HIV-related drug nephrotoxicity In sub-saharan africa

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Abstract

Sub-Saharan Africa (SSA) bears the greatest burden of HIV infection; however, there is limited data on nephrotoxicity from HIV-related treatments. Several studies have demonstrated the benefit of highly active antiretroviral therapy (HAART) in decreasing HIV-associated mortality in SSA. However, HAART and other therapies for HIV-related infections are associated with both short and long term toxicities including potentially life threatening renal toxicities. With HAART use increasing, clinicians must screen patients for kidney disease especially if the regimen used has nephrotoxic potential. It is also important that chronic kidney disease (CKD) is not a reason to avoid these effective drug combinations, since most drugs can be appropriately adjusted based of the estimated glomerular filtration rate (GFR). Early detection of the risk factors (some of which may be peculiar to SSA) as outlined in this paper, systematic screening for chronic causes of CKD, and human resource and capacity building for kidney disease management should be advocated for improved patient care. This article summarizes the available data on commonly used nephrotoxic agents in HIV-AIDS in SSA with an emphasis on prevention of kidney injury.

INTRODUCTION

Highly active antiretroviral therapy (HAART) has revolutionized the management of HIV-AIDS and is effective in reducing morbidity and mortality in HIV-positive individuals. Several studies have shown dramatic improvements in the survival of HIV-infected patients treated with anti-retroviral therapy (ART) around the world including Sub-Saharan Africa (SSA) [1, 2]. Kidney disorders are encountered at all stages of HIV infection, and they range from acute kidney injury (AKI) and divalent disorders commonly seen in hospitalized patients to chronic kidney disease (CKD) and end-stage renal disease (ESRD). Much has been written about HIV-associated nephropathy but as the disease evolves and people live longer, other causes of kidney diseases related to antiretroviral therapy and co-morbid conditions are becoming very important [3, 4].

HAART and other medical therapies for HIV-associated infections have been associated with both short and long term toxicities including nephrotoxicity. Though Africa is home to the greatest number of patients with HIV [5], there are limited data on nephrotoxicity from HIV related treatments. Moreover, most of the African countries have limited antiretroviral drug choices as most regimens are selected based on epidemiological data rather than individual factors [6]. In addition, patients often present late for clinical care and are more prone to the adverse effects of the limited drug choices. In a multi-country survey in resource limited settings, up to 80% of patients started treatment with a CD4 median count of 123 cells/micro liter [7].

The constraints in Africa and other developing countries have been well delineated [8]. These include economic constraints limiting the choices of accessible antiretroviral medications and poor laboratory monitoring, which delays the diagnosis of specific toxicities, thereby increasing their severity. Co-morbid conditions that are more prevalent in resource-limited regions, such as anemia and malnutrition; initial presentation with advanced immunosupression; use of concomitant anti-tuberculosis therapy; and use of herbal medications [9] may influence the incidence of adverse effects.

Finally, host genetics may be associated with drug toxicities [10-12]. This is a relevant issue, because most antiretroviral drugs have been validated in developed countries but are now widely used in developing countries, where the vast majority of HIV-infected people reside.

It is therefore important for clinicians in developing countries to prevent, recognize and manage kidney diseases in HIV patients. This article summarizes the available data on commonly used nephrotoxic agents in HIV-AIDS in SSA with an emphasis on prevention of kidney injury. Where there is no available data reference is made from work done

from developed countries.

EPIDEMIOLOGY OF ACUTE AND CHRONIC KIDNEY DISEASE IN SUB-SAHARAN AFRICA

Antiretroviral nephrotoxic effects accounted for 14% of late –onset AKI episodes in one retrospective study in United Kingdom but the incidence of AKI in SSA has not been well studied [13, 14]. In a recent review on the epidemiology of AKI in South Africa, 122 of 700 patients (17.4%) were HIV positive with a mean CD4 of 134 cells/$mm^{3.}$ Mortality was noted in 25 of 122 (20%) of the HIV-positive patients with AKI [15]. AKI in hospitalized HAART-naive HIV-1-infected patients is associated with a 6-fold higher risk of in-hospital mortality with the common risk factors being severe immunosupression (CD4 count, <200 cells/mm^3) and opportunistic infections [16]. In the post-HAART era, HIV-1-infected patients with AKI still have an increased risk of in-hospital mortality and these episodes of AKI seem more frequent in the first year of ART [15] probably due late presentation of patients and severe immunosupression with concurrent infections at the time of admission.

The prevalence of CKD was noted to be 11.5% (43 of 373 patients) when using the Cockcroft-Gault equation [11]. Emem et al in a study from Nigeria found a prevalence of 38% as determined by at least 1+ dipstick albuminuria and/or raised serum creatinine concentration (>132 micromol/l) in 400 HIV-AIDS patients. They attributed the high prevalence to late presentation as evidenced by low CD4 counts in the affected patients [17].

The Development of Anti-Retroviral Therapy in Africa (DART) trial, examined 3,316 symptomatic ART-naive adults from Uganda and Zimbabwe with CD4< 200 cells/mm^3 who were initiated on HAART with zidovudine-lamivudine plus tenofovir DF (74%), nevirapine (16%) or abacavir (9%). The study concluded that severe renal dysfunction (<30 ml/min as estimated by the Cockcroft-Gault formula) occurred in only 2.7% of patients on all regimens and renal disease contributed to death in a minority of patients, which was generally related to concurrent disease [18]. The major limitation was that renal tubular function was not assessed, yet there is evidence that tenofovir causes tubular injury which may manifest as nephrogenic diabetes insipidus (NDI) or as the Fanconi syndrome [19]. In a Zambian study, 33.5% of 25,799 patients treated with HAART had renal dysfunction; of these 8,456 participants, 3.1% had creatinine clearance <30 ml/min (severe), 23.4% between 30 and 59 ml/min (moderate) and 73.5% between 60 and 89 ml/min. Renal dysfunction was associated with increased mortality at 90 days in all three stages [20].

DRUGS WITH NEPHROTOXIC EFFECTS IN HIV PATIENTS IN SUB-SAHARAN AFRICA

ANTIRETROVIRAL DRUGS

There are over 20 drugs for HIV treatment on the market but the availability and choices of drug combinations are limited in SSA. The commonly prescribed HAART regimens vary from country to country [7]. However, the most commonly prescribed initial regimens include Nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and non-reverse transcriptase inhibitors (NNRTIs). Protease inhibitors (PIs), especially those boosted with ritonavir are becoming more available, particularly as second line therapies [21]. Newer drugs like fusion or entry inhibitors and integrase inhibitors are rarely available.

NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and nucleotide reverse transcriptase inhibitors inhibit the viral reverse transcriptase and halt viral DNA synthesis. The commonly prescribed NRTIs include zidovudine (AZT), lamivudine (3TC), stavudine (D4T), emtricitabine (FTC), abacavir (ABC), didanosine (DDI) and zalcitabine (DDC). The only nucleotide analog currently used is tenofovir (TDF), which is commonly used in combination with FTC as Truvada®.

All NRTIs except abacavir are primarily excreted by the kidney and require dose adjustments based on creatinine clearance. Lamivudine, stavudine, abacavir and didanosine have been implicated in case reports of Fanconi syndrome and nephrogenic diabetes insipidus [22-24]. Abacavir causes acute interstitial nephritis as part of the hypersensitivity reaction, which can be avoided by the HLA-B*5701 screening. Though this screening test is not readily available in sub-Saharan Africa, the rates of this allele are low [25, 26]. Didanosine and stavudine commonly cause mitochondrial toxicity which can manifest as hyperlactemia. Songa et al described 24 cases of symptomatic hyperlactemia attributable to stavudine in Uganda while Geddes found a high incidence of symptomatic hyperlactemia (up to 19 per 1000 person-years) among South African patients [27].

The nucleotide analog tenofovir is actively taken up into the proximal tubules and secreted into the lumen via multi-drug

resistance-associated protein 4 [28]. The TDF/FTC combination is fast becoming popular in SSA, especially with efforts to phase out stavudine due to its toxicity profile. The use of TDF/FTC is also likely to increase especially for post-HIV exposure prophylaxis and as part of treatment of choice for HIV patients co-infected with Hepatitis B.

A number of observational studies have documented tenofovir-associated nephrotoxicity following its widespread use in patients with multiple co-morbid conditions [29]. Tenofovir induced renal toxicity is more likely to occur in HIV patients with pre-existing renal insufficiency or poorly controlled HIV disease with longer overall antiviral treatment duration. Complications of tenofovir, alone or in combination with other antivirals, include AKI, nephrogenic diabetes insipidus, Fanconi syndrome, and severe hypokalemia [19, 30-32]. Most of these adverse reactions can be reversed with discontinuation of the drug, although some will develop CKD. Patients who are taking TDF in combination with protease inhibitors such as ritonavir appear more susceptible to renal toxicity.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

The non-nucleoside reverse transcriptase inhibitors inhibit HIV replication by binding to viral reverse transcriptase and inhibiting its function. The common NNRTIs used in Africa include nevirapine and efavirenz. The newer class, etravirin is not commonly available. As a class, NNRTIs have minimal nephrotoxic potential because they are primarily metabolized by the hepatic cytochrome p-450 system. Though efavirenz has been linked to podocyte injury causing minimal change disease in a case report, there is currently no literature from SSA showing this occurrence. However, Angel-Moreno-Maroto et al, described a Sub-Saharan patient with HIV infection and disseminated tuberculosis who developed acute, severe hypersensitivity reaction to Efavirenz. The patient developed AKI in addition to liver and lung involvement, in the absence of skin changes or blood eosinophilia [33].

PROTEASE INHIBITORS

Protease inhibitors inactivate the HIV protease enzyme, which is necessary for assembly and maturation of virions. With the exception of the newer agents (tipranavir and darunavir, which are not common in SSA), PIs have been associated with urinary stones (nephrolithiasis) and crystal nephropathy. The commonly implicated drugs are indinavir, amprenavir and atazanavir [34]. As these drugs often need refrigeration and are not readily available in SSA, they are not a significant cause of kidney injury in SSA. The commonly used PI, lopinavir/ritonavir is usually reserved for second line therapy [21, 35, 36]. However, lopinavir/ritonavir has also been described to cause renal calculi in rare case reports [37].

OTHER ANTIRETROVIRAL AGENTS

Other antiretroviral agents including entry inhibitors (enfuvirtide), CCR5 antagonists (miraviroc and vivciviroc), and integrase inhibitors (raltegravir and elvitegravir) are relatively new and rarely used in SSA. There is little evidence of nephrotoxicity from these agents [34].

OTHER COMMONLY USED THERAPY IN HIV WITH NEPHROTOXIC EFFECTS

In addition to ARVs, other drugs are used for prophylaxis and treatment of opportunistic infections. These include drugs such as trimethoprim/sulfamethoxazole, amphotericin B, acyclovir; and anti-tuberculous drugs as detailed in the AKI section.

TRADITIONAL MEDICINES

Traditional medicines are used commonly world wide, with rates of over 80% in some populations. In the developing world, folk remedies account for up to 35% of AKI that occurs [9]. In resource limited settings the use of local folk medicines is highly prevalent in the poorer communities due to reasons including spirituality as well as lack of access to medical care. Data on the effect of toxins in HIV-AIDS patients in SSA is scarce, but herbal ingestion has been noted to play a major role in causing kidney injury in concert with other causes [15].

ACUTE KIDNEY INJURY

AKI is a challenging problem in Africa because of limited resources coupled with late patient presentations to healthcare facilities. The pattern of AKI is vastly different from that in developed countries. Common causes of AKI include sepsis, hypotension, malaria, herbal toxins and medications commonly used in the treatment of HIV-related infections [15]. Medications associated with AKI include aminoglycosides, pentamidine, acyclovir, foscarnet, amphotericin, tenofovir, adefovir, and cidofovir [38]. In Sudan, cases of AKI due to hair dye (paraphenylene-daimene) were described in 12 patients and snake bites in 5 patients [39]. However, there was no mention of a relationship of AKI to their HIV status. Otherwise most cases of AKI in HIV patients are primarily of a pre-renal

origin [15]. This is very important, in particular for areas that have little or no access to dialysis and intensive care services, in which case timely fluid management could potentially reverse this problem. It is also important to remember that some patients may present with an acute on chronic insult and the management of the chronic condition needs to be put into perspective after the patient has been stabilized. This is not surprising as CKD is a common risk factor for AKI. Table I shows common risk factors for AKI in HIV infection.

Figure 1

Table 1 Risk Factors for AKI in HIV Infection

Table 1 Risk Factors for AKI in HIV Infection
Older age (> 65 year)
Diabetes mellitus
Chronic kidney disease
Liver disease/hepatitis C
Low CD4 count
High HIV-RNA level
History of AIDS-defining illness
Herbal/traditional medicines
History of antiretroviral exposure

Non-steroidal anti-inflammatory drugs (NSAIDs), trimethoprim/sulfamethoxazole, and rifampin are often used in HIV-infected patients and are known to cause acute interstitial nephritis [16]. NSAIDS may also promote pre-renal azotemia in patients with true effective volume depletion. Sulfadiazine, acyclovir, indinavir, atazanavir and rarely trimethoprim-sulfamethoxazole are associated with the precipitation of crystals that cause tubular obstruction and the entity known as crystal nephropathy. Indinavir, atazanavir and sulfadiazine may also form stones that cause ureteral obstruction [38]. In a small study conducted in South African HIV-infected patients with cerebral toxoplasmosis, renal dysfunction occurred in 17% of patients taking pyrimethamine-sulfadiazine and none in the cotrimoxazole treated group [40].

A selective list of drugs causing AKI is shown in table 2.

Figure 2

Table 2: Selective drugs causing AKI in HIV-infected patients

Drugs	Acute tubular injury (ATI) or AKI	Acute interstitial nephritis	Other associated abnormalities
TMP-SMX (Bactrim)		+++	Hyperkalemia, Crystalluria
β-lactams		++	
Sulfadiazine		++	Crystalluria, nephrolithiasis
Fluroquinolones		+	
Rifampin	+	+	Hypokalemia, hypouricemia, hypernatremia, vasculitis
INH		+	Overdose leads to high anion gap metabolic acidosis
NSAIDs	+/-	+	Proteinuria, secondary minimal change disease, papillary necrosis
Dapsone	+/-		Papillary necrosis
Amphotericin B	+++		Hypokalemia,hypomagnesemia, hypernatremia, NDI
Pentamidine	+++		Crystalluria, hyperkalemia
Foscarnet	+++		Hypercalcemia/ hypernatremia, Glomerular crystals
Gancyclovir	+		
Acyclovir	+	+/-	Crystalluria
Indinavir, atazanavir		+	Crystalluria, nephrolithiasis
Abacavir		+/-	
Tenofovir	++		Fanconi, NDI

Key: + mild, ++ moderate, +++ severe injury. NDI- nephrogenic diabetes insipidus

ELECTROLYTE ABNORMALITIES ASSOCIATED WITH HIV INFECTION

Electrolyte abnormalities can be caused by a myriad of drugs used in HIV patients. Drugs such as amphothericin B and trimethoprim/sulfamethoxazole, which are commonly used to treat cryptococcal meningitis and pneumocytis jirovecii pneumonia, respectively, are worthy of special mention [41-43]. Kiweewa studied 116 HIV-positive patients with a diagnosis of cryptococcal meningitis treated with amphotericin B in Uganda [44]. He found that amphotericin B caused nephrotoxicity (defined as 50% increase in baseline creatinine) in up to 59.1% of cryptococcal meningitis patients compared to 15.9% in the control group ($p = 0.0001$). Among other electrolyte imbalances, hypokalemia was the commonest derangement, occurring at frequencies of 26%, 39.5%, and 62.7% by the third, seventh, and fourteenth day of treatment, respectively. Ambisomal amphotericin B may be a better option for preventing kidney injury but the cost of this agent is prohibitive.

Trimethoprim/sulfamethoxazole (Tmp/Smx) is routinely used for prophylaxis against PCP, toxoplasmosis and other diarrheal diseases. In fact, some countries like Uganda recommend use of Tmp/Smx for all HIV positive patients irrespective of their CD4 counts, while other countries prescribe based on the level of CD4 counts. The risk for

hyperkalemia, which is due to trimethoprim blockade of the epithelial sodium channel in the cortical collecting duct cells causing an amiloride effect, is greatest when it is used in high doses to treat pneumocystis pneumonia [45]. Several studies from developed countries have explored this in great detail [46-48]. However, no data are available on this drug in SSA.

CHRONIC KIDNEY DISEASE

The Infectious Disease Society of America recommends that at the time of HIV diagnosis, all patients should be assessed for evidence of CKD, and if present, be appropriately staged for kidney disease. CKD has been defined as:

1. 1) Evidence of structural or functional kidney damage (abnormal urinalysis, imaging studies, or histology) present for at least 3 months with or without a decreased glomerular filtration rate (GFR); or,

2. 2) Decreased kidney function (GFR <60 mL/min per 1.73 m2), with or without evidence of kidney damage [49].

In clinical practice, creatinine-based equations, such as the Cockcroft-Gault (CG) equation that calculates creatinine clearance, the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations that estimate GFR are used to assess renal function, instead of serum creatinine measurement alone [49, 50]. Although the CKD-EPI equation has been reported to be more accurate than the MDRD Study equation overall and across most subgroups [50]; it is yet to be validated in a SSA cohort. Fortunately both the CG and MDRD formulae have been validated in an African setting by the DART trial [51]. The researchers investigated differences between the two formulae in baseline GFR, GFR changes, and incidence of impaired GFR after initiation of antiretroviral therapy in 3,316 HIV-infected adults in Africa. Sex, age, body mass index and baseline laboratory parameters were factored in the renal function assessment. They found that severe GFR impairments are similarly classified by the two formulae, but moderate impairments were more frequently identified using CG-GFR versus MDRD-GFR (with Black ethnicity correction factor 1.21). Serum creatinine concentration alone had low sensitivity. This validation is particularly important as the CG formula is easy to use and all the parameters needed are often available to calculate it. Most laboratories in resource limited settings don't offer an automated eGFR value, which requires clinicians to calculate it manually. The easily accessible computerized formulae in developed countries may not readily be available in these settings. Future Studies on CKD in SSA should endeavor to use the CKD-EPI formula especially when estimating GFR levels above 60 mL/min/1.73 m^2 [50].

Risk factors for CKD that have been identified in the HIV population include increasing age, low BMI, malnutrition (low serum albumin), anemia, and low CD4+ counts [17].

Several other studies from other African countries have confirmed the benefit of HAART in patients with underlying CKD [52]. In this Ugandan study, the researchers assessed the effect of HAART on renal function in 508 patients with HIV and creatinine clearance greater than 25 ml/min. After 2 years of HAART, the median serum creatinine level decreased by 16% and the median creatinine clearance increased by 21%. The median creatinine clearance of patients with renal dysfunction at study initiation (that is, creatinine clearance of 25–50 ml/min) increased by 53%. In multivariate analysis, baseline serum creatinine above 1.5 mg/dl, weight gain of more than 5 kg at 2 years, female gender, and WHO stage 4 classifications were all associated with greater improvements in creatinine clearance. However, the patients in the study were on stavudine and lamivudine with either nevirapine (98%) or efavirenz (2%); drugs that have not been directly implicated in causing kidney injury, in part explaining the lack of adverse renal effect. As HIV patients are more likely to require multiple drug regimens, a number of significant adverse drug interactions may occur.

Tenofovir-induced renal toxicity is more likely to occur in HIV patients with pre-existing renal insufficiency or poorly controlled HIV disease with longer overall antiviral treatment duration. Complications of tenofovir, alone or in combination with other antiviral agents have been well described. Although most of these adverse reactions can be reversed with discontinuation of the drug, patients who are taking TDF in combination with protease inhibitors such as ritonavir are more susceptible to renal toxicity [30, 31, 53]. It is often challenging to distinguish antiretroviral-related renal toxicity from either direct effects of HIV-1 on the kidney or from a multitude of non–HIV-related kidney diseases [29]. Severe GFR decreases in many patients may simply be predominantly a reflection of acute intercurrent illness rather than ongoing drug nephotoxicity. The scenario is further complicated by the fact that HIV-AIDS patients are now living longer and are more predisposed to age

related chronic diseases [54].

Chronic kidney diseases due to diabetes mellitus, hypertension, renovascular disease, and chronic glomerulonephritis are on the rise [4, 55] and these contribute to renal dysfunction, sometimes through drug interactions [56]. These diseases are likely to be missed if they are not actively searched for in the HIV programs.

CLINICAL ISSUES OF DIAGNOSIS AND MANAGEMENT

The evaluation of an HIV-infected patient with suspected kidney disease should follow the usual guidelines as for non-HIV-infected patients. AKI should be approached with the usual practice of looking for pre-renal, renal and post-renal causes. The common causes of AKI in the HIV-patient as outlined in the previous sections should be actively sought and addressed.

Before starting antiretroviral treatment, all patients should be screened for kidney disease according to the Infectious Disease Society of America guidelines [49]. When this is not possible, as is often the case in resource limited settings, a urine dipstick should be performed at minimum. Use of spot urine protein/creatinine ratio and urine microscopy can be a powerful diagnostic tool in patients with kidney injury [57, 58]. For patients to be initiated on drugs known to cause nephrotoxicity, renal function tests should routinely be performed. This may help to prevent development of CKD, which would require further resource utilization [59]. It is also important to remember that many patients with HIV may present with muscle wasting while receiving HAART, which can lower serum creatinine concentrations and falsely support the presence of normal kidney function. In such patients, serum creatinine measurement alone is an insensitive measurement of glomerular filtration rate, and patients could have significant renal insufficiency with normal serum creatinine levels.

Clinicians should therefore make appropriate adjustments in drug dosage based on the patient's creatinine clearance as calculated by the Cockcroft-Gault equation. In a study by Peters carried out in Uganda, no renal dose adjustments for HAART were made once kidney function improved, to avoid risking significant under dosing. The authors concluded that renal function may not need to be measured at the time of drug initiation, which could save precious clinical resources [52]. However, renal function may need to be monitored later in the course of therapy to identify drug-related nephrotoxicity. Importantly, we should note that in as much as the kidney function improved in these patients, none of the patients were on tenofovir-based regimens, which have been shown to have a higher potential for nephrotoxicity in the DART trial [29]. Moreover, without measurement of baseline kidney function, it is harder to attribute any abnormalities to drug nephrotoxicity.

The selected regimen should be dose adjusted based on the established guidelines using the estimated GFR and stage of kidney disease.

Most NNRTIs, PIs, fusion inhibitors, integrase inhibitors, and CCR5 antagonists do not require dose modification in CKD or ESRD. However, several drugs need special mention because of their increased use and/or demonstrated adverse effects on the kidneys. The usual dosage of tenofovir for HIV patients without significant renal insufficiency is 300 mg daily. Tenofovir requires dose adjustments at creatinine clearance (CrCl) levels below 50 mL/min as indicated in Table 3.

Combination therapy such as TDF/FTC (which includes 300mg TDF and 200mg of FTC) also requires dose adjustments for CrCl of 30-49 mL/min. Most importantly, the TDF/FTC combination pill is not recommended for patients with CrCl below 30mL/min. Clinicians may therefore opt to prescribe tenofovir as a separate drug that is renally adjusted, in combination with other HAART regimens. There is also significant drug interaction between tenofovir and didanosine. Thus, when co-administered with tenofovir, it is important to make appropriate reduction in dose adjustments of DDI in patients weighing 60 kilograms or more [49]. Because the potential toxic interactions between tenofovir and DDI are concerning, this combination should probably be avoided. Fortunately, DDI is not commonly used as a first line drug [8].

Figure 3

Table 3: Dose adjustment for commonly used NRTIs

Agent	Normal dose	Estimated GFR (creatinine clearance: CrCl)
zidovudine	300 mg twice a day orally	100 mg thrice a day orally
lamivudine	150 mg twice a day orally	30-49 ml/min= 150 mg once a day orally 15-29 ml/min= 100 mg once a day orally 5-14 ml/min= 50 mg once a day orally <5 ml/min= 25 mg once a day orally
stavudine	30 mg twice a day orally	26-50 ml/min= 15 mg twice a day orally <26 ml/min= 15 mg once a day orally
didanosine	>60 kg: 200 mg twice a day orally <60 kg,125 mg twice a day orally	30-59 ml/min= 200 mg once a day orally 10-29 ml/min= 150 mg once a day orally <10 ml/min= 100 mg once a day orally 30-59 ml/min= 150 mg once a day orally 10-29 ml/min= 100 mg once a day orally <10 ml/min= 75 mg once a day orally
tenofovir	300 mg once a day orally	30-49 ml/min= 300 mg every second day 10-29 ml/min= 300 mg every third day <10 ml/min= 300 mg once weekly

(Note: no dose adjustment necessary for abacavir)

Indinavir is also not commonly used in SSA. If on this drug, however, patients should drink about 2-3 liters of fluid per day to avoid crystal nephropathy and nephrolithiasis [49].

As patients with HIV continue to live longer, their risk factors from other chronic diseases increase. These include hypertension and diabetes mellitus, which should be systematically screened for in this population [60].

Early referral of patients with CKD to clinicians skilled in management of kidney disease may improve patient outcomes. Currently there is little evidence to support this position in SSA. Patients who progress to ESRD should be managed with the available modes of renal replacement therapy (RRT) in the country. All modes of RRT should be available for HIV infected patients with end stage renal disease. Although HIV-infected patients managed with peritoneal dialysis had worse outcomes in pre-HAART era [61], currently the choice of dialysis modality between hemodialysis and peritoneal dialysis is not a factor in predicting survival, if patients are stable on HAART [62]. However, it is notable that HIV is capable of replicating in peritoneal dialysis tubing and effluent bags for up to 7 days, so effluent should be treated for at least 30 minutes with bleach and fluid, tubing, and bags disposed of as biohazard waste [63]. Standard disinfection and sterilization procedures are sufficient to prevent patient exposures, and isolation of HIV-infected patients or use of dedicated hemodialysis machines is not required. Hemodialysis filters may be reused in HIV-infected patients [60, 64].

Patients with HIV and ESRD can receive kidney transplants. Renal transplantation is both safe and effective in HIV. Although rejection rates are higher in these patients, these rejections respond well to therapy. Several drug interactions between HAART and immunosuppressants exist, and should be taken into consideration when devising the immunosupression regimens [65]. Some experts have argued for transplant of HIV infected patients with kidneys from HIV infected donors following the ground breaking kidney transplant from an HIV positive donor in South Africa [66].

On the whole, the proper management of kidney diseases and nephrotoxicity will be further facilitated by training more specialists in kidney disease management in resource limited settings and working together with international partners to ensure proper screening, management and prevention of kidney diseases.

SCREENING AND PREVENTION

The best approach to any disease, including kidney disease is prevention through early detection of risk factors, adjusting therapeutic agents according to renal function, and prompt treatment of those who present with kidney disease. Human resource and capacity building for renal disease management will be a cornerstone to improved care of these patients. Prevention of chronic kidney disease and vascular diseases such as hypertension and diabetes mellitus is a viable health strategy in the developing world [67].

CONCLUSION

Although sub-Saharan Africa bears the greatest burden of HIV infection, there is limited data on nephrotoxicity from HIV-related treatments. Several studies have demonstrated the benefit of HAART in decreasing HIV-associated mortality in SSA. However, HAART and other medical therapies for HIV-related infections have been associated with both short and long term toxicities including nephrotoxicity. With the increase in HAART use, clinicians must screen patients for the development of kidney disease especially if the regimen employed increases risk of kidney injury. It is also important that patients with CKD are not denied the best combinations, especially since most drugs can be adjusted based of the estimated GFR. Early detection of risk factors (some of which may be peculiar to SSA) as outlined in this paper, systematic screening for chronic causes of CKD, and human resource and capacity building for kidney disease management should be advocated for improved patient care.

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