Acute Kidney Injury in HIV-Infected Patients

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Summary: Acute kidney injury is common in human immunodeficiency virus (HIV)-infected patients, and has been associated with increased morbidity and mortality. Before 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 still commonly is 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, preexisting chronic kidney disease, and hepatitis co-infection or liver disease.
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Kidney disease in human immunodeficiency virus (HIV)-infected individuals initially was described more than 2 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 acquired immune deficiency syndrome (AIDS) and mortality, as well as a reduced incidence of opportunistic infections.[2,3] Subsequently, non-AIDS complications such as kidney, liver, and cardiovascular disease have emerged as important problems in ART-treated patients.[3,4] 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 decrease 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 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-ART and post-ART studies to understand the changing epidemiology, etiologies, risk factors, and outcomes of AKI in HIV-infected patients.

EPIDEMIOLOGY AND ETIOLOGY OF AKI IN HIV INFECTION

Several studies have described the incidence and causes of AKI in patients with HIV over the past 2 decades; however, direct comparisons

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before and after the advent of ART are difficult because of 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 level greater than 1.5 mg/dL, or greater than 1.3 times the upper limit of normal at the respective clinical laboratory, that returns to baseline values within 3 months.[7] A recent interdisciplinary consensus panel has classified AKI in the general population according to a change from baseline serum creatinine level or a decrease in urine output, but this classification system has not been widely adopted.[8]

Early Studies: AKI in the Pre-ART Era

Although 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 to 1986, nearly 20% of patients experienced an episode of AKI, defined as an increase in serum creatinine level 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 causes of AKI in this retrospective cohort study were volume depletion (38%) and medication toxicity (32%). Nephrotoxicity was attributed most often 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 level, ≥6 mg/dL) 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, nonsteroidal anti-inflammatory use, and rhabdomyolysis. When compared with 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 level from normal to greater than 2 mg/dL within 20 days.[11] It is likely that patients at risk for ischemic damage owing 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 and HIV-associated nephropathy.[11]

More recently, administrative data from the New York State Planning and Research Cooperative System database were used to identify diagnoses of AKI based on International Classification of Diseases (ICD)-9 codes.[6] This study examined the incidence of AKI among hospitalized patients in both the pre-ART and post-ART eras. In 1995, AKI was reported in 2.9% of 52,580 hospital admissions among HIV-infected patients, compared with only 1% of hospitalizations among noninfected patients during that same year ($P < .001$). Data on the etiology of AKI were not available in this study.[6]

AKI 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 also may have changed. Based on data from the New York State Planning and Research Cooperative System database, the inci-

dence 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] Although 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 an increase in serum creatinine level lasting 2 or more days, with the level of increase dependent on the baseline creatinine level. 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 also was 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, showing 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 owing 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 in the article by Atta et al in this issue (p. 563), 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 nonopportunistic infections, malignancy, and liver disease. Lower CD4 nadir consistently was associated with AKI, whereas 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]

Table 1. Causes of AKI in HIV-Infected Patients

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

Abbreviation: HIVAN, HIV-associated nephropathy.

Other Etiologies of AKI in HIV Infection

In addition to the common causes of AKI discussed earlier, HIV-infected patients are also at

Table 2. Antiretroviral Nephrotoxicity and Dose Adjustment in AKI

Antiretroviral Drug Class	Reported Nephrotoxicity	Dose Adjustment in AKI
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
Nonnucleoside reverse-transcriptase inhibitors	Rare reports of AKI	None Limited data for etravirine
Fusion inhibitors	Single case of MPGN Enfurvitide	None Limited data
Integrase inhibitor	Rare reports of AKI	None

Abbreviation: MPGN, membranoproliferative glomerulonephritis.

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 HIV-associated nephropathy 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 recently have been 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 in the article by Kopp et al in this issue (p. 595).

Another rare cause of AKI in the HIV-positive patient, essentially limited to case reports, is AIN secondary to the immune restoration inflammatory syndrome.[19,20] The immune restoration inflammatory syndrome is a systemic inflammatory response to infections or to noninfectious 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, immune restoration inflammatory syndrome was considered a potential contributor to 6 of 144 AKI events. All 6 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 also has been reported in the setting of acute HIV infection.[23,24]

Thrombotic microangiopathy also should 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 hemolytic uremic syndrome/thrombotic thrombocytopenic purpura may be worse.[26] The clinical presentation and management of HIV-related thrombotic microangiopathy are reviewed in detail in the article by Fine et al in this issue (p. 545).

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 level of less than 135 mEq/L.[28] Other studies showed 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 attributed most often to volume depletion, which may result from gastrointestinal losses, fever, or poor oral intake. Adrenal insufficiency and the syndrome of inappropriate antidiuretic hormone secretion 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 showed a relatively low prevalence of hyponatremia, but identified a high frequency of other electrolyte abnormalities, including hypophosphatemia, low serum bicarbonate, and hyper- and hypo-magnesemia.[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/mm^3, but also may reflect the inclusion of a heterogenous population of ambulatory and acutely ill patients.[29] Although the spectrum of electrolyte disorders has changed in the ART era, antiretroviral agents also have 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 the article by Atta et al in this issue (p. 563).

RISK FACTORS FOR AKI 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

Table 3. Risk Factors for AKI in HIV Infection

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

exposure and AKI, individual antiretroviral agents rarely are implicated.[12,13] Age, baseline serum creatinine level, and history of hypertension or diabetes were not associated independently with AKI in 2 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 shown 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 also have 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 proinflammatory 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 AKI IN HIV INFECTION

Prognosis in AKI varies with severity and etiology. Studies have shown 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]

CONCLUSIONS

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 used in the HIV-infected patient, including ART and antibiotic medications, also should be investigated further to decrease toxicity. Future studies of AKI in HIV-infected patients should attempt to use standard definitions to allow for comparison across studies.

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