decreased progression to AIDS and mortality, as well as a reduced incidence of opportunistic infections.²³ Subsequently, non-AIDS complications such as kidney, liver, and cardiovascular disease have emerged as important problems in ART-treated patients.³⁴ Acute kidney injury (AKI) is a common and clinically significant form of kidney disease in HIV-infected patients.

Although definitions of AKI vary significantly across different reports, it is generally distinguished from chronic kidney disease by a precipitous drop in glomerular filtration rate. In the general population, AKI is associated with increased morbidity and mortality.⁵ Electrolyte derangements, metabolic acidosis, volume overload, and encephalopathy are just some of the life-threatening sequelae. Understanding the epidemiology and etiologies of AKI is a powerful tool in identifying patients at risk. This challenge is magnified when considering

Corresponding Author: Christina M. Wyatt, MD, Box 1243, Division of Nephrology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, Phone: (212) 241-6689, Fax: (212) 987-0389, Email: E-mail: christina.wyatt@mssm.edu.

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the HIV-infected patient with multiple comorbidities, co-infections, and nephrotoxic drug regimens complicating their management. In the ART era, these HIV-related risk factors must be considered in conjunction with traditional risk factors for AKI, such as older age, diabetes, and chronic kidney disease.⁶ This review examines the common and unique features of AKI in patients with HIV infection, incorporating data from both pre- and post-ART studies to understand the changing epidemiology, etiologies, risk factors, and outcomes of AKI in HIV-infected patients.

Epidemiology and Etiology of Acute Kidney Injury in HIV Infection

Several studies have described the incidence and causes of AKI in patients with HIV over the past two decades; however, direct comparisons before and after the advent of ART are difficult due to the lack of consistent inclusion criteria or definitions of AKI. Consensus guidelines for the management of kidney disease in patients with HIV recommend a definition of acute renal failure based on an increase in serum creatinine >1.5 mg/dL, or >1.3 times the upper limit of normal at the respective clinical laboratory, that returns to baseline values within three months.⁷ A recent interdisciplinary consensus panel has classified AKI in the general population according to a change from baseline serum creatinine or a decrease in urine output, but this classification system has not been widely adopted.⁸

Early Studies: Acute Kidney Injury in the Pre-ART Era

While the recent consensus definition of AKI was designed to capture the full spectrum of AKI, studies from the pre-ART era typically included only severe cases. In a series of 449 AIDS patients admitted to a New York City hospital from 1983–1986, nearly 20% of patients experienced an episode of AKI, defined as an increase in serum creatinine of at least 2.0 mg/dL from baseline.⁹ The incidence of AKI in patients with AIDS was considerably greater than the 5% incidence observed in a general non-AIDS hospital population that the authors cite as an adequate historical control. The most common etiologies of AKI in this retrospective cohort study were volume depletion (38%) and medication toxicity (32%). Nephrotoxicity was most often attributed to direct toxicity from pentamidine, amphotericin, or aminoglycosides, and to acute interstitial nephritis (AIN) related to trimethoprim-sulfamethoxazole. Other etiologies of AKI included acute tubular necrosis (ATN) from shock or sepsis, and radiocontrast nephropathy.⁹

In a retrospective review of all renal consultations for severe AKI (serum creatinine 6mg/dL or greater) at another New York City institution between 1984 and 1993, nearly one-third occurred in HIV-infected patients, most of whom met criteria for AIDS.¹⁰ Fifty-two percent of AKI cases in HIV-infected patients were caused by ischemic renal insult from septicemia, and 23% were attributed to nephrotoxic medications, including aminoglycosides, amphotericin B, pentamidine, and acyclovir. Other causes included medication-induced AIN, non-steroidal anti-inflammatory (NSAID) use, and rhabdomyolysis. When compared to HIV-negative patients, AKI in HIV-infected patients was significantly more likely to be attributed to sepsis (52% versus 24%), and less likely to be the result of obstruction.¹⁰

Both of these studies implicated volume depletion, sepsis, and medication toxicity as the leading causes of AKI in the pre-ART era. In contrast, there was a high prevalence of vascular and glomerular disease in a series of 92 HIV-infected patients admitted to a nephrology unit with AKI, defined as an increase in serum creatinine from normal to >2 mg/dL within 20 days.¹¹ It is likely that patients at risk for ischemic damage due to hypovolemia or septicemia were excluded from this referral population. In addition, many of the patients in this study had some exposure to antiretroviral monotherapy. Fifty-four percent of AKI cases were attributed to vascular or glomerular diseases, most commonly hemolytic uremic syndrome (HUS) and HIV-associated nephropathy (HIVAN).¹¹

More recently, administrative data from the New York State Planning and Research Cooperative System (SPARCS) database were used to identify diagnoses of AKI based on ICD-9 codes.⁶ This study examined the incidence of AKI among hospitalized patients in both the pre- and post-ART eras. In 1995, AKI was reported in 2.9% of 52,580 hospital admissions among HIV-infected patients, compared to only 1% of hospitalizations among non-infected patients during that same year ($p < 0.001$). Data on the etiology of AKI were not available in this study.⁶

Acute Kidney Injury in the ART Era

With the advent of combination ART came a decrease in opportunistic infections and mortality, with an increase in the importance of non-AIDS comorbidities.^{3,4} As such, the incidence and etiology of AKI in HIV-infected patients may have also changed. Based on data from the New York SPARCS database, the incidence of documented AKI in HIV-related hospitalizations during 2003 remained significantly higher than that observed in admissions for HIV-negative patients (6% versus 2.7%), and was more than double that reported in 1995.⁶ While the observed increase in incidence between 1995 and 2003 may reflect changes in reporting, as well as an increase in the acuity of hospital admissions, it is notable that the incidence of AKI has not decreased in the post-ART era.

In a prospective observational study of 754 ambulatory HIV-positive patients followed between 2000 and 2002, the incidence of AKI was 5.9 cases per 100 patient-years, with at least one episode in nearly 10% of patients.¹² AKI was defined as a rise in serum creatinine lasting 2 or more days, with the level of increase dependent on the baseline creatinine. Intrinsic renal causes were the most common etiology of AKI (46%), with the majority of these cases attributed to ischemic ATN or nephrotoxic drugs, and to a lesser degree radiocontrast nephropathy (Table 1). Pre-renal acute renal failure was also common (38%), and was attributed to volume depletion, sepsis, and liver disease. Unknown causes and obstruction (stones, crystalluria, and gross hematuria) constituted the remainder of cases. Overall, 52% of the AKI events were associated with an infection, presumably leading to either a pre-renal state or ischemic ATN. The majority of these infections were AIDS-defining, demonstrating that even among ambulatory patients in the post-ART era, opportunistic infections are still a common underlying cause of AKI. Medications were associated with one-third of events, causing ATN, AIN, crystalluria with obstruction, or volume depletion due to symptomatic gastrointestinal losses. Antibiotics and antiretrovirals were the most common offending agents, with amphotericin and indinavir being the most commonly implicated.¹² Antiretroviral nephrotoxicity is discussed in detail elsewhere in this issue, and special considerations for antiretroviral dosing and toxicity are summarized in Table 2.

Nephrotoxic drugs were also a common contributor to AKI among HIV-infected patients evaluated at a London hospital between 1998 and 2005.¹³ In this cohort of 2,274 patients, nearly 6% of patients experienced at least one episode of AKI during the study period.

More than half of the cases occurred within the first 3 months of HIV care, and it is possible that AKI was the primary presentation of HIV infection in some patients. The most common factors contributing to AKI were nephrotoxic drugs, opportunistic and non-opportunistic infections, malignancy, and liver disease. Lower CD4 nadir was consistently associated with AKI, while hepatitis C virus (HCV) co-infection and intravenous drug use were associated with the development of AKI after the first 3 months of HIV care.¹³

Other Etiologies of Acute Kidney Injury in HIV Infection

In addition to the common causes of AKI discussed above, HIV-infected patients are also at risk for several unique forms of AKI. Urinary obstruction is a relatively rare cause of AKI in

the HIV-positive patient.¹⁴ Post-renal causes of AKI in patients with HIV include both intrarenal obstruction, such as medication-induced crystalluria or hyperuricosuria from tumor lysis syndrome, and extrarenal obstruction, including retroperitoneal fibrosis, pelvic lymphadenopathy, bladder dysfunction, fungus balls, and nephrolithiasis.^{14,15} Crystalluria and nephrolithiasis have received the most attention in the literature. Deposition of insoluble crystals leading to AKI has been associated with sulfadiazine, acyclovir, indinavir, and foscarnet.¹⁵ Volume depletion, underlying kidney disease, and hypoalbuminemia increase the risk for precipitation and subsequent crystal-induced AKI.¹⁶ More recently, atazanavir has been associated with nephrolithiasis, but unlike indinavir this protease inhibitor has not been associated with obstructive AKI or with AIN.¹⁷

Also rare but of particular relevance to the HIV-positive patient are forms of AKI that result from direct infection of the kidney. Although HIVAN is the most common and well-recognized example, a variety of other infectious agents can affect the kidney. These rare causes of renal infection and injury have been recently reviewed elsewhere, and include parenchymal fungal infections, granulomatous nephritis from mycobacterium, and interstitial nephritis secondary to Epstein Barr virus, cytomegalovirus, and polyoma viruses.¹⁸ Further discussions of kidney disease caused by viruses other than HIV are reviewed elsewhere in this issue.

Another rare cause of AKI in the HIV-positive patient, essentially limited to case reports, is AIN secondary to the immune restoration inflammatory syndrome (IRIS).^{19,20} IRIS is a systemic inflammatory response to infections or to non-infectious diseases that can manifest as the immune system is restored after the initiation of ART. This diagnosis should be considered after other causes of AKI have been excluded, and may be supported by kidney biopsy showing granulomatous nephritis. Case reports suggest that renal function may improve with initiation of corticosteroid therapy.^{19,20} In a recently reported cohort study from London, IRIS was considered a potential contributor to 6 of 144 AKI events. All six cases occurred within 90 days of initiating ART and were associated with activation or exacerbation of underlying infections, including mycobacterium avium, *Pneumocystis*, *Cryptococcus*, and hepatitis B.¹³ (15) Rhabdomyolysis has been reported as a rare cause of AKI in HIV-positive patients, particularly in association with the use of heroin, cocaine, and statins.^{21,22} Rhabdomyolysis has also been reported in the setting of acute HIV infection.^{23,24}

Thrombotic microangiopathy should also be considered in HIV-infected patients with AKI, although this diagnosis appears to be less common in the ART era.^{12,25} Although the clinical presentation is similar to that observed in the general population, the prognosis of HIV-related HUS/ thrombotic thrombocytopenic purpura may be worse.²⁶ The clinical presentation and management of HIV-related thrombotic microangiopathy are reviewed in detail elsewhere in this issue.

Electrolyte Disorders in HIV Infection

Hyponatremia was the most common electrolyte abnormality in AIDS patients in the pre-ART era.²⁷ In a 3-month prospective study of 212 hospitalized patients with AIDS, 38% of patients developed hyponatremia, defined as a serum sodium <135 mEq/L.²⁸ Other studies demonstrated the frequency of hyponatremia to be as high as 75% among hospitalized AIDS patients, with either estimate being higher than the incidence in the general population.²⁷ Hyponatremia was most often attributed to volume depletion, which may result from gastrointestinal losses, fever, or poor oral intake. Adrenal insufficiency and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) secondary to pulmonary infections or central nervous system disease are other potential causes of hyponatremia in patients with advanced HIV/ AIDS.^{27,28}

Data on hyponatremia and other electrolyte abnormalities in the ART era are limited, and direct comparisons are difficult. A cross-sectional study including both ambulatory and hospitalized patients in Paris demonstrated a relatively low prevalence of hyponatremia, but identified a high frequency of other electrolyte abnormalities, including hypophosphatemia, low serum bicarbonate, and hyper- and hypomagnesemia.²⁹ Hyperkalemia, which may be associated with trimethoprim or pentamidine,¹⁵ was rare in this population. Differences in the frequency of electrolyte abnormalities in this study may be related to improved control of HIV infection, with a mean CD4 cell count of 420 cells/mm³, but may also reflect the inclusion of a heterogeneous population of ambulatory and acutely ill patients.²⁹ Although the spectrum of electrolyte disorders has changed in the ART era, antiretroviral agents have also been associated with electrolyte disorders, including lactic acidosis observed with nucleoside reverse transcriptase inhibitors and proximal tubulopathy related to the nucleotide reverse transcriptase inhibitor tenofovir.¹⁵ Antiretroviral nephrotoxicity is reviewed in detail elsewhere in this issue.

Risk Factors for Acute Kidney Injury in HIV Infection

Recognition of common risk factors for AKI in HIV-infected patients is important to guide efforts aimed at prevention and early diagnosis (Table 3). Among ambulatory patients, AKI has been associated with lower CD4 cell counts, history of AIDS, higher HIV RNA level, HCV co-infection, and history of ART exposure.^{12,13} Despite an observed association between ART exposure and AKI, individual antiretroviral agents are rarely implicated.^{12,13} Age, baseline serum creatinine, and history of hypertension or diabetes were not independently associated with AKI in two recent studies including a large number of ambulatory patients.^{12,13} In contrast, AKI among hospitalized HIV-infected patients has been associated with traditional risk factors for kidney disease, including older age, diabetes, and pre-existing chronic kidney disease.⁶ Interestingly, none of these recent studies have demonstrated an association between black race and AKI, despite the strong association between black race and chronic kidney disease.

Hepatitis co-infection and other forms of liver disease have also been associated with AKI in hospitalized and ambulatory patients with HIV infection.^{6,13,30} The identification of liver disease as a significant risk factor for AKI is notable in light of the high prevalence of HCV co-infection among HIV-positive patients in the United States.³¹

Novel research may uncover more direct mechanisms in the future, but such studies are currently lacking. HIV infection of renal tubular epithelial cells results in expression of numerous pro-inflammatory mediators, creating a possible link between HIV infection, tubulointerstitial inflammation, and renal injury.³² Whether such direct inflammatory effects potentiate AKI remains to be seen.

Outcomes of Acute Kidney Injury in HIV Infection

Prognosis in AKI varies with severity and etiology. Studies have demonstrated higher mortality in patients with AKI secondary to ATN and hemodynamic instability,^{9,11} with similar overall mortality rates in AIDS versus non-AIDS patients.^{10,11} Nevertheless, AKI remains a strong predictor of mortality in the ART era. In a recent cohort study from London, mortality was 31% among HIV-infected patients with AKI.¹³ Among hospitalized patients in New York State, a documented diagnosis of AKI was independently associated with a nearly 6-fold increase in mortality among HIV-infected patients.⁶

Conclusion

AKI remains common in HIV-infected patients, despite improvements in morbidity and mortality in the ART era. Beyond identifying patients at risk for AKI, successful prevention depends on optimizing immune status, as well as identifying and aggressively treating diabetes, chronic kidney disease, and hepatitis co-infection. The importance of prevention or early recognition of AKI is highlighted by the strong association between AKI and mortality among HIV-infected patients. Recognition of AKI is also essential to ensure proper dose adjustment of ART and medications used to treat the acute illness that often accompanies AKI.

Further studies are needed to determine if AKI is an independent predictor of mortality or rather a marker for greater systemic illness. The acute and chronic impact of various medications employed in the HIV-infected patient, including ART and antibiotic medications, should also be further investigated in order to decrease toxicity. Future studies of AKI in HIV-infected patients should attempt to use standard definitions to allow for comparison across studies.

Acknowledgements

Grant Support: Supported in part by NIH grant K23DK077568.

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Table 1
Causes of Acute Kidney Injury in HIV-Infected Patients

<u>Pre-renal Causes</u>	
Hypovolemia: diarrhea, nausea/ vomiting, decreased oral intake	
Effective Hypovolemia: hypotension, sepsis, liver disease, hypoalbuminemia (nephrotic syndrome, proteinuria, malnutrition)	
<u>Intrinsic Renal Injury</u>	
Acute tubular necrosis	
Ischemic: hypovolemia, shock, sepsis, cardiopulmonary compromise	
Nephrotoxic: medications, radiocontrast	
Rhabdomyolysis	
Parenchymal infection (mycobacterial, fungal, viral)	
Interstitial nephritis	
Hemolytic uremic syndrome	
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Glomerular disease: HIVAN, glomerulonephritis	
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<u>Post-renal Causes</u>	
Intra-renal tubular obstruction: crystalluria from medications, tumor lysis syndrome	
Ureter or bladder obstruction: nephrolithiasis, lymphadenopathy/ tumor, fungus ball, blood clots, neurogenic bladder	

Table 2
Antiretroviral Nephrotoxicity and Dose Adjustment in Acute Kidney Injury

Antiretroviral Drug Class	Reported Nephrotoxicity	Dose Adjustment in Acute Kidney Injury
Protease inhibitors	Crystalluria/ obstruction Indinavir Atazanavir Case reports with other agents Interstitial nephritis Indinavir Enhanced nucleotide toxicity? Ritonavir	None Maintain hydration with indinavir, atazanavir
Nucleoside reverse transcriptase inhibitors	Lactic acidosis Especially didanosine Enhanced nucleotide toxicity Didanosine Rare reports of AKI	Estimated GFR<50 Exceptions: abacavir (none), zidovudine (GFR<10)
Nucleotide reverse transcriptase inhibitors	Proximal tubulopathy Nephrogenic diabetes insipidus AKI	Estimated GFR<50
Non-nucleoside reverse transcriptase inhibitors	Rare reports of AKI	None Limited data for etravirine
Fusion inhibitors	Single case of MPGN Enfuvirtide	None Limited data
Integrase inhibitor	Rare reports of AKI	None

AKI=acute kidney injury; MPGN=membranoproliferative glomerulonephritis

Table 3
Risk Factors for Acute Kidney Injury in HIV Infection

Older age
Diabetes mellitus
Chronic kidney disease
Liver disease/ Hepatitis C
Low CD4 count
High HIV RNA
History of AIDS-defining illness
History of antiretroviral exposure