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.

 seks transf infect 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, although the most common cause of renal failure in the era of highly active antiretroviral therapy (HAART) is the syndrome of HIV associated nephropathy (HIVAN).13-20

**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 available1-11 (table 1). But with the advent of HAART, there have been dramatic falls in the occurrence of AIDS and AIDS related deaths.12-23 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 x10^3/l) and/or symptomatic disease when they are first diagnosed with HIV.13-25 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.1,2,4,8

**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.13-20,26 The other striking feature of HIVAN is the predominance of black patients.13-20

**Pathology**

The most common and characteristic histological finding on renal biopsy or necropsy is focal and segmental glomerulosclerosis (FSGS).1,2,5,8,15-16 There may also be glomerular collapse and microcystic tubulointerstitial disease.13 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.4,13 Electron microscopy changes are also distinctive and include wrinkling, retraction pleating, and thickening of the glomerular basement membrane and foot process effacement.4 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 leucocytes8 (fig 1).

The exact cause of HIVAN is not fully understood although proliferation of renal epithelial cells with concurrent apoptosis is a feature.4,13-27 There are some in vitro data suggesting that HIV-1 can infect renal tubular epithelial cells29 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.30 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>
<tr>
<td>Intrarenal and extrarenal obstructive nephropathy (mostly drug induced)†</td>
<td></td>
</tr>
<tr>
<td>HIV associated nephropathy</td>
<td></td>
</tr>
<tr>
<td>Acute interstitial nephritis</td>
<td></td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis‡</td>
<td></td>
</tr>
<tr>
<td>Lupus-like glomerulonephritis</td>
<td></td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td></td>
</tr>
</tbody>
</table>

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

Figure 1  Electron micrograph, HIVAN. Typical tubuloreticular bodies (centre). (Courtesy of Dr A Palmer).

have a role in the pathogenesis, perhaps stimulated by HIV-1 proteins such as gp-120,30–32 Podocyte damage with resulting loss of function seems to have a significant role in the loss of renal function.33

Clinical features

ADULTS
Most patients have late stage HIV infection with a high viral load and low (<250 × 10⁹/l) CD4+ lymphocyte count.14–15 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 hypoalbuminaemia (<30 g/dl), peripheral oedema is surprisingly uncommon.13 14 18 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.16–19 The progression 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.14

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.

Management
SPECIFIC THERAPY
The prognosis of HIVAN has improved dramatically in the past 2 years.15 16 Before HAART the prognosis of patients with HIVAN was poor;15 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>
</tr>
</thead>
<tbody>
<tr>
<td>Non-black ethnicity</td>
</tr>
<tr>
<td>Nephrotic drugs taken recently</td>
</tr>
<tr>
<td>Renal vein disease (acutely obstructive)</td>
</tr>
<tr>
<td>Renal colic (obstructive uropathy)</td>
</tr>
<tr>
<td>Haematuria (other than glomerulonephritis)</td>
</tr>
<tr>
<td>Myoglobinuria, myalgia (rhabdomyolysis)</td>
</tr>
</tbody>
</table>

**Examination**

Acute sepsis/hypotension (ATN)

**Investigations**

Haematuria/myoglobinuria (non-HIVAN glomerulonephritis)

Fragmented blood red cells/thrombocytopenia (haemolytic uraemic syndrome)

Antinuclear antibody/serum complement (lupus nephritis)

Serological tests for hepatitis B and C (membranoproliferative glomerulonephritis)

Protein electrophoresis and cryoglobulins (non-HIVAN glomerulonephritis)

Dilated urinary collecting system on ultrasound/IVU (obstructive uropathy)

---

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Nucleoside analogues</th>
<th>Non-nucleoside RTVs</th>
<th>Protease inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30–60 ml/min (mild)</td>
<td>10–30 ml/min (moderate)</td>
<td>30–60 ml/min (mild)</td>
</tr>
<tr>
<td></td>
<td>10–30 ml/min (moderate)</td>
<td>60–80 ml/min (moderate)</td>
<td>10–30 ml/min (moderate)</td>
</tr>
<tr>
<td></td>
<td>&lt;10 ml/min (severe)</td>
<td>&lt;10 ml/min (severe)</td>
<td>&lt;10 ml/min (severe)</td>
</tr>
<tr>
<td>Abacavir</td>
<td>No change</td>
<td>No change</td>
<td>Unknown, theoretically dose</td>
</tr>
<tr>
<td>Didanosine</td>
<td>No change</td>
<td>No change</td>
<td>no dose change required</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>200 mg once daily</td>
<td>200 mg once daily</td>
<td>No change</td>
</tr>
<tr>
<td>Stavudine</td>
<td>150 mg once daily</td>
<td>100 mg once daily</td>
<td>No change</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>20 mg twice daily</td>
<td>20 mg once daily</td>
<td>No change</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>No change</td>
<td>0.75 mg twice daily</td>
<td>No change</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Nevirapine</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>

---

**Dosage adjustments in adults related to creatinine clearance (degree of renal impairment):**

- **Nucleoside analogues:**
  - Abacavir: No change
  - Didanosine: 200 mg once daily
  - Lamivudine: 150 mg once daily
  - Stavudine: 20 mg twice daily
  - Zalcitabine: No change
  - Tenofovir: No change
  - Delavirdine: Unknown, theoretically no dose change required
  - Efavirenz: No change
  - Nevirapine: Unknown, theoretically no dose change required
  - Amprenavir: No change
  - Indinavir: No change
  - Nelfinavir: No change
  - Ritonavir: No change
  - Saquinavir: No change

**Non-nucleoside RTVs:**

- Stavudine: 20 mg once daily
- Tenofovir: 100 mg once daily

**Protease inhibitors:**

- Abacavir: No change
- Didanosine: No change
- Lamivudine: No change
- Stavudine: 20 mg once daily
- Zalcitabine: No change
- Tenofovir: No change
- Delavirdine: Unknown, theoretically no dose change required
- Efavirenz: No change
- Nevirapine: No change
- Amprenavir: No change
- Indinavir: No change
- Nelfinavir: No change
- Ritonavir: No change
- Saquinavir: No change

---

**Notes:**

- 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 at CrCl <50 ml/min, second dose reduction at CrCl <30 ml/min, third dose reduction at CrCl <15 ml/min.
- d Further dose reduction to 25 mg once daily at CrCl <5 ml/min.
- e These dose changes recommended at CrCl <50 and <25 ml/min respectively.
- f This dose recommended at CrCl ≤40 ml/min.
- g The non-nucleoside reverse transcriptase inhibitors are primarily liver metabolised and plasma levels should not be affected by renal disease.
- i Although data are limited, it is suggested that these doses also apply to haemodialysis and peritoneal dialysis and doses should be administered after haemodialysis.
- k 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 proved 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). It should be remembered that frequent dosage changes may be required as the renal function improves.

---

**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.

---
