Nephropathies in HIV-infected patients: an overview

S Lai1,2*, A Mariotti3, C Lai1, M Testorio2, M Carta1, G Innico1, N Frasetti1, GE Russo2

Abstract

Introduction
The incidence and spectrum of kidney disease in Human Immunodeficiency Virus-infected patients have been altered by the diffused use of highly active antiretroviral therapy; indeed, acute and chronic kidney disease has emerged as a significant cause of morbidity and mortality among Human Immunodeficiency Virus-infected population. Risk factors associated with kidney disease in such Human Immunodeficiency Virus-infected population include aging, hypertension, diabetes mellitus, co-infection with hepatitis C virus, low CD4 cell count, and high Human Immunodeficiency Virus viral load. The aim of this review was to discuss nephropathies in Human Immunodeficiency Virus-infected patients.

Materials and Methods
We conduct a review on the actual knowledge of acute and chronic Human Immunodeficiency Virus-associated renal disease, metabolic alterations and related nephropathies, and the side effects of highly active antiretroviral therapy.

Results
We examined all the randomised controlled trials and quasi-randomised controlled trials that evaluate the current knowledge on acute and chronic HIV and highly active antiretroviral therapy associated renal disease. After quality appraisal, 170 met the inclusion criteria for the review. The studies included in the review were grouped into two areas: nephropathy HIV associated and nephropathy highly active antiretroviral therapy associated.

Conclusion
Early identification and treatment of kidney disease is imperative for preventing further renal damage in Human Immunodeficiency Virus-infected populations and for instituting appropriate management efficiently. The Infectious Diseases Society of America guidelines recommend urinalysis and estimation of kidney function for all Human Immunodeficiency Virus-infected persons at the time of Human Immunodeficiency Virus diagnosis. Periodic monitoring of albuminuria, tubular parameters such as low-molecular-weight proteinuria, and the estimated glomerular filtration rate may be useful for early diagnosis of patients at risk for acute or chronic renal disease.

Introduction
Over the last two decades, the number of individuals infected with HIV has markedly increased. Since the introduction of the highly active antiretroviral therapy (HAART) at the end of 1995, the number of deaths caused by HIV infection or by an acquired immunodeficiency syndrome (AIDS)-defining disease has dramatically decreased. HAART has increased survival and therefore extended the mean age of our population, but this prolongation has been accompanied by the emergence of acute and chronic kidney disease (CKD) and subsequent end-stage renal disease (ESRD) as major causes of morbidity and mortality in these patients.

Now, nephrologists are faced with several challenges regarding kidney disease in HIV-infected populations including identifying early signs of kidney disease, and working in collaboration with HIV experts to provide the best treatment to patients with renal disease. Renal disease is becoming an increasingly prevalent entity in HIV-infected patients and occurs at all stages of HIV infection. Renal pathology in HIV patients can be caused by a variety of mechanisms creating a broad spectrum of clinical disease. HIV-related renal impairment can present as acute or chronic kidney disease; it can be caused directly or indirectly by HIV and/or by drug-related effects that are directly nephrotoxic or lead to changes in renal function by inducing metabolic vacuolopathy and renal damage. The aim of this review was to give an overview of nephropathies in HIV-infected patients.

Acute renal failure in HIV-infected patients
RIFLE and AKI (the acronyms for diagnosis and classification of acute renal dysfunction) criteria are frequently used, and aim to standardize the definition of acute kidney injury (AKI) by stratifying patients based on changes in serum creatinine levels from baseline and/or an abrupt decrease in urine output. Tubular dysfunction is defined as an abnormal presence of markers in urine (e.g., hyperaminoaciduria, euglycemic glucosuria, beta2-microglobulinuria, and hyperphosphaturia). AKI is a common finding in HIV-infected patients and has been associated with advanced stages of HIV infection (e.g., CD4 cell count of < 200 cells/mm³ and HIV RNA level of > 10,000 copies/mL), with prior renal impairment, HCV co-infection, liver disease, and a history of HAART. HIV-infected patients are also at increased risk for AKI development, related to volume
depletion, sepsis, radiocontrast, and the administration of nephrotoxic medications used in the treatment of opportunistic infections, such as antibiotics (aminoglycosides), anti-fungals (amphotericin B), antivirals (acyclovir, ganciclovir), antituberculosis drugs, pentamidine, and anti-inflammatory drugs. A study that evaluated the incidence and aetiology in a prospective analysis of 754 HIV-infected patients reported an incidence of 5.9 cases of AKI per 100 patient-years3. In the HAART era, the reported incidence of AKI in hospitalized HIV-infected patients ranged from 6% to 20%, and AKI was associated with increased in-hospital mortality4. Acute interstitial nephritis (AIN) can occur as a result of HIV infection of the kidney itself, as in 28% of autopsy findings in HIV-infected patients4. Interruption of the potential liable agent is the pivot of therapy. These complications can be prevented or minimized with wide fluid intake4. In severe cases, immunosuppressive therapy has been employed. Electrolyte disturbances of hypo-hypernatraemia, hypophosphataemia, hypocalcaemia, and hypomagnesaemia are common. Hyponatraemia is often found in HIV-infected patients with gastroenteritis. The syndrome of inappropriate anti-diuretic hormone secretion (SIADH) is usually due to intracranial and respiratory infections such as pulmonary tuberculosis (TB), pneumocystis pneumonia, and toxoplasmosis. Hypokalaemia due to gastrointestinal losses, renal tubular loss, and severe malnutrition is also often found. Toxicity from HAART such as tenofovir can cause Fanconi syndrome and nephrogenic diabetes insipidus. Therefore, the dosing of nephrotoxic drugs should be adjusted to the eGFR in patients with acute or chronic kidney damage. There is a higher prevalence of urinary tract infections (UTIs) and seems to be more due to malnutrition than from immunosuppression due to HIV infection. Pulmonary and disseminated TB and other viral infections such as cytomegalovirus (CMV), hepatitis B (HBV), and HCV should be included in the differential diagnosis of acute or chronic renal failure. It has been shown that patients who survive AKI have a greater rate of long-term mortality. Choi and colleagues evaluated the long-term consequences of AKI in 17,325 HIV-infected patients during their first hospitalization. Over a mean follow-up period of 5.7 years, they found that AKI was associated with increased mortality and long-term risk of heart failure, cardiovascular disease, and end-stage renal disease3.

Chronic Renal Disease in HIV-Infected Patients

The prevalence of CKD in the various stages of HIV infection is difficult to assess. Proteinuria and elevated creatinine level have been found in 7.2%–32% of HIV-seropositive patients in a study of 2038 female HIV-infected patients7. Autopsy studies yield a prevalence of up to 43% of pathological changes on histological examination8. The cause of CKD in HIV-infected patients can be difficult to assess on clinical grounds alone and can most often only be determined by renal biopsy. CKD is defined by KDIGO and is divided into groups based on confirmed eGFR levels (≥ 3 months)9. CKD can be caused by multiple pathophysiological mechanisms; HIV itself seems to directly mediate the development of HIV-associated nephropathy (HIVAN) and thrombotic thrombocytopenic purpura. One of the main causes of CKD is HIVAN, a clinicopathologic entity characterized by severe proteinuria, renal failure, rapid progression to ESRD, and frequently enlarged kidneys visible on renal ultrasound10–13. It was initially described in 1984 by Rao, who reported a pattern of focal segmental glomerulosclerosis, often of the collapsing variant, and microcystic tubulointerstitial disease in HIV-seropositive patients in New York City. It was directly linked to infection of epithelial cells by HIV14, and was recently found to be related to polymorphisms in the APOL1 gene; indeed, almost all patients developing HIVAN are of African origin14,15. Renal biopsy is the only means of establishing the diagnosis of HIVAN. Without adequate treatment, the prognosis of HIVAN is poor; risk factors for the development of HIVAN include a CD4 cell count < 200 cells/mm3 and a high viral burden16. Pharmacologic agents used for the treatment of HIVAN include HAART17, steroids, and angiotensin-converting enzyme inhibitors (ACEI). Recently, cyclosporin has been used as another option in children, but clinical experience with it is limited1. The introduction of HAART was shown to be associated with a reduction in HIVAN incidence17. Thrombotic microangiopathy, haemolytic uraemic syndrome, and thrombotic thrombocytopenic purpura present a spectrum of diseases characterized by haemolytic anaemia, thrombocytopenia, renal insufficiency, and clinical features, such as fever and neurological manifestations. Several reports have linked thrombotic microangiopathy to HIV infection, suggesting that HIV proteins may mediate endothelial dysfunction, leading to platelet deposition in the microvasculature. Therapeutic options consist of plasma infusion and plasmapheresis, which have had variable success. Other attempted therapies include glucocorticoids, immunoglobulin infusions, antiplatelet drugs, vincristine, and splenectomy, although general treatment recommendations are lacking12. Other pathophysiological pathways comprise indirect viral effects, such as various forms of deposition of HIV immune-complex kidney disease (HIVICK). The prevalence of HIVICK is highly variable in the different studies. A study of 60 biopsies found that some form of HIVICK was present in 37% of biopsy specimens. HIVICK may present as post-infectious...
glomerulonephritis and includes membranous nephropathy, IgA nephropathy, lupus-like glomerulonephritis, immunotactoid glomerulopathy, and membranoproliferative glomerulonephritis. Cryoglobulinemic membranoproliferative glomerulonephritis (MPGN) is the more characteristic renal disease associated with HCV infection; indeed, HCV co-infection in HIV patients is a very common problem, affecting approximately 30% of HIV-infected patients. Patients with HIV/HCV seem to benefit from treatment with ACEi, glucocorticoids, and antiretrovirals. CKD is a serious complication of long-term intravenous drug use (IVDU). Renal disease-related IVDU has been reported since the 1970s, mostly in the context of heroin-associated nephropathy, characterized by nephritic syndrome and rapid progression. Two recent studies from Europe observed changing patterns of renal disease in patients with IVDU, with concomitant chronic HIV, HBV, and HCV infections, reporting an increased prevalence of renal AA-amyloidosis. Renal AA-amyloidosis is a complication of chronic and/or recurrent inflammatory disease. Severe proteinuria, nephrotic syndrome, as well as renal insufficiency are the typical clinical manifestations of renal AA-amyloidosis. Successful treatment of the underlying inflammation, by immunosuppressants for autoimmune diseases or by antimicrobials for chronic infections, can lead to stabilization of or even improvements in renal function.

Renal adverse effects of HAART

The use of HAART has changed the natural history and spectrum of kidney disease in HIV-positive patients. HAART is effective in controlling the viral replication, restoring immune function, and decreasing the occurrence of HIV-related complications; however, it may be associated with nephrotoxicity or with increased rates of dyslipidaemia, hypertension, and diabetes, with an increase in secondary renal damage, such as hypertensive nephrosclerosis and diabetic glomerulopathy as well as vascular complications. Antiretroviral therapy has been associated with impaired glucose tolerance. A study of 17,852 HIV-seropositive patients evaluated a prevalence of diabetes of 2.5% that was significantly associated with antiretroviral treatment, and a study that is ob. Another study, including 60 kidney biopsies performed during AKI served a cohort of 5578 patients during 1984–2003 revealed an incidence of hypertension in 7.3% of HIV-seropositive patients. Renal damage caused by HAART can result in a variety of toxic drug effects presenting as acute renal failure, tubular necrosis, kidney stones, or CKD. HAART-associated nephrotoxicity has been described in many case reports and systematic observational studies; most studies, however, conclude that the occurrence is relatively low, but warrant clinical attention due to the potentially serious complications. One study found that HAART-related nephrotoxicity accounted for 14% of all AKI cases among HIV-positive individuals. Another study, including 60 kidney biopsies performed during AKI, found 5% were HAART-related. For tenofovir, Gilead has reported a 0.5% incidence of serious adverse renal events. There are several direct and indirect ways in which HAART can induce damage to renal structures, as shown in Table 1. There is an ongoing and unresolved discussion whether HAART-induced nephrotoxicity is reversible. Several studies demonstrate that only some patients reached pre-exposure levels, whereas several safety studies indicate a faster and more complete resolution after discontinuation. The contribution of HIV as well as HAART to bone disease, which may include loss of bone mineral content and aseptic necrosis of the femoral head, remains unclear. HIV patients are at an increased risk of osteoporosis, which is four times higher than the general population. According to the information Italian cohort naïve antiretro viral (ICONA), more than 54% of patients with HIV infection lack vitamin D. The virus has a direct responsibility in the pathogenesis of osteoporosis by acting on osteoblasts and osteoclasts. HAART also promotes the toxic action of the HIV virus on bone, as demonstrated by Brown in 2006 and by the SMART study. These drugs act on the mitochondrial DNA, resulting in an increased production of lactic acid. Chronic metabolic acidosis causes an increase in osteoclastic activity and a reduction in osteoblastic activity. Acid–base disturbances are common in HIV-infected patients and are mainly due to drugs and sepsis. Lactic acidosis may possibly be due to drug-induced mitochondrial dysfunction reported with zidovudine, stavudine, lamivudine, and diadanosine, and could be present in a mild form in 5%–25% of patients. Non-anion gap metabolic acidosis can result from intestinal loss of bicarbonate due to diarrhoea or renal losses due to drug toxicity, most commonly amphotericin B and tenofovir.

Materials and methods

We conducted a review of the current knowledge on acute and chronic HIV-associated renal disease, metabolic alterations and related nephropathies, and toxic drug effects of HAART.

Types of studies

All RCTs and quasi-RCTs evaluate the current knowledge on acute and chronic HIV-associated renal disease, metabolic alterations and related nephropathies, and toxic drug effects of HAART.

Electronic searches

- Cochrane Renal Group’s specialized register
- AEGIS database (AIDS Education Global Information System)
Table 1 Nephrotoxicity of HAART (Highly Active Antiretroviral Therapy)

<table>
<thead>
<tr>
<th>HAART</th>
<th>Action point</th>
<th>Mechanism of action</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Interstitium</td>
<td>Hypersensitivity reaction</td>
<td>AKI</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Tubules</td>
<td>Crystal formation</td>
<td>Urolithias</td>
</tr>
<tr>
<td></td>
<td>Interstitium</td>
<td>Hypersensitivity reaction</td>
<td>AIN</td>
</tr>
<tr>
<td>Nucleoside/nucleotide reverse transcriptase inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>Tubules, Interstitium</td>
<td>Hypersensitivity reaction</td>
<td>AIN, Fanconi syndrome, CKD</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Tubules</td>
<td>mitochondrial toxicity</td>
<td>Fanconi syndrome, NDI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Known to increase tenofovir toxicity</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Proximal tubules</td>
<td>Mitochondrial toxicity and transporter dysfunction/inhibition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interstitium</td>
<td>Mitochondrial toxicity and transporter dysfunction/inhibition</td>
<td>Tubular dysfunction (Fanconi syndrome, hyperphosphatemia, euglycemic glucosuria, bicarbonaturia) AKI</td>
</tr>
<tr>
<td>Glomerulus</td>
<td>Unknown</td>
<td></td>
<td>CKD</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Tubules</td>
<td>mitochondrial toxicity</td>
<td>Fanconi syndrome</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Tubules</td>
<td>mitochondrial toxicity</td>
<td>Fanconi syndrome</td>
</tr>
<tr>
<td>Protease inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Tubules</td>
<td>Crystal formation</td>
<td>Urolithias</td>
</tr>
<tr>
<td></td>
<td>Interstitium</td>
<td>Allergic</td>
<td>AIN, AKI, CKD</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Tubules, Interstitium</td>
<td>Crystal formation</td>
<td>Urolithias, papillary necrosis,tubulointerstitial nephritis, AIN, AKI, CKD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Tubules</td>
<td>Crystal formation</td>
<td>Urolithias</td>
</tr>
<tr>
<td></td>
<td>Interstitium</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glomerulus</td>
<td>Unknown</td>
<td>CKD</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Tubules</td>
<td>Crystal formation</td>
<td>Urolithias</td>
</tr>
<tr>
<td></td>
<td>Interstitium</td>
<td>MRP4 inhibition, CytP450 interaction</td>
<td>AKI</td>
</tr>
<tr>
<td></td>
<td>Glomerulus</td>
<td>Unknown</td>
<td>CKD</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Tubules</td>
<td>Crystal formation</td>
<td>Urolithias</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Tubules</td>
<td>Crystal formation</td>
<td>Urolithias</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Tubules</td>
<td>Crystal formation</td>
<td>Urolithias</td>
</tr>
<tr>
<td>Fusion inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>Glomerulus</td>
<td>Hypersensitivity reaction</td>
<td>Membranoproliferative GN</td>
</tr>
</tbody>
</table>

AKI: acute kidney injury; AIN: acute interstitial nephritis; GN: glomerulonephritis; CKD: chronic kidney disease; NDI: nephrogenic diabetes insipidus.
Results of the research infected patients with proteinuria, opsy should be considered in all HIV-treated specific treatments. Renal bi


discussion


evaluation of the Modification of Diet in Renal Disease (MDRD) equation to estimate kidney function in HIV-infected individuals, CKD Epidemiology Collaboration (CKD-EPI) is considered the most precise. The new Japanese coefficient for eGFR based on insulin clearance data has been shown to be more accurate for the Japanese population than the previously reported equations. Serum cystatin C has been evaluated as an alternative or additional renal biomarker for estimating kidney function. However, the serum cystatin C level can be influenced by age, sex, race, and other non-renal factors. Periodic monitoring of urinary low molecular weight proteins, such as N-acetyl-β-d-glucosaminidase, β2 microglobulin, α2 microglobulin, etc., might be useful in early identification of tubular damage, specifically in patients receiving HAART. In the pre-HAART era, dialysis was not offered to patients with HIV infection because of poor survival and with high infection rates. Currently, both peritoneal dialysis and haemodialysis are effective modes of renal replacement therapy in these patients. Prior to the introduction of HAART, the morbidity and mortality of HIV-infected patients was too high to justify using scarce resources to transplant HIV-infected patients. The ability to suppress HIV replication with HAART, as well as improved prophylaxis and treatment of opportunistic infections, encouraged the transplant community to select patients with HIV to be included on the transplant list.

Conclusion

All HIV-infected persons should be screened at regular intervals for a history of metabolic disease, dyslipidaemia, diabetes, hypertension, and alteration of body composition; cardiovascular risk and renal function should also be assessed. The IDSA guidelines recommend biannual screening for proteinuria, glycosuria, eGFR, and phosphate of patients on tenofovir with eGFR<90 mL/min, concomitant boosted protease inhibitors (PI) usage, or renal risk factors. Referral should be considered in patients with decreasing eGFR, lingering proteinuria, hematuria, or pyuria. Adaptation of dosages might be required in the case of more drugs. Kidney biopsies are commonly recommended to ascertain an accurate diagnosis, except contraindications. Lifestyle interventions should focus on counselling to stop smoking, follow a healthy diet, restrict salt intake, exercise, and to maintain normal body weight to reduce dyslipidaemia; if not effective, a change in HAART should be considered, followed by the use of statins. A pre-emptive switch from thymidine analogues is recommended to reduce the risk of development or progression of lipoatrophy. Intra-abdominal fat accumulation is best managed by exercise and diet, in cases where lipoatrophy has developed, reversal is slow and gradual. Prevention and management of diabetes and hypertension follow guidelines used in the general population. When using medical interventions to prevent

Figure 1: Results of the research

- ClinicalTrials.gov
- WHO International Clinical Trials Registry Platform
- MEDLINE

We checked the reference lists of nephrology textbooks, review articles, and relevant studies.

Results

We analysed 945 studies, out of which 578 were excluded for wrong population or intervention and 197 deemed unfit. After quality appraisal, 170 met the inclusion criteria for the review. The studies included in the review were grouped into two areas: nephropathy HIV associated and nephropathy HAART associated. Please refer Figure 1.

Discussion

The incidence and spectrum of kidney disease in HIV-infected patients has changed considerably over the years. Identification of the cause of renal damage may be crucial in directing specific treatments. Renal biopsy should be considered in all HIV-infected patients with proteinuria, whatever their renal function, CD4+ count, or viral load. Through the use of ultrasound-guided renal biopsy and automatic biopsy devices, percutaneous renal biopsy has become safe. Transjugal renal biopsy may represent a relatively safe and reliable alternative to conventional percutaneous biopsy in patients with risk factors for bleeding such as thrombocytopenia. Periodic monitoring of albuminuria, tubular parameters, and eGFR may be useful in the early diagnosis of patients at risk for acute or chronic kidney disease. Estimates of kidney function have not been thoroughly validated in HIV-infected individuals and may be insensitive to early decrements in kidney function. The gold standards for determination of renal function are expensive and inconvenient. Although the current IDSA guidelines recommend using the Modification of Diet in Renal Disease (MDRD) equation to estimate kidney function in HIV-infected individuals, the Epidemiology Collaboration (CKD-EPI) is considered the most precise. The new Japanese coefficient for eGFR based on insulin clearance data has been shown to be more accurate for the Japanese population than the previously reported equations. Serum cystatin C has been evaluated as an alternative or additional renal biomarker for estimating kidney function. However, the serum cystatin C level can be influenced by age, sex, race, and other non-renal factors. Periodic monitoring of urinary low molecular weight proteins, such as N-acetyl-β-d-glucosaminidase, β2 microglobulin, α2 microglobulin, etc., might be useful in early identification of tubular damage, especially in patients receiving HAART. In the pre-HAART era, dialysis was not offered to patients with HIV infection because of poor survival and with high infection rates. Currently, both peritoneal dialysis and haemodialysis are effective modes of renal replacement therapy in these patients. Prior to the introduction of HAART, the morbidity and mortality of HIV-infected patients was too high to justify using scarce resources to transplant HIV-infected patients. The ability to suppress HIV replication with HAART, as well as improved prophylaxis and treatment of opportunistic infections, encouraged the transplant community to select patients with HIV to be included on the transplant list.
and/or treat metabolic diseases, impairment of the efficacy of HAART should be prevented by considering the possibility of pharmacokinetic interactions and compromised adherence. Treatment of HCV co-infection should be considered when patients have HCV-related nephropathy proved by renal biopsy. However, as yet, the safety and efficacy of interferon treatment for HCV infection in HIV-infected individuals has not been documented. Specialists in HIV and experts in metabolic diseases should consult each other.

Abbreviations list

ACEi, angiotensin-converting enzyme inhibitors; AEGIS, AIDS Education Global Information System; AIDS, acquired immunodeficiency syndrome; AIN, acute interstitial nephritis; AKI, acute kidney injury; CKD, chronic kidney disease; CKD-EPI, CKD Epidemiology Collaboration; CMV, cytomegalovirus; ESRD, end-stage renal disease; HAART, highly active antiretroviral therapy; HBV, hepatitis B; HIV, Human Immunodeficiency Virus; HIVAN, HIV-associated nephropathy; HIVICK, HIV immune-complex kidney disease; IVDU, intravenous drug use; MDRD, Modification of Diet in Renal Disease; MPGN, membranoproliferative glomerulonephritis; PI, protease inhibitors; SIADH, syndrome of inappropriate anti-diuretic hormone secretion; TB, tuberculosis; UTI, urinary tract infection

References


Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)