HIV ASSOCIATED NEPHROPATHY

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INTRODUCTION

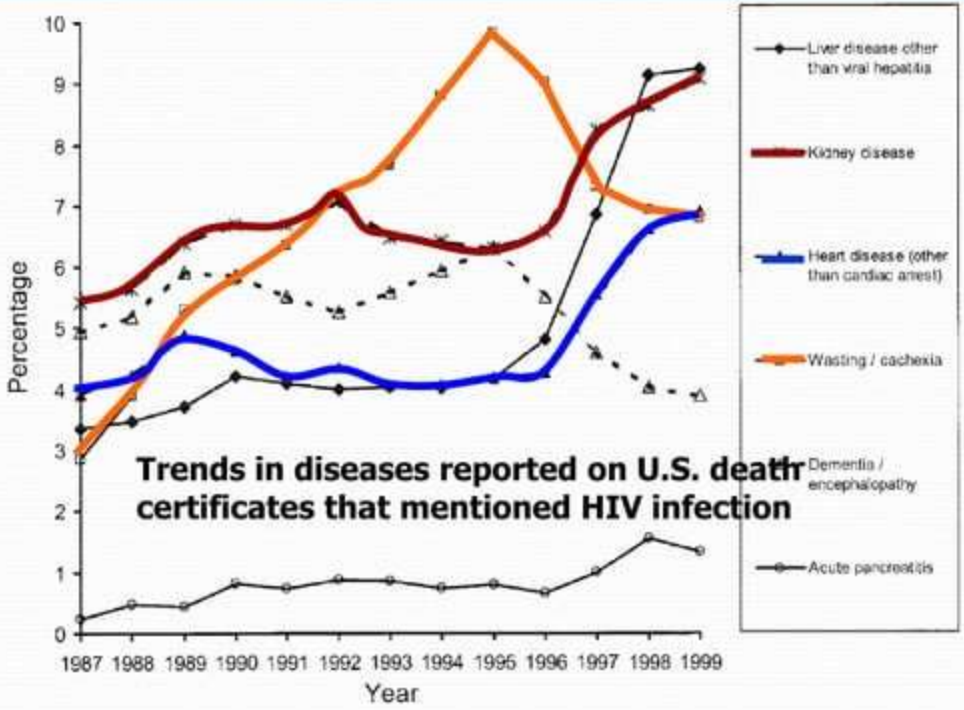
- Association btw HIV and renal disease was first reported in 1984 in New York City and Miami.
- Reported series of HIV-sero+ve patient who developed a renal syndrome characterized by progressive renal failure and proteinuria.
- Most common biopsy finding was Focal segmental Glomerulosclerosis(FSGS).

- HIV –associated nephropathy (HIVAN), formerly known as AIDs-associated nephropathy , is characterised by the following findings
- 1. Nephrotic range proteinuria
- 2. Azotemia
- 3. Normal to large kidney on ultrasonographic images
- 4. Normal pressure
- 5. Focal segmental glomerulosclerosis(FSGS) on biopsy findings

Epidemiology

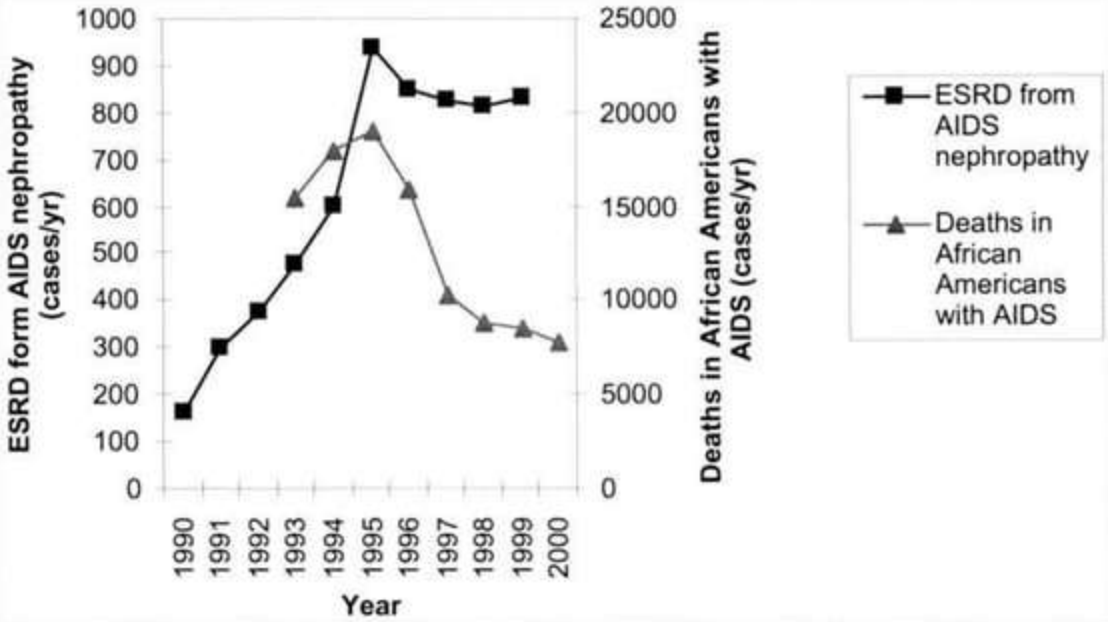
- Incidence of end-stage renal disease(ESRD) due to HIVAN has increased more rapidly than any other etiology of renal disease.
- In 1999, HIVAN became the 3rd leading cause of ESRD in Africa Americans aged 20-64
- Since introduction of HAART, the incidence of ESRD due to HIVAN has decreased.

Kidney Disease is on the Rise in HIV Patients in the United States



Selik, JAIDS. 2002 Apr 1;29(4):378-87.

2001 USRDS annual report



Racial Predilection of HIVAN

- The marked racial predilection of HIVAN for blacks and Hispanic patients has been reported previously.
- The marked racial disparity in HIVAN suggests genetic factors are important determinant of HIVAN pathogenesis(*Hailemariam et al*)
- Nearly 25% of patients with HIVAN have 1st degree or 2nd degree family member with ESRD, and black patient with HIVAN are 5.4times more likely to have a 1st degree or 2nd degree relative with ESRD than are black patients without renal disease.

- The Duffy antigen/receptor for chemokines(DARC) has been proposed as a candidate gene involved in HIVAN pathogenesis.
- The DARC promoter has a high prevalence of polymorphisms in black patients
- *Liu et al* have demonstrated increased DARC expression in renal specimens from children with HIVAN and haemolytic uremic syndrome.

Pathogenesis OF HIVAN

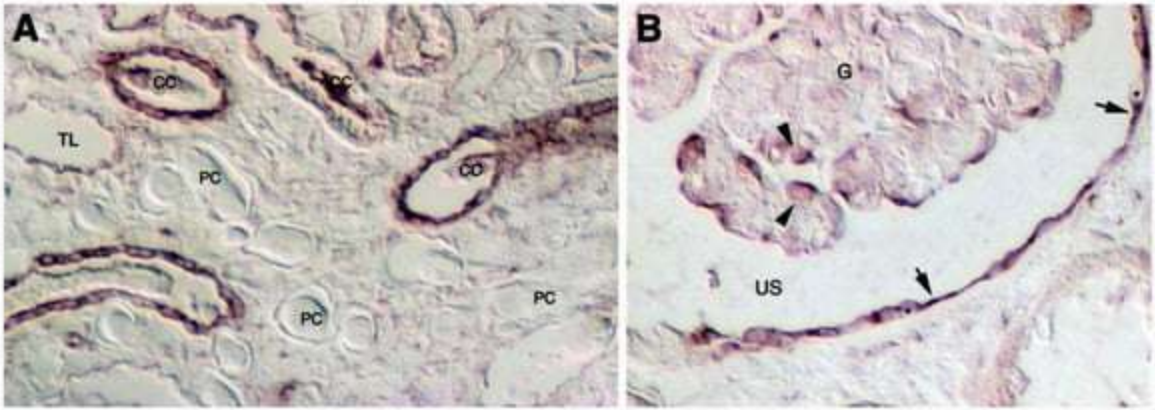
- ***Role of HIV infection of Renal Epithelial Cells***

Until recently, it was unknown whether HIV infection of renal parenchymal cell caused HIVAN directly or Whether HIVAN was an indirect renal response to HIV-induced immune dysregulation.

Studies using an HIV transgenic mouse model of HIVAN have provided important insight into HIVAN pathogenesis.

- HIV-transgene is expressed in renal glomerular and tubular epithelial cells that transgene expression in renal epithelial cells was required for development of the HIVAN phenotype.
- Further support for a role of direct infection of renal parenchymal cells in HIVAN was provided by a macque model of HIV-induced renal disease(*stephen et al)*

In situ hybridization for HIV-mRNA in HIVAN.



- The mechanism by which HIV gain entry into renal epithelial cells is *unknown*. CD_4, receptor for HIV and CCR_5 and $CXCR_4$, the major co-receptors for HIV are not expressed in most renal epithelial cells.

The kidney as a Reservior for HIV

- Infection of renal epithelial cells by HIV has important implication for HIV seropositive patient not only because it contributes to renal disease but also the kidney may be an important reservoir for HIV.
- *Bruggeman et al* detected HIV detected HIV by both RNA *in situ* hybridization and DNA *in situ* PCR in three patients who had undetectable viral load in peripheral blood samples.

- *Winston et al* reported despite an undetectable viral load in the peripheral blood while on HAART, the patients continued to express HIV in renal epithelial cells as determined by RNA in situ hybridization.

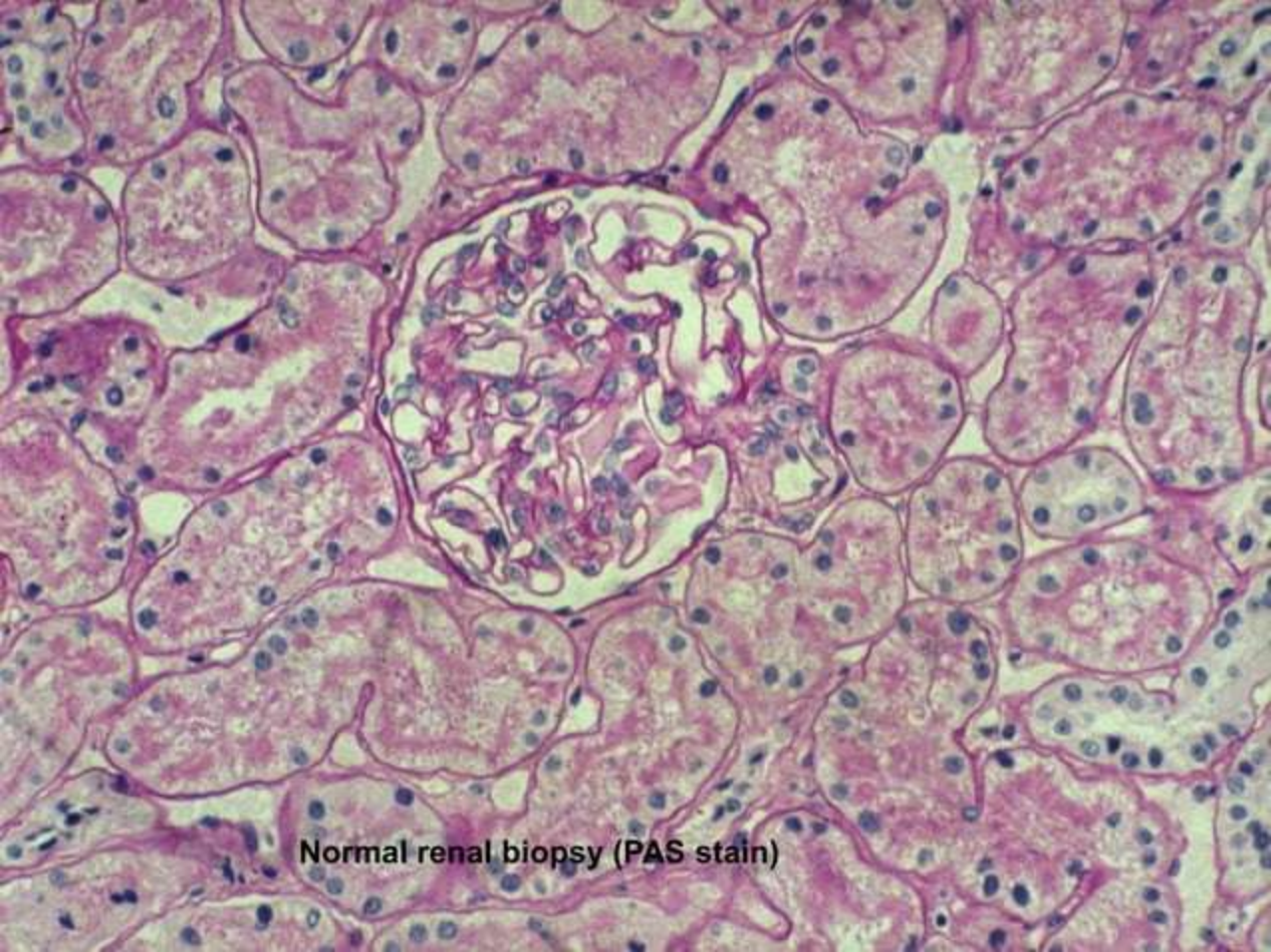
- Thus , even in the face of an optimal virologic response to antiretroviral therapy and clinical remission of HIVAN.
- HIV infection persisted in the renal epithelium and the virus remained transciptionally active at a low level

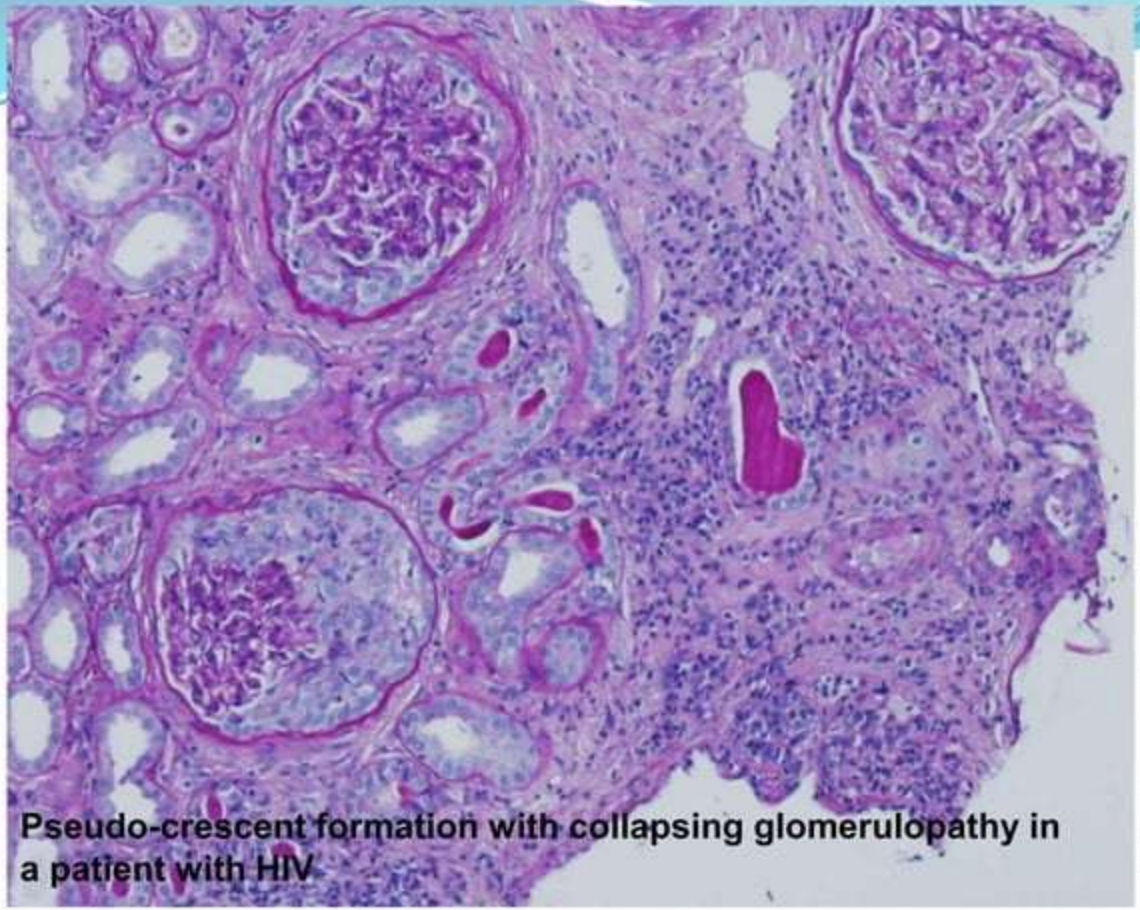
HISTOPATHOLOGICAL ASPECTS

Patterns of glomerular and tubulo-interstitial disease in HIV positive patients

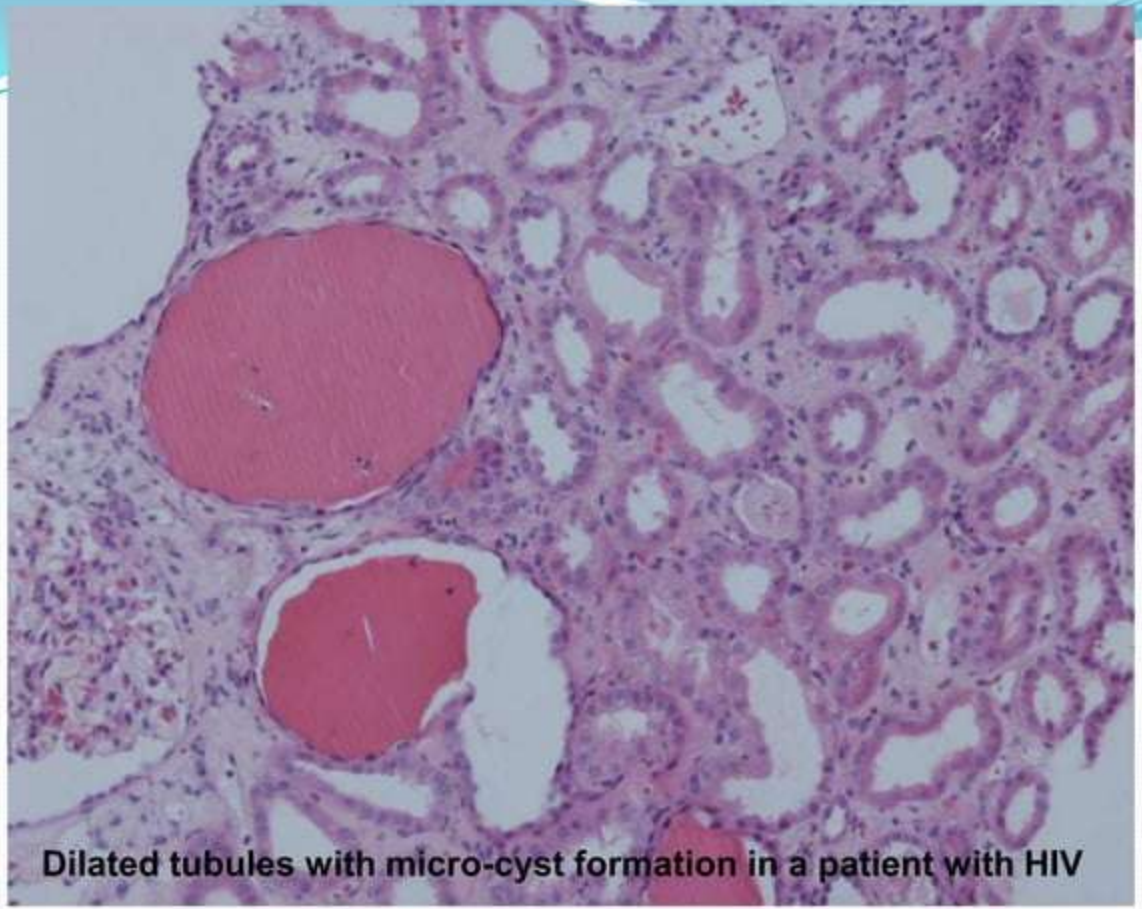
Focal segmental glomerulosclerosis	88	Interstitial nephritis	5
		Drug induced	2
		Idiopathic	3
Membrano-proliferative GN	13		
		Acute tubular necrosis	3
Minimal change disease	6	Malignant lymphoma	1
Membranous glomerulopathy	5		
Lupus-like nephritis	4		
Amyloidosis	4		
Acute post-infectious GN	2		
Focal segmental necrotising GN	1		
Haemolytic uraemic syndrome	1		
IgA nephropathy	1		
Immunotactoid glomerulopathy	1		
End-stage kidney	1		

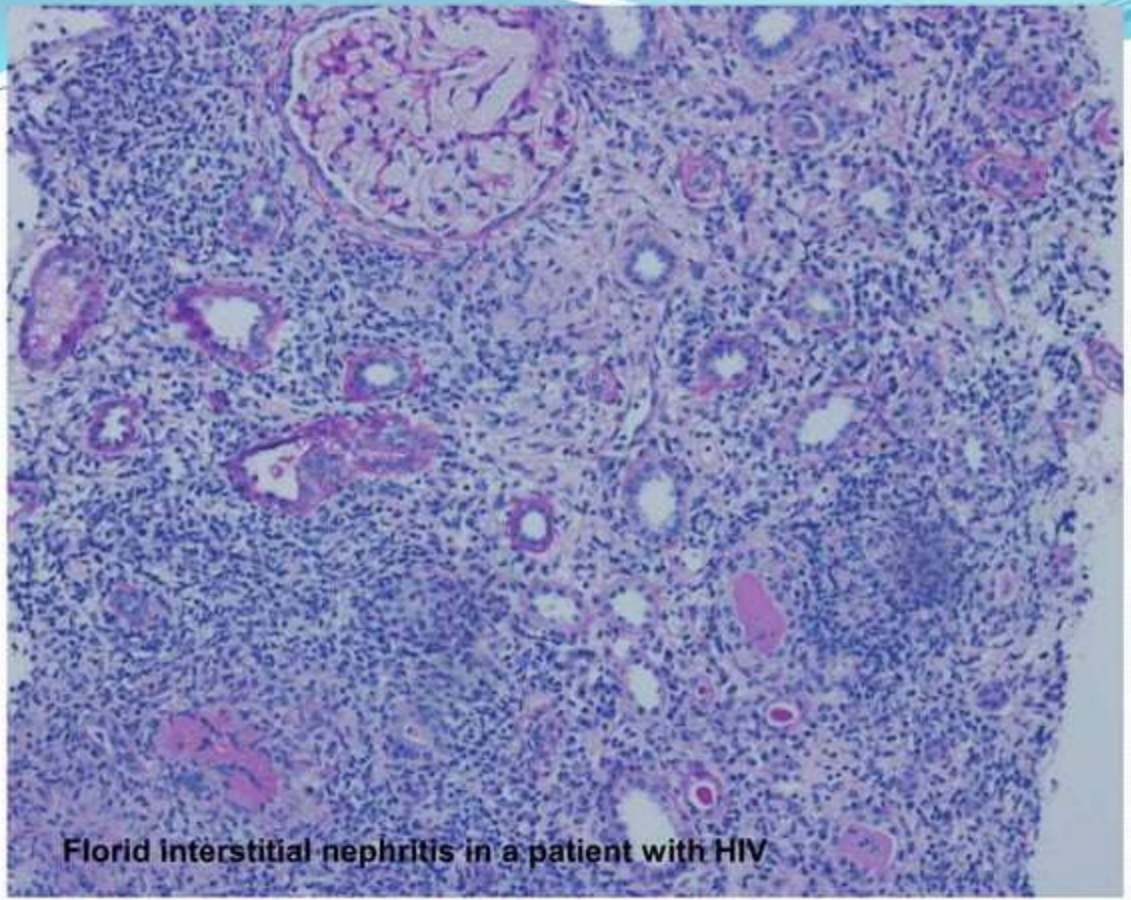
D'Agati & Appel 1998

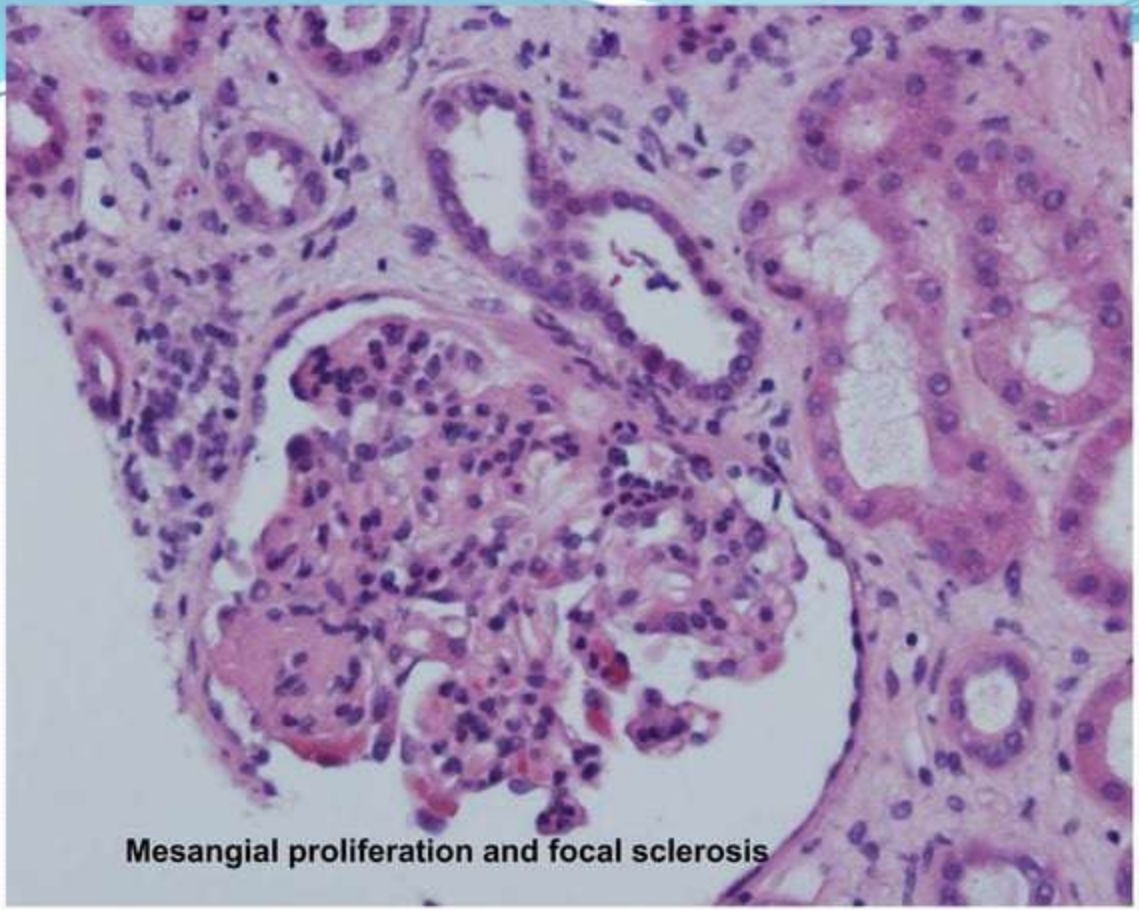

Normal renal biopsy (PAS stain)



Pseudo-crescent formation with collapsing glomerulopathy in a patient with HIV


Dilated tubules with micro-cyst formation in a patient with HIV


Florid interstitial nephritis in a patient with HIV

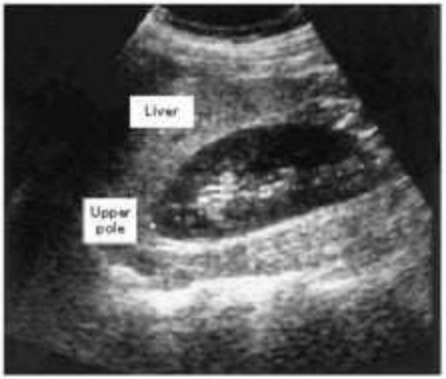

Mesangial proliferation and focal sclerosis

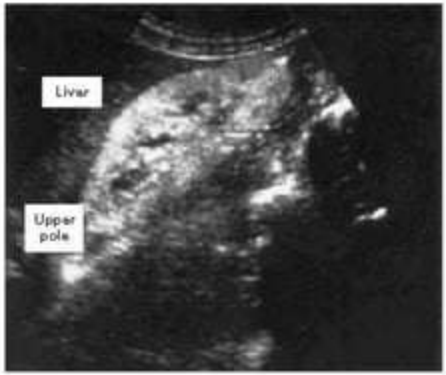
- One of the pathologic hallmark of HIVAN is focal Glomerulosclerosis, often of the collapsing type.
- The collapsing lesions are associated with vigorous podocyte proliferation and loss of podocyte differentiationmarkers, including synaptopodin, podocalyxin.

HIVAN: *Investigations*

- Nephrotic range proteinuria is usually present
- Serum complement levels normal
- CD4 counts variable, from normal to low
- Presence of HIV antibodies

- Renal ultrasound - usually shows echogenic kidneys with preserved or enlarged size of more than 12 cm in spite of severe renal insufficiency





Treatment

- The following discussion will focus on the best available evidence concerning the efficacy of:-
- 1. HAART
- 2.ACE-inhibitors
- 3. Steroids in treatment of HIVAN

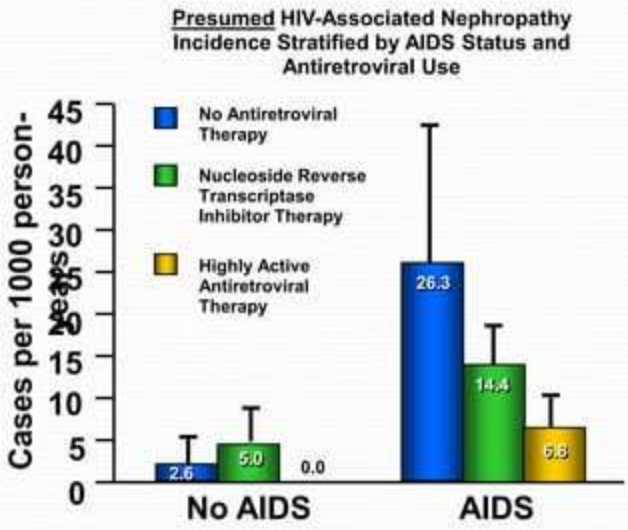
HIVAN: *Possible mechanisms of benefit of HAART*

- Suppression of viral replication felt to be a key factor
- ?viral proteins/cytokines released during active viral replication directly cytopathic to kidneys
  - Recent evidence (Foster, 2004) suggests 'non-viral' actions of HAART may be equally important
  - Protease inhibitors shown to inhibit reactive O_2 species (ROS) generation and ROS-linked apoptosis of murine mesangial cells independent of HIV gene expression
  - This anti-apoptotic non-virologic effect of protease inhibitors may be important in humans

HAART and HIVAN Incidence

12-Year Cohort Study

- Risk of HIVAN low in patients without AIDS
- **NO HIVAN when HAART used without AIDS occurrence**
- Lower HIVAN associated with NRTI and HAART use compared with no ART in patients with AIDS ($p < 0.001$ for trend)



Numbers in bars represent point estimates for HIV-associated nephropathy incidence in cases per 1000 person-years. Brackets above bars represent upper limits of 95% confidence intervals.

Lucas GM, et al. *AIDS*. 2004;20:18(3):541-546.

ACE-inhibitors

- The effect of ACE inhibitors on HIVAN progression has also been studied.
- *Kimmel et al* reported an increase in renal survival associated with captopril usage in a retrospective case-control study of 18 patients with biopsy proven HIVAN
- *Burns et al* offered 10mg/d fosiniopril after 12-24wk, renal function remained stable.

Steriods

- Prednisone has been found in several studies to be associated with reduced risk of progressive renal failure with HIVAN
- The only study in the HAART era evaluating the efficacy of prednisone in patients with HIVAN was recently published by *Szczech et al.*
- After multivariate analysis of several clinical variable , the association between prednisone and reduced rate of decline in Creatinine clearance remained highly significant

Differential Diagnosis of ARF in HIV

- HIV Related
  - HIVAN
  - Thrombotic Microangiopathy
  - Membranoproliferative GN
  - Immune Complex GN (MPGN or Lupus Like)
  - Medication
    - Indinavir, Tenofovir, Sulfadiazine, Pentamidine, Sulfamethoxazole and trimethoprim
- Other
  - **Usual causes** in general population – pre-renal, etc
  - AIN – multiple medication exposures
  - Hepatitis B and C related disease
  - Rhabdomyolysis – statins and PI's

Prognosis

- The data regarding prognosis for renal and patient survival after diagnosis of HIVAN are biased by the fact the majority of patients are referred to nephrologist late in the course of their renal disease and HIV infection.
- Patients with HIVAN who are not treated with HAART, ACE-inhibitors, or prednisone, generally have a poor prognosis with a mean time to progression to ESRD of 1 to 3 months.

- Clinical variables associated with progression of renal failure including:
- 1. Elevated serum Creatinine
- 2. Low CD4 count
- 3. High HIV viral load
- 4. Higher Level of proteinuria
- 5. Previous antiretroviral therapy

Conclusion

- HIVAN was 1st described 26years ago, its important cause of renal failure among black patients.
- Since introduction of HAART, the incidence ESRD has decreased.
- Although data are lacking, the prevalence of HIVAN is probably highest in Africa, where it will likely emerge as a major cause of morbidity and mortality as the prognosis of AIDS survival improves.
- HIV infection of renal epithelial cells components of HIVAN pathogenesis.

- Renal epithelial cells are a newly identified viral reservoir and a separate replicating compartments distinct from blood.
- Viral genes are necessary for causing renal disease.

Questions?