HIV ASSOCIATED NEPHROPATHIES (HIVAN): 30 YEARS LATER

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Worldwide 33.2 million people are estimated to be living with HIV/AIDS infection.
Kidney disease in HIV-positive children.

Renal complication 40%

- 10-15% HIV-AN
HIV-associated nephropathy: HIVAN

- Diagnosed first in HIV-infected adults patients in New York (Rao) and Miami (Pardo) in 1984.

- African Americans, nephrotic syndrome and rapid progression to ESRD.

- Renal histology: FSGS and renal enlargement with tubular microcystic changes.

- Drug abuse, late stage of AIDS/HIV-infection.
HIVAN: CLASSIC FEATURES

- HIV infection, Black race
- Proteinuria
- Progressive Renal Insufficiency
- Large, echogenic kidneys
- Extensive glomerular capillary collapse
- Focal and Segmental Sclerotic
- Severe tubulo-interstitial injury
- Dilated tubules with large cysts
- Frequent Tubulo Reticular Inclusions

- First complete description of the pathogenic role of HIV infection in the associated nephropathy in children.

- Confirmation that HIV-1 infection per se can induce a new type of renal disease.

- Description of an “Spectrum” of various histopathologic lesions
HIV Nephropathy in Infants and Children

Clinical Complications/Outcome

- Total Patients: 84
- Nephrotic: 56%
- Renal Failure: 19%
- Dialysis: 6%
- Death: 50%

Legend:
- HIV(+)
- AIDS
HIVAN: Spectrum of Diseases

- Proteinuria / nephrotic syndrome
- Fluid / electrolyte abnormalities
- Renal tubular acidosis
- Acute or Chronic renal insufficiency
- Hematuria
- UTI
HIVAN: Spectrum of Diseases

- Autoimmune/vasculitis (Lupus-Like)
- Takayasu’s Arteritis
- Interstitial nephritis
- Infiltrative diseases
- Nephrocalcinosis / Stone disease
- Hemolytic Uremic Syndrome
- Drug toxicity
**RENAL INSUFFICIENCY IN HIV**

- Acute renal failure is uncommon. No hemodynamic instability or risk factors.
- Intravascular volume depletion and nephrotoxic agents due to:

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KIDNEY BIOPSY: WHEN?

- Unexplained kidney disease in children with HIV
- Heavy proteinuria
- Decreased kidney function
- Acute renal failure (HIV vs HAART)
Renal Histopathology

• Findings suggestive of HIVAN:
  1. Tendency to collapse and sclerosis of the entire glomerular tuft.
  2. Severe tubular injury with proliferative microcyst formation and tubular degeneration.
  3. Tubuloreticular structures in the glomerular endothelial cells on EM.
“HIVAN”: SPECTRUM OF PATHOLOGIES

- Focal Segmental/Global Sclerosis
- Collapsing Glomerulonephritis
- Mesangial GN
- Minimal Change
- MPGN
- Necrotizing ICGN (Lupus-Like)
- HUS/TTP
- IgA Nephropathy
- TIN (Drug induced, Infectious)
What are the basis that HIV-1 is involved in the pathogenesis?

• HIVN in children with vertical transmission

• HIV-1 transgenic model in mice carrying a defective HIV-1 provirus develop HIVN in absence of immunosupression and viral replication

• Improvement of clinical outcomes of children and adults treated with HAART
PROPOSED MECHANISMS OF HIVAN

• Direct injury to renal epithelial cells by cytopathic effect of viral infection
• Indirect injury to the kidney by renal cellular uptake of circulating viral encoded molecules
• Indirect injury to the kidney through release of cytokines by infected lympho/monocytes in circulation or infiltrating the kidney
• Nature of host response (HLA-linked) to HIV-1 infection
• Abnormal pattern of gene expression of renal cells due to cytokines and growth factors
Proteinuria in paediatric patients with human immunodeficiency virus infection

Vania Giacomet, Paola Erba, Francesca Di Nello, Sonia Coletto, Alessandra Viganò, GianVincenzo Zuccotti
HIVAN: Current Status

• Significant reduction in mortality and risk of progression to AIDS with HAART
• Renal complications of long-standing HIV infection and therapy have become increasingly important
• CKD has become a frequent complication
• Renal risks secondary to HAART may be minimized by identification of children affected with HIVAN

**Objectives:** To determine the prevalence of proteinuria in HIV-infected children and their outcome during treatment with HAART.

- **Conclusions:** Control of viral load with HAART appears to prevent the progression of HIV associated renal disease and improve survival rates in HIV-infected children.
Results

• medical records of 315 HIV-1 infected children followed between 1998-2003 were reviewed for this study.
• 286 met eligibility criteria for this study
  282 (98.6%) acquired HIV-1 via vertical transmission
  3 (1%) acquired the infection via sexual transmission
  1 patient through blood transfusion
• Age ranged from 0.19 to 22 years, median 9.8 y, mean of 9.6
• Mean number of U P/Cr per patient was 2.77.
• Overall mortality at the time of study analysis was 3.8% and 10 of the 11 deaths occurred in children who had CDC category C3 disease.

Of 286 patients,
46 (16.1%) patients had persistent proteinuria alone (PP)
39 patients (13.6%) had HIVN
Figure 2. HIV viral load and proteinuria. A, At baseline, increasing viral load correlated positively to increasing proteinuria ($r = 0.5; P < .01; n = 286$). B, At follow-up, after an average of 5.6 ± 0.1 years of HAART, this association persisted ($r = 0.5; P < .0001; n = 241$).
Clinical outcomes for the 39 patients with HIVN

- 15 had renal insufficiency (38.5%)
- 8 patients had nephrotic syndrome (20.5%)
- 3 patients were receiving dialysis (7.7%)
- 6 patients had died (15.3%)
  - 3 of them were on hemodialysis (HD) and died of complications of ESRD
Figure 3. Kaplan-Meier survival curves. Comparison of group survival with Kaplan-Meier method showed that survival rates decreased significantly as severity of groups’ proteinuria increased (log-rank test for trend; \( P < .001 \)). Median survival was 19.5 years for the nephrotic range proteinuria (NeP) group compared with other 2 groups, which both had survival estimates greater than 50% at end of study period.
Renal Effects of HAART

- Zidovudine: None
- Didanosine: Fanconi Syndrome, AKI, Lactic Acidosis, Nephrogenic DI (NDI)
- Lamivudine: RTA, Hypophosphatemia
- Tenofovir: Fanconi Syndrome, NDI, AKI
- Indinavir: AKI, TIN, Crystalluria, Urolithiasis, Papillary Necrosis, Hypertension
- Ritonavir: AKI
Recommendations when using HAART

- Screen for underlying kidney disease
- Proper selection and dose adjustment in cases with existing kidney disease
- Monitor renal function closely (serum P, Ca, Mg, Lactic acid)
- Avoid use of CCCB and B-blockers for HTN (interactions with HAART)
- Avoid Tenovir + ddi or Statins, Acyclovir combinations
HIVAN THERAPY

- Anti-retroviral therapy (HAART)
- Proteinuria: ACE-inhibitors/ARB
- Steroids ?
- Other immunosuppressors? CsA, MMF?
- Correct electrolyte, fluid, acid/base abnormalities, nutritional support
- Pathology-specific therapy (???)
- ESRD : dialysis transplantation?
Dialysis Experience in HIVAN

- Review of 20 year experience (1983-2003) with dialysis in HIV and ESRD at Holtz Children’s Hospital in Miami
- 20 patients; Mean Age: 10 years (range 1-18)
- 14 Vertical transmission, 3 Sexual, 3 Acquired HIV without HIVAN
- Patient Treatment Months: 505
Dialysis Experience in HIVAN

• Long-term survival of pediatric HIVAN in dialysis is possible
• Peritoneal dialysis remains a poor option due to significant infectious complications
SELECTION CRITERIA FOR KIDNEY TRANSPLANT

• CD4 Count >200 /ml
• Stable anti-retroviral therapy
• Viral load <50 copies or undetectable
• No opportunistic infections
• No advanced cardio-pulmonary involvement
• No Hx of Neoplasms
Renal Transplantation in HIV

- Kidney TX is both SAFE and EFFECTIVE
- Graft survival at 3 and 5 years are similar than in non-HIV recipients
- Rejection rates are higher but respond to RX
- Several interactions between HAART and immunosuppressants exist and should be carefully monitored
- Many immunosuppressants have anti-retroviral effects (selective inhibition of infected cell growth)
1. In children without evidence of existing renal disease, screening evaluation for the development of HIVAN should include complete urinalysis (proteinuria) and testing to determine serum electrolyte levels, blood urea nitrogen levels, and creatinine levels (estimated creatinine clearance or GFR) every 6 months.
2. Pediatric HIVAN and other proteinuric nephropathies in HIV-infected children should be treated with HAART; the addition of ACE-inhibition or ARB should also be considered for patients with more-severe proteinuria (grade 1+ by urine dipstick analysis or a protein-to-creatinine ratio 0.2 g/g for 3 separate specimens). Steroid use is not recommended for this population.
Future Studies

- Urine biomarker profile to detect children with early HIVAN
- A single urine marker may not be sufficient
- A battery of tests should be sought
- This approach may avoid need for kidney biopsy
IN SUMMARY,

• Screening, early diagnosis and early therapy for kidney disease is recommended for ALL patients with HIV

• Spectrum of kidney diseases include AKI, electrolyte-acid base disturbances, HIV Associated Glomerular diseases, Acute on chronic kidney disease and adverse effects of HAART

• Prevalence of CKD in children with HIVAN is related to viral load and black race

• Development of novel urinary biomarkers are needed to detect early kidney disease
SAVE THE DATE!

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