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.

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 ×10^9/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. 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.

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Table 1 Common causes of renal failure in HIV

<table>
<thead>
<tr>
<th>Acute renal failure</th>
<th>Related to hepatitis C or B.11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug related nephrotoxicity*</td>
<td>Related to sulphonamides and indinavir.41</td>
</tr>
<tr>
<td>Hemolytic uraemic syndrome</td>
<td>For example, amphotericin B, foscarnet.</td>
</tr>
<tr>
<td>Acute tubular necrosis (toxic/ischaemic)</td>
<td>Acute interstitial nephritis†</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>HIV associated nephropathy</td>
</tr>
<tr>
<td>Intrarenal and extrarenal obstructive nephropathy (mostly drug induced)‡</td>
<td>Membranoproliferative glomerulonephritis‡</td>
</tr>
<tr>
<td>HIV associated nephropathy</td>
<td>Lupus-like glomerulonephritis</td>
</tr>
<tr>
<td>Acute interstitial nephritis</td>
<td>IgA nephropathy</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis‡</td>
<td>*For example, amphotericin B, foscarnet.</td>
</tr>
<tr>
<td>Membranous glomerulonephritis</td>
<td>†Related to sulphonamides and indinavir.41</td>
</tr>
<tr>
<td>HIV associated nephropathy</td>
<td>‡Usually related to hepatitis C or B.11</td>
</tr>
</tbody>
</table>
| IgA nephropathy | Chronic renal failure

*For example, amphotericin B, foscarnet.
†Related to sulphonamides and indinavir.‡
‡Usually 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.15–17 In the majority of reported case series the HIVAN has been diagnosed as a result of routine investigations of HIV infected patients and presents 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 hypoaalbuminaemia (<30 g/dl), peripheral oedema is surprisingly uncommon.15–18 Hypertension is also uncommon.12

Black African or Afro-Caribbean patients predominate, forming 85–97% of patients with this diagnosis.14 15 17 18 Conversely, HIVAN is uncommon in other races except when associated with intravenous heroin misuse.5 6 20 although between 5% and 50% of black adult patients with HIVAN have also been reported to be injecting drug users.13–14

Data on long term follow up of adults come mainly from the pre-HAART era and suggest a median time to death of approximately one year although there is a wide range. Death is usually due to other HIV related problems.2 14 The prognosis of disease can also vary from a slow deterioration over years to rapid onset of end stage renal disease within weeks. Prognosis worsens the higher the proteinuria or serum creatinine, or the lower the CD4+ lymphocyte count or the haemoglobin.11

CHILDREN

Black children are as prone to HIVAN as adults and the natural history in this group has been well documented.16 Early features include proteinuria, urinary casts, fluid/electrolyte disorders, and enlarged echogenic kidneys on ultrasound. The mean time to development of renal failure or frank nephrotic syndrome after diagnosis of early disease is about 20 months. All 30 children in this cohort had other features of symptomatic HIV disease which included cardiomyopathy in 65%.16 Hypertension was uncommon and haematuria (microscopic or macroscopic) was rare, and so when present would suggest an alternative cause for the renal dysfunction.

Diagnosis

HIVAN is a disease that may be diagnosed in many patients with reasonable confidence without the need for renal biopsy,16 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.25 Other causes of renal failure (table 1) should be excluded (table 2)34 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.35 36 Before HAART the prognosis of patients with HIVAN was poor31–33 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>Non-black ethnicity</th>
<th>Nephrotic drugs taken recently</th>
<th>Renal vein thrombosis (acute tubular necrosis)</th>
<th>Renal colic (obstructive uropathy)</th>
<th>Haematuria (other types of glomerulonephritis)</th>
<th>Myoglobinuria, myalgia (rhabdomyolysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examination</td>
<td>Acute sepsis/hypotension (ATN)</td>
<td>Investigations</td>
<td>Haematuria/myoglobinuria (non-HIVAN glomerulonephritis)</td>
<td>Fragmented red blood cells/thrombocytopenia (haemolytic uraemic syndrome)</td>
<td>Antinuclear antibody/serum complement (lupus nephritis)</td>
<td>Serological tests for hepatitis B and C (membranoproliferative glomerulonephritis)</td>
</tr>
</tbody>
</table>

Table 3 Dose modification of anti-retroviral therapy in adult HIV infected patients with renal failure45–52

<table>
<thead>
<tr>
<th>Drug</th>
<th>30–60 ml/min (mild)</th>
<th>10–30 ml/min (moderate)</th>
<th>&lt;10 ml/min (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside analogues</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Abacavir&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No change</td>
<td>No change</td>
<td>No change&lt;sup&gt;66&lt;/sup&gt;</td>
</tr>
<tr>
<td>Didanosine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>200 mg once daily</td>
<td>150 mg once daily</td>
<td>100 mg once daily</td>
</tr>
<tr>
<td>Lamivudine&lt;sup&gt;c&lt;/sup&gt;</td>
<td>150 mg once daily</td>
<td>100 mg once daily</td>
<td>50 mg once daily&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stavudine&lt;sup&gt;e&lt;/sup&gt;</td>
<td>20 mg twice daily</td>
<td>20 mg once daily&lt;sup&gt;d&lt;/sup&gt;</td>
<td>20 mg once daily</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>No change</td>
<td>0.75 mg twice daily&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.75 mg once daily</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>No change</td>
<td>No change</td>
<td>300–400 mg once daily</td>
</tr>
<tr>
<td>Non-nucleoside RTI&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Unknown, theoretically no dose change required</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Delavirdine&lt;sup&gt;e&lt;/sup&gt;</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Efavirenz&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Unknown, theoretically no dose change required</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Nevirapine&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Unknown, theoretically no dose change required</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Protease inhibitors&lt;sup&gt;i&lt;/sup&gt;</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Indinavir</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>

<sup>a</sup> The manufacturers recommend avoidance in “severe” renal impairment. Preliminary evidence suggests no dose change required for any level of renal impairment.<sup>66</sup>  
<sup>b</sup> Further dose reductions if weight <60 kg.  
<sup>c</sup> 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 <15 ml/min.  
<sup>d</sup> Further dose reduction to 25 mg once daily at CrCl <5 ml/min.  
<sup>e</sup> These dose changes recommended at CrCl <50 and <25 ml/min respectively.  
<sup>f</sup> Do this dose recommended at CrCl <40 ml/min.  
<sup>i</sup> Although data are limited, it is suggested that these doses also apply to haemodialysis and peritoneal dialysis and doses should be administered after haemodialysis.<sup>45, 46</sup>

in renal function and prolonged survival.43–47 There are also a few case reports of cyclosporin use with little success.37, 42 However, many patients eventually needed haemodialysis30, 32 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,36, 37 which is confirmed by the personal experience of the authors. One reported patient<sup>7</sup> 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 the serum creatinine fell almost to normal. Needless to say, to 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).45–52 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.19, 28, 41 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 electrolyte levels, including calcium, should be measured regularly.

Renal support with haemodialysis or continuous ambulatory peritoneal dialysis may still be required,29, 33, 34 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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