HIV and the kidney in the acute medical unit

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ABSTRACT

Acute kidney injury (AKI) is encountered commonly in HIV-positive patients admitted to the acute medical unit. The spectrum of AKI has changed in the era of combination anti-retroviral therapy, and now includes adverse effects of commonly used anti-retroviral drugs in addition to traditional precipitants such as severe sepsis or exposure to nephrotoxic antimicrobials. An accurate diagnosis requires careful integration of clinical data including volume status, history of potentially nephrotoxic exposures and consideration of immuno-virological status. This article provides an overview of common causes of AKI in HIV and presents a framework by which the acute care physician may approach the finding of an elevated serum creatinine in a patient with HIV.

Introduction

Acute kidney injury (AKI) remains a common problem in HIV-positive individuals. Many risk factors for AKI are shared with the general population, including pre-existent chronic kidney disease (CKD), hypertension, diabetes and use of angiotensin-converting-enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), each serving to lower the threshold for renal injury in the context of hypovolaemia or sepsis.[1] In addition, HIV-infected patients often have unique risk factors for AKI, either associated with immunodeficiency, immune reconstitution or nephrotoxic effects of anti-retroviral therapy (ART).[2–4] It is common for AKI to reflect the multifactorial effects of these renal 'stressors', and careful evaluation of the patient's pre-morbid condition, immuno-virological status, current clinical condition and recent nephrotoxic exposures is required for an accurate diagnosis and to individualise treatment. The 'STOP' (sepsis, toxins, obstruction, parenchymal disease) mnemonic remains a useful aide memoire for considering contributing factors of AKI in HIV, as per the general population.

A number of 'intrinsic' renal diseases, most notably HIV-associated nephropathy (HIVAN),[5] may present as AKI in HIV (Table 1). The presence of blood and protein on urine dipstick may point to glomerulonephritis (eg HIV-associated immune complex glomerulonephritis, post-infectious glomerulonephritis or bacterial endocarditis), rhabdomyolysis or thrombotic microangiopathy (TMA), although urinalysis is a poor predictor of the renal 'compartment of injury' (ie glomerular vs tubulo-interstitial injury) in HIV.[6] Traditional pointers to tubulo-interstitial nephritis (TIN), such as fever, rash and peripheral eosinophilia, are equally insensitive.[6] Hence, renal biopsy represents an important definitive diagnostic tool in unexplained or non-resolving AKI.

AKI should be staged using the 'kidney disease: improving global outcomes' (KDIGO) criteria (Table 2) and early nephrology input sought in cases of progressive renal impairment or AKI stage III. Fluid resuscitation to correct any prevailing volume deficit is of paramount importance, and should follow recently published guidance from NICE.[8] Renally excreted drugs, such as zidovudine, lamivudine, tenofovir and emtricitabine, require dose adjustment in renal impairment. Indications for renal replacement therapy are the same as those for the general population.

Beside AKI, renal presentations encountered in HIV include nephrotic syndrome (eg HIVAN, immune complex glomerulonephritis), chronic kidney disease (Table 3) and disorders of fluid and electrolytes (eg Fanconi syndrome due to tenofovir). While these syndromes are discussed in brief where relevant, the main focus of this article is AKI.

Drugs and AKI

Medications, in particular anti-microbial drugs, frequently cause or contribute to AKI in HIV (Table 1). Common mechanisms of injury include acute tubular injury, TIN or crystalluria with sludging and tubular obstruction. AKI should be pre-empted when drugs prone to crystallising in urine (eg aciclovir, sulphadiazine) are prescribed, by careful dose adjustment for reductions in glomerular filtration rate (GFR) and maintenance of good hydration and urinary flow rate. Drug withdrawal is sufficient to reverse AKI in most scenarios, although corticosteroid treatment may be warranted in severe cases of TIN.

ACE-I or ARB use is now common among HIV-positive patients. While these medications can exert long-term nephroprotective effects through lowering of glomerular filtration pressure, this property impairs renal autoregulation in the face of circulatory stress, and may compound AKI and hyperkalaemia. ACE-I and ARB should be stopped immediately in patients presenting with AKI, and suspended pre-emptively in dehydration or sepsis. Non-steroidal anti-inflammatory

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Table 1. The spectrum of AKI encountered in patients with HIV.

Commonly encountered conditions	Examples
> Acute tubular injury	> Hypovolaemia, sepsis, nephrotoxic drugs
> 'Acute' presentations of CKD	> See table 3
Immunodeficiency-associated	
> Anti-microbial toxicity	> ATI (eg co-trimoxazole, amphotericin)
	> TIN (eg co-trimoxazole, rifampicin)
	> Crystalluria (aciclovir and sulphadiazine)
> Renal parenchymal infection	> Renal TB
	> Viral nephropathies (eg CMV, BK – rare)
> Neoplasia	> Infiltration/obstruction eg by lymphoma
HIV treatment-associated	
> cART nephropathy	> ATI (tenofovir)
	> Crystalluria/stone obstruction (atazanavir or indinavir)
	> TIN (especially atazanavir)
> Immune reconstitution inflammatory syndrome (IRIS)	
HIV-virus associated (rare)	
> HIVAN	
> Immune complex glomerulonephritis	
> Thrombotic microangiopathy	
> Diffuse infiltrative lymphocytic syndrome	
Other conditions	
> Rhabdomyloysis	
> Recreational drug toxicity	> Cocaine (vasospasm, hypertension, rhabdo)
	> Ketamine (obstructive uropathy)
> Acute glomerulonephritis	> Bacterial endocarditis
	> HBV / HCV co-infection
	> Post-infectious glomerulonephritis
> Tubulo-interstital nephritis	> Drug induced eg antibiotics, PPIs

AKI = acute kidney injury; ATI = acute tubular injury; cART = combination anti-retroviral therapy; CMV = cytomegalovirus; HIVAN = HIV-associated nephropathy; PI = protease inhibitor; PPI = proton-pump inhibitor; TIN = tubulo-interstitial nephritis.

drugs (NSAIDs) are also commonly implicated in AKI and should be stopped; their use should be avoided in those with pre-existing CKD. Many episodes of severe AKI may be avoided through patient education to suspend ACE-I, ARB or NSAIDs during periods of intercurrent illness until medical advice has been sought.

Several anti-retrovirals (dolutegravir, rilpivirine, ritonavir and cobicistat) may increase serum creatinine concentrations by inhibiting renal tubular transporters and others (tenofovir, atazanavir and lopinavir) have been associated with the development of CKD.[9,10] Two drugs, tenofovir and atazanavir, may cause kidney injury which should be considered in patients presenting with AKI.[11]

Tenofovir

Tenofovir disoproxil fumarate (TDF), a widely used nucleotide reverse transcriptase inhibitor may cause severe proximal renal tubulopathy (Fanconi syndrome) characterised by hypophosphataemia, tubular (low molecular weight) proteinuria, glycosuria, hypokalaemia and metabolic acidosis.[12] Hypophosphataemia may be severe and present acutely with

Table 2. KDIGO staging of AKI.

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥26.5 µmol/L increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	≥ 3.0 times baseline OR ≥354 µmol/L OR initiation of RRT	<0.3 mL/kg/h for ≥24 h OR anuria for ≥12 h

AKI = acute kidney injury; RRT = renal replacement therapy. Adapted with permission.[7]

Table 3. Spectrum of CKD in patients with HIV infection.

CKD	Characteristics
HIVAN	> Almost exclusively African/Caribbean patients
	> Often low CD4 count at presentation
	> Nephrotic range proteinuria common, often little oedema despite low albumin
	> Classical 'collapsing' glomeruli on biopsy with tubular microcystic changes
	> Disease may stabilise with initiation of cART
HIV-ICKD	> Patients may be of any ethnicity or HIV risk group
	> Less likely to be severely immunodeficient/viraemic compared to HIVAN
	> Proteinuria +/– haematuria +/– ↑creatinine – may be nephrotic range proteinuria
	> Often clinically indistinguishable from HIVAN – biopsy required
	> Benefit of cART less clear cut; most would initiate regardless of CD4 count
IgA nephropathy	> Clinical and histological features identical to general population
	> HIV antigens have been found in renal IgA immune complexes but pathogenical role of virus unclear
	> Role for cART in modifying disease uncertain
FSGS (non-collapsing variant)	> More commonly seen in African/Caribbean patients
	> Epidemiology similar to HIVAN
	> Proportion of cases may represent HIVAN (eg collapsed glomeruli not seen due to sampling error)
Chronic tubulointerstitial nephritis	> Progressive CKD, often with little proteinuria or haematuria
	> Range of causes including drug exposures (eg indinavir), infections (eg tuberculosis), neoplasms (eg lymphoma) and inflammatory disease (eg sarcoid)
	> Presence or absence of granulomas on biopsy may aid differential diagnosis
	> Treatment is removal of offending agent or treatment of underlying cause
AA amyloid	> Nephrotic syndrome, progressive CKD – often relentlessly so
	> Typically seen in intravenous drugs users – likely due to recurrent suppurative skin infection
Diabetic nephropathy	> Increasingly common in the cART era as the HIV population ages
	> Typically causes proteinuria (up to nephrotic range) and progressive CKD
	> More likely if end-organ disease elsewhere (eg retinopathy)

cART = combination antiretroviral therapy; CKD = chronic kidney disease; HIVAN = HIV-associated nephropathy; HIV-ICKD = HIV immune-complex kidney disease; MCGN = mesangio-capillary glomerulonephritis; NOS = not otherwise specified; VL = viral load.

Key points

Remember important causes of AKI in HIV with 'STOP' mnemonic.

Assessment of fluid status and early fluid resuscitation is paramount.

Seek, treat and monitor for complications of AKI (eg hyperkalaemia).

Adjust drug doses (including antiretrovirals) for renal function.

Tenofovir and atazanavir have renal adverse effects which may present as AKI.

Involve the multidisciplinary team early (HIV team, renal team, pharmacist).

KEYWORDS: HIV, AKI, ART, tenofovir, atazanavir ■

bone pain or pathological fracture due to osteomalacia.[13] Risk is highest in older patients, those with prior CKD and those who take tenofovir with ritonavir-boosted protease inhibitors (PIs).[12] Elevated creatinine may be a late feature.

Patients taking TDF are also at risk of developing acute tubular injury without features of Fanconi syndrome, sometimes triggered by sepsis or volume depletion. Kidney biopsy in such cases typically shows enlarged distorted mitochondria within proximal tubular cells, frequently visible as eosinophilic inclusions on light microscopy.[14] Tenofovir should be substituted in stage II or III AKI and advice sought from an HIV physician regarding appropriate alternatives. A new formulation of tenofovir (tenofovir alafenamide) with an improved renal safety profile is currently in development.[15]

Atazanavir

Atazanavir is a PI frequently used in combination with ritonavir (as a 'boosting' agent). Like indinavir, an obsolete

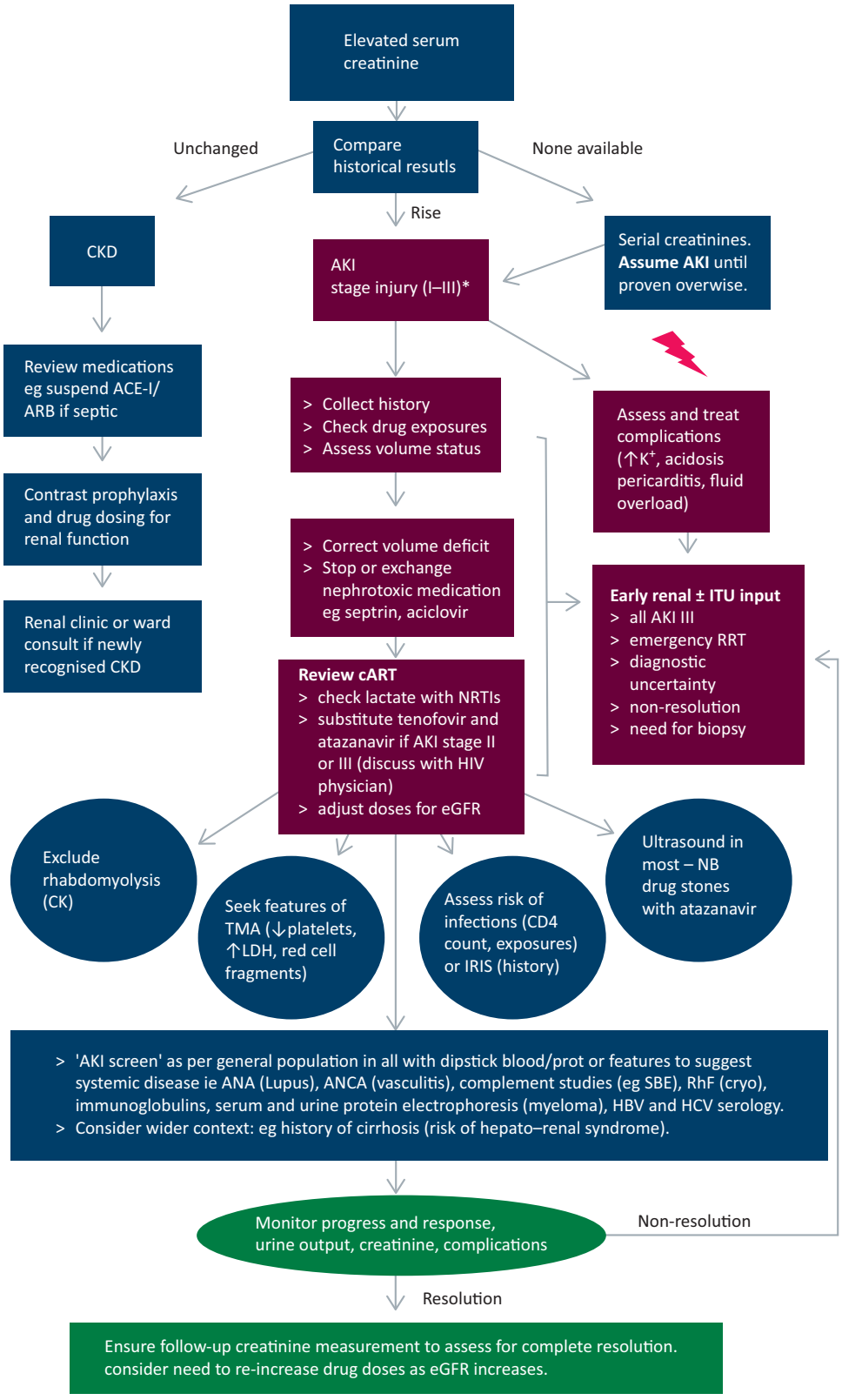

Fig 1. Approach to the HIV-infected patient presenting with an elevated serum creatinine. *See Table 2 for KDIGO staging of AKI. ACE-I = angiotensin converting enzyme inhibitor; AKI = acute kidney injury; ANA = anti-nuclear antibody; ANCA = anti-neutrophic cytoplasmic antibody; ARB = angiotensin receptor blocker; CK = creatine kinase; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; IRIS = immune reconstitution inflammatory syndrome; LDH = lactate dehydrogenase; NRTI = nucleoside reverse transcriptase inhibitor; RhF = rheumatoid factor; RRT = renal replacement therapy; SBE = subacute bacterial endocarditis; TMA = thrombotic microangiopathy.

first-generation PI, atazanavir may be associated with renal tract crystallisation and radiolucent calculi, albeit at lower frequency.[16] Although rare, atazanavir has also been associated with acute TIN, and a more insidious, scarring chronic granulomatous TIN driven by intra-tubular crystal deposition.[17] Atazanavir is best avoided in the setting of AKI.

Infection, malignancy and liver disease

While ischaemic acute tubular injury commonly complicates severe opportunistic infection, direct renal injury by infective agents is also relatively common. Tuberculosis may present with sub-acute progressive renal impairment, with or without the classic 'sterile' pyuria and granulomatous interstitial inflammation on biopsy. Syphilis remains common among men who have sex with men and may induce an abrupt onset nephrotic syndrome of membranous type. Viral infections, including cytomegalovirus and adenovirus, may rarely cause renal tubulo-interstitial inflammation in the severely immunocompromised host, and viral inclusion bodies may be visible on histology.

Lymphoma remains common in HIV-positive patients and may be associated with renal impairment or AKI either due to direct lymphomatous infiltration of the kidney, ureteric compression or indirect effects including nephrotoxic chemotherapy and tumour lysis syndrome. Chronic liver disease, for instance due to co-infection with hepatitis B virus (HBV) or C (HCV), is a common comorbid condition among patients presenting with AKI, and hepato–renal syndrome may need to be considered where AKI is unresponsive to fluid resuscitation. Co-infection should also prompt consideration of viral glomerulonephritis (eg membranous nephropathy with HBV) or cryoglobulinaemia (HCV).

'Acute' presentations of CKD

The spectrum of disorders presenting as CKD in HIV differs considerably from those presenting as AKI (Table 3). It is not uncommon for HIVAN to present as AKI or rapidly progressive renal impairment over weeks to months, and for HIVAN to be the first manifestation of previously unrecognised HIV infection.[5] Nephrotic-range proteinuria, a common feature of HIVAN, also lowers the threshold for acute tubular injury during intercurrent illness. In the absence of previous creatinine measurements for comparison, serial blood tests are essential to determine if renal function is stable or deteriorating acutely. While reduced renal size on imaging signifies chronicity, the inverse does not hold true; renal size is often normal or increased in chronic disorders such as HIVAN where renal volume is expanded by tubular microcystic dilatation.

Immune disorders and thrombotic microangiopathy

Immune reconstitution inflammatory syndrome (IRIS), triggered by the recent introduction of ART with consequent rise in CD4 count, may present as AKI. Renal IRIS usually manifests as granulomatous interstitial nephritis with a $CD4^+$-rich lymphocytic infiltrate, most commonly directed against previously unrecognised mycobacterial infection.[18] ART can be continued in the majority of cases, with addition of oral corticosteroids and relevant anti-microbial therapy (eg anti-tuberculous chemotherapy).

Diffuse infiltrative lymphocytosis syndrome (DILS) is uncommon since the advent of widespread ART, but may present with progressive renal impairment as a consequence of tubulo-interstitial renal infiltration by oligoclonal $CD8^+$ T cells. DILS presents classically as a Sjogren-like syndrome with parotid enlargement and sicca symptoms due to lymphocyte infiltration.[19] Initiation of ART is the mainstay of treatment, although corticosteroids do appear to have an adjunctive role in the presence of significant renal disease.

TMA, manifesting either as thrombotic thrombocytopaenic purpura or haemolytic uraemic syndrome, is associated with severe immunodeficiency and is now encountered rarely. The association of AKI with thrombocytopaenia in HIV should trigger evaluation for other features of TMA such as red cell fragments on blood film, elevated serum lactate dehydrogenase or depressed haptoglobins. Treatment includes plasma exchange, prompt initiation of ART (preferably as a once-daily regimen and dosed post-plasmapheresis) and supportive therapy including haemodialysis where necessary.[20]

Approach to the HIV patient with AKI

A framework by which to approach AKI encountered in a patient with HIV is presented in Fig 1. Review of historical renal function tests will provide immediate insight into whether an elevated serum creatinine represents AKI or CKD. Life-threatening complications of AKI (including hyperkalaemia and severe acidosis) should be sought early and treatment initiated as appropriate. Dehydration should be corrected with intravenous fluid therapy, and nephrotoxic medication (including NSAIDs, ACE-I or ARB) suspended. ART should be reviewed, doses adjusted for GFR, and tenofovir and atazanavir suspended or substituted in stage II or III AKI. Further history, examination and investigations should be tailored toward the differential diagnosis of AKI presented in Table 1.

Response to treatment should be monitored by tracking urine output and serial creatinine measurements. Severe AKI (including all stage III), diagnostic uncertainty or non-resolution should trigger nephrology consultation. Criteria for renal replacement therapy are identical to AKI in the general population.

Conclusion

While the incidence of AKI in HIV-positive patients has declined with widespread use of ART, those with immunodeficiency and comorbidities remain at increased risk of AKI. Tenofovir and atazanavir may infrequently be a cause of AKI and are best avoided in patients with AKI. The management of AKI is supportive, with appropriate fluid resuscitation, avoidance of nephrotoxic medications and treatment of underlying diseases. ■

Disclosures

JWB has received conference funding from Shire Pharmaceuticals. FAP has received funding to attend conferences or educational meetings, honoraria and/or research grants from Gilead Sciences, Bristol-Myers Squibb, Janssen-Cilag, GlaxoSmithKline/ViiV healthcare and Merck.

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Clinical Medicine 2015 Vol 15, No 6: 576–80 CME RENAL MEDICINE

Isolated microscopic haematuria of glomerular origin: clinical significance and diagnosis in the 21st century

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ABSTRACT

Isolated microscopic, or non-visible, haematuria of glomerular origin was previously regarded a benign finding, but it is now known that, even in the absence of proteinuria, hypertension or renal impairment at presentation, haematuria is associated with increased risk of kidney failure in the long term. The most common causes of isolated microscopic haematuria among children and young adults are IgA nephropathy, Alport syndrome (AS), and thin basement membrane nephropathy (TBMN). AS, which is usually inherited as an X-linked or autosomal recessive trait, and TBMN, which is usually autosomal dominant, are caused by mutations in the genes encoding type-IV collagen, an abundant component of the glomerular basement membrane. A detailed family history with screening of at-risk relatives is important, allowing prompt diagnosis of affected relatives and helping determine the mode of transmission. As costs fall and availability increases, genetic testing is increasingly being used in clinical practice to provide diagnostic and predictive information for patients and their families.

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