HIV associated nephropathy: a treatable condition

M Gary Brook, Robert F Miller

Objectives: To describe current knowledge on the aetiology, pathology, diagnosis, and treatment of HIV associated nephropathy.

Methods: A Medline search was performed using the key words “HIV,” “nephropathy,” “renal,” and “kidney.” A further search was performed for each of the currently licensed antiretroviral agents linked to key words “renal” or “kidney” and also using the MeSH heading “pharmacokinetics.”

Results: HIV associated nephropathy is a common complication of HIV in black African and Afro-Caribbean patients and presents with progressive renal failure and heavy proteinuria. As other causes of renal failure are likely to fall in incidence among patients successfully treated with highly active antiretroviral therapy (HAART), HIV associated nephropathy will become increasingly prominent as a cause of renal impairment in HIV infected patients. Recent evidence suggests that HIV associated nephropathy will respond to HAART with a dramatic improvement in renal function.

Conclusion: HIV associated nephropathy is a treatable condition. This condition should be actively sought in HIV infected patients if they are to receive the benefits of therapy.

(Sex Transm Inf 2001;77:97–100)

Keywords: HIV; nephropathy; HAART

Introduction
Renal impairment in patients with HIV infection may arise through a variety of different mechanisms. The majority of causes are related to problems complicating HIV associated immunodeficiency or the drugs used to treat these complications, albeit the most common cause of renal failure in the era of highly active antiretroviral therapy (HAART) is the syndrome of HIV associated nephropathy (HIVAN).

Renal impairment unrelated to HIVAN
Renal failure related to treatment, immune dysregulation, or secondary infection used to be common during the course of HIV, particularly before HAART became available (table 1). But with the advent of HAART, there have been dramatic falls in the occurrence of AIDS and AIDS related deaths. Also as a consequence of HAART, renal failure due to secondary infections and their treatment is seen less frequently. None the less, as many as 50% of patients present with a low CD4 count (<350 cells x10^9/l) and/or symptomatic disease when they are first diagnosed with HIV. Renal failure will therefore continue to be an important part of the repertoire of disease seen in those with HIV. Unlike HIVAN, there seems to be no link between ethnicity and these other causes of renal disease.

HIV associated nephropathy
Evidence has accumulated over the past 15 years that HIV itself may cause specific renal pathology characterised histologically by focal and segmental glomerulosclerosis with related mesangiopathies and clinically by acute or subacute progressive renal failure with heavy proteinuria and abnormal echogenic kidneys on ultrasonography. The other striking feature of HIVAN is the predominance of black patients. The exact cause of HIVAN is not fully understood although proliferation of renal epithelial cells with concurrent apoptosis is a feature. Electron microscopy changes are also distinctive and include wrinkling, retraction pleating, and thickening of the glomerular basement membrane and foot process effacement. Particulary distinctive is the presence of numerous tubuloreticular inclusions within the cytoplasm of the glomerular endothelial cells, interstitial capillary, and arterial endothelial cells and interstitial leucocytes.

The most common and characteristic pathological finding on renal biopsy or necropsy is focal and segmental glomerulosclerosis (FSGS). There may also be glomerular collapse and microcystic tubulointerstitial disease. However, this histology is not unique and may be seen in HIV negative patients. Other features suggestive of HIVAN include podocyte swelling, intracytoplasmic protein resorption droplets, and less hyalinosis than is seen in FSGS of other causes, such as that associated with intravenous heroin misuse or the idiopathic non-HIV form.

Pathology
The most common and characteristic histological finding on renal biopsy or necropsy is focal and segmental glomerulosclerosis (FSGS). There may also be glomerular collapse and microcystic tubulointerstitial disease. However, this histology is not unique and may be seen in HIV negative patients. Other features suggestive of HIVAN include podocyte swelling, intracytoplasmic protein resorption droplets, and less hyalinosis than is seen in FSGS of other causes, such as that associated with intravenous heroin misuse or the idiopathic non-HIV form.

Electron microscopy changes are also distinctive and include wrinkling, retraction pleating, and thickening of the glomerular basement membrane and foot process effacement. Particularly distinctive is the presence of numerous tubuloreticular inclusions within the cytoplasm of the glomerular endothelial cells, interstitial capillary, and arterial endothelial cells and interstitial leucocytes.

The exact cause of HIVAN is not fully understood although proliferation of renal epithelial cells with concurrent apoptosis is a feature. There are some in vitro data suggesting that HIV-1 can infect renal tubular epithelial cells causing a failure of growth and regeneration. HIV-1 infected monocytes, under the influence of locally secreted interleukin-6 and tissue necrosis factor α, may also be an important factor. Cytokines such as transforming growth factor β and macrophage chemoattractant protein are also thought to
Table 1  Common causes of renal failure in HIV

<table>
<thead>
<tr>
<th>Acute renal failure</th>
<th>Chronic renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug related nephrotoxicity*</td>
<td>HIV associated nephropathy</td>
</tr>
<tr>
<td>Haemolytic uraemic syndrome</td>
<td>Membranous glomerulonephritis</td>
</tr>
<tr>
<td>Acute tubular necrosis (toxic/ischaemic)</td>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>IgA nephropathy</td>
</tr>
</tbody>
</table>
| Intrarenal and extrarenal obstructive nephropathy (mostly drug induced)† | |}

*For example, amphotericin B, foscarnet.
†Related to sulphonamides and indinavir.
‡Usually related to hepatitis C or B.
‡‡Related to hepatitis C or B.

Clinical features

ADULTS
Most patients have late stage HIV infection with a high viral load and low (<250 × 10⁷/L) CD4+ lymphocyte count. In the majority of reported case series the HIVAN has been diagnosed as a result of routine investigations of HIV infected patients and such as acute or chronic renal failure. Symptoms are non-specific but may include fatigue, malaise, anorexia, and pruritus. Although 40–75% of patients have nephrotic range proteinuria (>3 g/24 hours) at presentation and many have full blown nephrotic syndrome with hyperalbuminaemia (<30 g/dl), peripheral oedema is surprisingly uncommon. Hypertension is also uncommon.

Black African or Afro-Caribbean patients predominate, forming 85–97% of patients with this diagnosis. Conversely, HIVAN is uncommon in other races except when associated with intravenous heroin misuse, although between 5% and 50% of black adult patients with HIVAN have also been reported to be injecting drug users.

Diagnosis

HIVAN is a disease that may be diagnosed in many patients with reasonable confidence without the need for renal biopsy, especially now that response to antiretroviral therapy can be added as further supporting evidence (see below). The characteristic findings are of a black patient with relatively late stage HIV disease presenting with proteinuria (>1 g/24 hours), rising serum creatinine, and enlarged echogenic kidneys on ultrasound. Other causes of renal failure (table 1) should be excluded (table 2) and a renal biopsy will be necessary in cases not typical of HIVAN (table 2) or in patients failing to respond to therapy which includes HAART.

Management

SPECIFIC THERAPY
The prognosis of HIVAN has improved dramatically in the past 2 years. Before HAART the prognosis of patients with HIVAN was poor although therapy with steroids, angiotensin converting enzyme inhibitors, and zidovudine monotherapy all had met with limited success in terms of modest improvement.
Table 2  Features suggesting an aetiology of renal failure other than HIVAN

<table>
<thead>
<tr>
<th>History</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-black ethnicity</td>
<td>Haematuria/myoglobinuria (non-HIVAN glomerulonephritis)</td>
</tr>
<tr>
<td>Nephrotic drugs taken recently</td>
<td>Fragmented blood cells/thrombocytopenia (haemolytic uraemic syndrome)</td>
</tr>
<tr>
<td>Renal infarction</td>
<td>Antinuclear antibody/serum complement (lupus nephritis)</td>
</tr>
<tr>
<td>Renal colic (obstructive uropathy)</td>
<td>Serumological tests for hepatitis B and C (membranoproliferative glomerulonephritis)</td>
</tr>
<tr>
<td>Haematuria (other types of glomerulonephritis)</td>
<td>Protein electrophoresis and cryoglobulins (non-HIVAN glomerulonephritis)</td>
</tr>
<tr>
<td>Myoglobinuria, myalgia (rhabdomyolysis)</td>
<td>Dilated urinary collecting system on ultrasound/IVU (obstructive uropathy)</td>
</tr>
</tbody>
</table>

Table 3  Dose modification of anti-retroviral therapy in adult HIV infected patients with renal failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage adjustments in adults related to creatinine clearance (degree of renal impairment):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30–60 ml/min (mild)</td>
</tr>
<tr>
<td>Nucleoside analogues</td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>No change</td>
</tr>
<tr>
<td>Didanosine</td>
<td>200 mg once daily</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>150 mg once daily</td>
</tr>
<tr>
<td>stavudine</td>
<td>20 mg twice daily</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>No change</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>No change</td>
</tr>
<tr>
<td>Non-nucleoside RTI</td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Unknown, theoretically no dose change required</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>No change</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Unknown, theoretically no dose change required</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>Amprenavir</td>
<td>No change</td>
</tr>
<tr>
<td>Indinavir</td>
<td>No change</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>No change</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>No change</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>No change</td>
</tr>
</tbody>
</table>

a  The manufacturers recommend avoidance in “severe” renal impairment. Preliminary evidence suggests no dose change required for any level of renal impairment. |
| b  Further dose reductions if weight <60 kg. |
| c  Manufacturers recommend a loading dose and first dose reduction at CrCl <50 ml/min, second dose reduction at CrCl <30 ml/min, third dose reduction at CrCl 10–30 ml/min respectively. |
| d  Further dose reduction to 25 mg once daily at CrCl <50 ml/min and <25 ml/min respectively. |
| e  This dose recommended at CrCl <40 ml/min. |
| f  Further dose reductions if weight <60 kg. |
| g  The non-nucleoside reverse transcriptase inhibitors are primarily liver metabolised and plasma levels should not be affected by renal disease. |

10  Although data are limited, it is suggested that these doses also apply to haemodialysis and peritoneal dialysis and doses should be administered after haemodialysis.

In renal function and prolonged survival. There are also a few case reports of cyclosporin use with little success. However, many patients eventually needed haemodialysis if they had not died of other HIV related problems. Fortunately, in recent years it has become apparent that disease progression in patients with HIVAN can be reversed and renal function improved following the use of HAART, which is confirmed by the personal experience of the authors. One reported patient was dialysis dependent with biopsy proven HIVAN, but following HAART the need for dialysis ceased. A second renal biopsy subsequently showed a dramatic improvement in histology and creatinine fell almost to normal. Needless to say, to have a high degree of HAART treatment adherence is required and one of the authors (MGB) is currently managing two non-adherent patients with worsening renal function, one of whom is now on haemodialysis. Dosage adjustments according to serum creatinine/creatinine clearance are required for many of the nucleoside analogues but not usually for protease inhibitors or non-nucleoside reverse transcriptase inhibitors (table 3). It should be remembered that frequent dosage changes may be required as the renal function improves.

OTHER TREATMENT CONSIDERATIONS

Care of patients with HIVAN, as with any patient with renal impairment, should include monitoring the patient’s blood pressure and the use of an ACE inhibitor to keep the systolic and diastolic pressures below 150 and 90 mm Hg, respectively. However, black patients may not respond well to ACE inhibitors and therefore diuretics or calcium channel antagonists may also be required. Anaemia is also commonly associated with renal failure and, providing alternative causes other than renal failure have been excluded, may require treatment with blood transfusion or erythropoetin. Similarly, serum electrolytes levels, including calcium, should be measured regularly.

Renal support with haemodialysis or continuous ambulatory peritoneal dialysis may still be required, particularly in patients presenting with severe renal failure or who do not respond to HAART for whatever reason. At present, there is a reluctance to offer organ transplantation to HIV positive patients because of the uncertain prognosis, but given the recent improvements in outlook because of HIV therapy, renal transplantation may become a reasonable option for irreversible renal failure.

Conclusion

HIVAN is a treatable condition and there is good reason for optimism with regard to the prognosis of such patients.

Conflict of interest: none.

Contributors: MGB and RFM jointly contributed to writing the manuscript; MGB performed the literature search.

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Sex Transm Infect 2001 77: 97-100
doi: 10.1136/sti.77.2.97

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