Original article

HIV associated nephropathy: a treatable condition

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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.
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Keywords: HIV; nephropathy; HAART

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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[1–12] 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 available[1–11] (table 1). But with the advent of HAART, there have been dramatic falls in the occurrence of AIDS and AIDS related deaths.[21–23] 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 $\times 10^9$/l) and/or symptomatic disease when they are first diagnosed with HIV.[24 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.[2 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 13–16] There may also be glomerular collapse and microcystic tubulointerstitial disease.[8 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.[8 13] Electron microscopy changes are also distinctive and include wrinkling, retraction pleating, and thickening of the glomerular basement membrane and foot process effacement.[8] 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[8] (fig 1).

The exact cause of HIVAN is not fully understood although proliferation of renal epithelial cells with concurrent apoptosis is a feature.[17 27] There are some in vitro data suggesting that HIV-1 can infect renal tubular epithelial cells[28] 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.[29] Cytokines such as transforming growth factor β and macrophage chemoattractant protein are also thought to

Table 1 Common causes of renal failure in HIV

Acute renal failure[1 2 4 9–11]
Drug related nephrotoxicity*
Heamolytic uraemic syndrome
Acute tubular necrosis (toxic/ischaemic)
Rhabdomyolysis
Intrarenal and extrarenal obstructive nephropathy (mostly drug induced)†
HIV associated nephropathy
Acute interstitial nephritis
Membranoproliferative glomerulonephritis‡
Lupus-like glomerulonephritis
IgA nephropathy
Chronic renal failure[2 8]
HIV associated nephropathy
Membranous glomerulonephritis
Membranoproliferative glomerulonephritis
IgA nephropathy

*For example, amphotericin B, foscarnet.
†Related to sulphonamides and indinavir.[4 12]
‡Usually related to hepatitis C or B.[1 11]

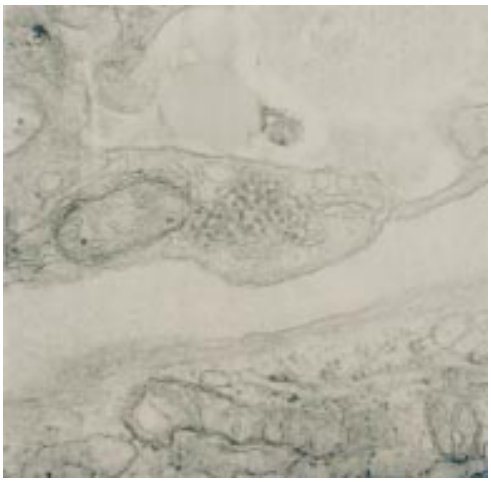

Figure 1 Electron micrograph, HIVAN. Typical tubuloreticular bodies (centre). (Courtesy of Dr A Palmer).

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 × 10^9/l) CD4+ lymphocyte count.[13–16] 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 is also uncommon.[13]

Black African or Afro-Caribbean patients predominate, forming 85–97% of patients with this diagnosis.[14 15 17 19] 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]

Estimates from the United States suggest that HIVAN affects 10% of black HIV infected adults and children and is the third leading cause of end stage renal disease in the black population between the ages of 20 and 64 years.[15–17] Part of the explanation seems to be a genetic predisposition to renal disease, as shown by the familial clustering of end stage renal disease in black patients with HIVAN.[19] There is no difference in incidence between the sexes.[20] Reports from the United States show a trebling in incidence from 1991 to 1996 although it is not clear whether this rise is related to increased incidence or better reporting/case finding.[18]

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 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.

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.[26] 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 poor[13–18] 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

History
Non-black ethnicity
Nephrotoxic drugs taken recently
Recent acute sepsis, hypotension (acute tubular necrosis)
Renal colic (obstructive uropathy)
Haematuria (other types of glomerulonephritis)
Myoglobinuria, myalgia (rhabdomyolisis)
Examination
Acute sepsis/hypotension (ATN)
Investigations
Haematuria/myoglobunuria (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[45–52]

	Dosage adjustments in adults related to creatinine clearance (degree of renal impairment):		
Drug	*30–60 ml/min (mild)*	*10–30 ml/min (moderate)*	*<10 ml/min (severe)*[i]
Nucleoside analogues			
Abacavir[a]	No change	No change	No change[48]
Didanosine[b]	200 mg once daily	150 mg once daily	100 mg once daily
Lamivudine[c]	150 mg once daily	100 mg once daily	50 mg once daily[d]
Stavudine[b]	20 mg twice daily	20 mg once daily[e]	20 mg once daily
Zalcitabine	No change	0.75 mg twice daily[f]	0.75 mg once daily
Zidovudine	No change	No change	300–400 mg once daily
Non-nucleoside RTI[49–51]			
Delavirdine[g]	Unknown, theoretically no dose change required		
Efavirenz[g]	No change	No change	No change
Nevirapine[g]	Unknown, theoretically no dose change required		
Protease inhibitors[h]			
Amprenavir	No change	No change	No change
Indinavir	No change	No change	No change
Nelfinavir	No change	No change	No change
Ritonavir	No change	No change	No change
Saquinavir	No change	No change	No change

a The manufacturers recommend avoidance in "severe" renal impairment. Preliminary evidence suggests no dose change required for any level of renal impairment.[48]
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 ar 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 of <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.[49–51] Of the non-nucleoside reverse transcriptase inhibitors, only efavirenz is recommended by its manufacturers for use in renal disease with "caution" in "severe" renal impairment.[45]
h Protease inhibitors are liver metabolised and so dose adjustment is not necessary in renal disease.[45–47]
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.[52]

in renal function and prolonged survival.[37–41] There are also a few case reports of cyclosporin use with little success.[37 42] However, many patients eventually needed haemodialysis[19 43 44] 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,[35 36] which is confirmed by the personal experience of the authors. One reported patient[35] 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, 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.[37 38 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 erythropoietin. Similarly, serum electrolytes levels, including calcium, should be measured regularly.

Renal support with haemodialysis or continuous ambulatory peritoneal dialysis may still be required,[2 9 14 18 19] 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.

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