Renal Manifestations of HIV
& the implications of HAART

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Renal Manifestations of HIV

• Acute Kidney Injury
  – AKI in relation to medication
• Fluid & Electrolyte disorders
  – D/O of osmolality
  – Potassium disorders
  – Acid-Base disorders
• Chronic Kidney Disease
• HIV-associated Nephropathy
  – HIVAN vs. HIVIC vs. TTP
• End Stage Renal Disease
  – RRT
Acute Kidney Injury

• HIV specific risk factors: oHAART, AIDS-defining illnesses, low CD4, high VL, co-infection HBV/HCV.

• Causes:  - Prerenal (39%)
  - ATN (37%)
  - Crystalluria with obstruction (5%)
  - AIN (5%)

• Medication nephrotoxicity

• HIV-assn. TMA
Acute Kidney Injury in HIV infected patient

renal compartment

- **Interstitial**
  - interstitial nephritis
  - Drugs related
    - HIV associated lymphoma infiltration
  - Virus related
    - ATN
    - Mitochondrial toxicity
    - proximal tubular dysfunction

- **Tubular**
  - drug related
    - HIVAN
    - MCD
    - FSGS

- **Glomerular**
  - HIV infection related
  - altered immunity
    - HIVICK
    - can lead to
      - immune reconstitution syndrome
        - auto antibody production
      - IgA neph
      - Membranous GN
      - Cryoglobulinemic GN
      - Anti GBM

- **Vascular**
  - virus or drug related
    - TMA
AKI in relation to medication

• **Acute tubular necrosis (ATN)** -
  Aminoglycosides, Pentamidine, Acyclovir, Foscarnet, Amphoteracin, Adefovir, Cidofovir.
  *Tenofovir (AKI w/wo PCT dysfunction)*

• **Acute interstitial nephritis (AIN)** – NSAIDS, Bactrim, Rifampicin, HAART (Indinavir, ritonavir, abacavir, atazanavir), unidentified.

• **Obstructive (OU)** - Sulfadiazine crystals/stones, Acyclovir, Indinavir, Atazanavir.

• Interfere with **tubular secretion of creatinine**.
Nucleotide RTI’s

• Drugs enter PCT via OAT1 at basolateral membrane, accumulate in cell.
• Eliminated unchanged in urine by active secretion into PCT.
• Accumulation of drug in PCT cells and express cytotoxicity.
• NSAIDS and probenecid inhibits OAT1
• Adefovir – not registered!
• Cidofovir – CMV infection
• Tenofovir – sole NRTI
**Tenofovir**

- **Adv:** Useful for co-infection (HIV + HBV)
  Once daily dose/treatment adherence
- **Disadv:** Tubular dysfunction (not glomerular)
  Progressive renal failure
  Osteomalacia

- **Risk Factors for tubular dysfunction:**
  TDF Exposure, advancing age.
  Low CD4, diabetes, nephrotoxins, protease inhibitors, low body weight, pre-existing renal disease.
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Tenofovir

• RENAL TUBULAR TOXICITY:
  – RTA Type 2/PCT dysfunction/Fanconi’s Syndrome
  – Incomplete RTA Type 2
  – RTA Type 1/DCT dysfunction (NDI)
  – Background tubular proteinuria
  – Progressive renal dysfunction*

* In a cohort of more than 10000 pts starting TDF treatment, increases in creatinine levels >7mmol/L or >30mmol/L were observed in 2.2% and 0.6% respectively. This suggests that more severe impairment of glomerular function is uncommon. Nelson MR, Katlama C, Montaner JS. *The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years.* AIDS. 2007.
Tenofovir

• Histological Findings:
  Acute PCT damage
  Flattened epithelia
  Interstitial oedema
  Eosinophillic cytoplasmic inclusions formed of Giant/misshape mitochondria
Tenofovir

- Monitoring for Kidney toxicity with TDF:
- Symptoms – severe disabling bone pain

Criteria for screening:
(1) GFR <90ml/min
(2) use of other renally excreted meds (gancyclovir, acyclovir, cidofovir, adefovir)
(3) other comorbidity (DM, HPT)
(4) Ritonavir-boosted protease inhibitor regimen

3 monthly screening of: Tubular protein excretion
FePO4
Glycosuria
eGFR
Measure eGFR pre-treatment
- Reduce dose if eGFR < 60ml/min

Assess risk factors for kidney toxicity:
- Age
- Body weight
- eGFR < 90ml/min
- Other renally excreted drugs

Measure every 3 months for 1 year, then biannually:
1. eGFR
2. fractional excretion of phosphate
3. urine protein/creatinine ratio
4. urine glucose
5. tubular proteinuria (e.g. RBP) if available

- Stop drug if significant and sustained changes in 1-4
- Continue with monitoring if small increase in 5 only
- If in doubt, liaise with a nephrologist
Protease inhibitors

- **Indinavir**: reversible ARF, CRF, leukocyturia, microhaematuria, mild proteinuria, nephrolithiasis, papillary necrosis and crystalluria.

Symptoms may occur within a week. (Dysuria, colic, pain)

Crystallization of indinavir in tubule -> bladder.

Risk factors: upH >6.0, high dose, dehydration, warm temp, co-treatment with Bactrim or acyclovir.

Renal abnormalities reversed after 3 months.
Protease inhibitors

- **Nelfinavir**: RARE!
- **Ritonavir**: ARF, increase sCreat after 3 days, progress to dialysis. Reversible on discontinuing.
- **Saquinavir**: RARE! No renal toxicity.
Nucleoside RTI’s

• Less frequently nephrotoxic.
• 2 types of renal injury:
  – PCT dysfunction similar to Nucleotide RTI’s
  – ARF in Lactic acidosis secondary to nucleoside RTI-related acquired mitochondrial cytopathy.
• Abacavir – Acute interstitial nephritis
HIV-assn. TMA

- TTP is a diffuse thrombotic microangiopathy (TMA) which classically manifests with:
  1. microangiopathic haemolytic anaemia,
  2. thrombocytopenia,
  3. renal dysfunction,
  4. neurological symptoms,
  5. fever.

- Without appropriate treatment, TTP is a fatal, but improves with prompt plasma exchange or plasma infusion.

- TMA and HIV, which was first recognised in 1984, presents with similar PENTAD to non-infected patients.
HIV-assn. TMA

- Prevalence 1.4% in pre-HAART to 7% in hospitalised AIDS patients
- **CHORUS** cohort of 6022 pts only 17 pts with TMA
  - Males. Homosexuals. IV drug abusers
  - Lower CD4, Higher HIV RNA
  - Greater incidence of AIDS, MAC, HCV
  - Greater incidence of death
Laboratory features of HIV-TMA

- Anaemia.
- Thrombocytopenia.
- Presence of fragmented red blood cells or schistocytes.
- Raised serum indirect bilirubin and lactate dehydrogenase.
- Raised serum creatinine.
- Microscopic haematuria and proteinuria.
- Lack of laboratory evidence of coagulopathy.

Differential diagnosis of TMA

- Disseminated intravascular coagulation.
- Severe vasculitis.
- Sepsis (bacterial, viral, fungal, or rickettsial).
- Eclampsia.
- HELLP syndrome.
- Malignant hypertension.
- Catastrophic antiphospholipid syndrome.
Management of HIV-TMA

- Plasmapheresis and/or plasma infusion should be performed promptly.
- Use of corticosteroids should be individualised.
- Splenectomy should be reserved for those patients who are refractory to plasma therapy.
- Antiplatelet agents should be avoided as haemorrhagic diathesis commonly observed in HIV-TMA patients.
- Antiretroviral therapy is an important component of the management.
- Haemodialysis should be considered in patients with severe renal dysfunction.
Fluid & Electrolyte disorders

- Disorders of Osmolality
  - Hyponatraemia
- Potassium disorders
  - Hypokalaemia/Hyperkalaemia
- Tubular dysfunction
- Acid-Base disorders
  - Respiratory Acidosis/Alkalosis
  - NAGMA – GIT losses/RTA
  - HAGMA
Hyponatraemia:
Impaired ability to excrete water due to: - SIADH, Volume depletion, Adrenal insufficiency

Hyperkalaemia:
Due to: - Adrenal insufficiency, hyporeninemic hypoaldosteronism, trimethoprim/pentamidine, impaired renal function.

Lactic Acidosis:
Due to mitochondrial dysfunction (type B).

d4t >> ddi >> AZT

Hyperuricaemia, Hypophosphatemia
Chronic Kidneys Disease

- Risk factors: persistent proteinuria, advanced HIV infection, HCV co-infection, elevated baseline creatinine.
- Causes: HIV-independent (HPT, DN, AKI)
  HIV-dependent (HIVAN, HIVIC, Cryoglobulinaemia/MPGN – HCV/HBV)
HIV-associated Nephropathy

• In South Africa, HIV patients have been prejudiced by presenting late, being denied access to HAART, not being offered tertiary level of care, declined biopsy and dialysis.

• As such, documentation to the true prevalence is lacking.

• In USA, over the past 10yrs, HIV +ve patients developed ESRD and received HD at a rate of >20% per year!
Pathogenesis

• HIV infection of renal tubular cells and podocytes.
• Renal tubular cells in HIVAN constitutes a “viral reservoir” where active replication of HIV in independent of peripheral blood.
• HIV protein “Nef” – induces podocyte change
• Host factors, including genetic susceptibility.
  – MYH9 & APOL1 gene (Chr. 22)
  – Chr. 3
Clinical Manifestations

- Black Race. Male gender.
- Advanced HIV disease, Low CD4 <250.
- Heavy (nephrotic-range) proteinuria
- Mod to severe renal insufficiency at diagnosis
- Rapid decline in renal function to ESRD (<10 months)
- HPT and peripheral oedema are uncommon
- Haematuria
- Bilaterally enlarged echogenic kidneys
HIVAN. Who’s at risk?

- **UNITED STATES**
  - African Americans 12.2 times more likely to develop HIVAN than whites
  - Among those with ESRD secondary to HIV/AIDS: 88.4% were African American

- **EUROPE**
  - France 97/102 with HIVAN were black (95%)
  - London 17/17 with HIVAN were black (100%)

- **SOUTH AFRICA**
  - Cape Town 174/192 with HIVAN were black (89.6%) - 2012
• The only cause of ESRD more associated with African descent is

SICKLE CELL ANAEMIA
Clinical Manifestations

More common in:

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Histologic lesions of the HIV

• HIVAN (Collapsing focal segmental glomerulosclerosis)
LM - Collapsing FSGS
Microcystic tubular dilatation
Tubulo-Interstitial inflammation/scarring/atrophy

IF - +ve for Albumin & IgG in epithelial cells and for IgM, C3, & IgA in mesangial or sclerotic areas
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EM - wrinkling of the GBM, epithelial cell proliferation, & focal FP effacement.
Tubuloreticular structures in glomerular endothelial cells
Histologic lesions of the HIV

• HIVAN (Collapsing focal segmental glomerulosclerosis) 60%
• Membranoproliferative GN
• Minimal Change GN
• Membranous GN
• Amyloidosis
• Immune complex GN
• IgA Nephropathy 40%
Clinical Course & Treatment
Clinical Course & Treatment

Rate of Progression of Renal disease

• With the advent of HAART, the interval from diagnosis of disease to progression to ESRD has increased to 16.6 months.

• Dependent on degree of renal dysfunction, CD4 and HIV RNA level at diagnosis.

• Earlier diagnosis, general care & access, compliance and HAART has trended towards a slower rate of progression.
Clinical Course & Treatment

• Inhibitors of RAAS – ACEI +/- ARB
  – Proteinuria <1000mg/day
  – BP <130/80mmHg
• Glucocorticoids
• HAART
The Benefits of HAART

• Pre-HAART era, ACE inhibitors and prednisone rendered poor results. Progression to ESRD within 2 – 4 months of diagnosis.
• ARV’s were considered to DELAY not prevent ESRD.
• AZT. Protease inhibitors. HAART.
• Wali et al & Kirchner et al. (case studies)
• Szczech et al. (PI + prednisone in 19pts)
• Burckle et al. (improved renal survival by HAART)
• Prospective trial would be *ethically indefensible*.
• Role of HAART in non-HIVAN disease is uncertain.
Clinical Course & Treatment

• Inhibitors of RAAS – ACEI +/- ARB
  – Proteinuria <1000mg/day
  – BP <130/80mmHg

• Glucocorticoids

• HAART

• Routine CKD care

• Prognosis – POOR! Delay progression!!!

• Dialysis & transplantation
End Stage Renal Disease in HIV

- Renal Replacement Therapy
  - Haemodialysis (HD)
  - Continuous Ambulatory Peritoneal Dialysis (CAPD)
  - Transplantation
    - HIV –ve to HIV +ve
    - HIV +ve to HIV +ve
• HIV & Dialysis:
  - Dialysis isolation
  - Patient-to-patient transmission
  - Needlestick transmission
  - Viral levels in ultrafiltrate

• Dialysis modality:
  - Haemodialysis access, infections & complications
  - Dialyzer reuse
  - Peritonitis

• Anaemia
Renal transplantation:

- Safe and effective in HIV +ve patients.
- Acute rejection rates are increased, but respond to therapy.
- Drug interactions between HAART & immunosuppressants. (Cyto. P450 & P-gp 1 flux)
- Drugs: IL$_2$ receptor antagonist
  - MMF virostatic
  - CNI inhibit infected cell growth
  - Sirolimus decreases expression of CCR5
- Managing co-infection with HCV/HBV and HIV is challenging, as progressive rates of liver disease are increased.
- Multidisciplinary team approach is essential.
Evaluation of renal status

- Presence of proteinuria indicates glomerular disease.
- Urinalysis at every opportunity.
- 24hr protein quantification/PCR/ACR
- Serology – HCV, HBV, Syphilis.
- CD4, HIV RNA
- Renal Biopsy
Evaluation of renal status

• Renal Biopsy:
  - Nephrotic range proteinuria
  - Rapid decline in renal function
  - Positive serology for another disease
  - Active urinary sediment
  - Pt not fitting the appropriate phenotype.

Ultimately if the biopsy will contribute to a change in clinical therapy, it should be done!!!
The South African Experiences

- A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa.

- HIV-related nephropathy: a South African perspective

- The acute, the chronic and the news of HIV-related renal disease in Africa.

- Renal transplantation between HIV-positive donors and recipients.

- The spectrum of renal histologies seen in HIV with outcomes, prognostic indicators and clinical correlations.
  Werne N, Swanepoel CR, Boulle A. NDT 2012
HIV assn. Immune complex disease (HIVICK)

- 40% alternative diagnosis to HIVAN
- MGN, MPGN, Mesangial proliferative, Lupus-like. (IgAN)
- Characteristic “ball in cup” basement membrane reaction first described in a South African biopsy series.
HIV-assn. Immune complex disease (HIVICK)

- 40% alternative diagnosis to HIVAN
- MGN, MPGN, Mesangial proliferative, Lupus-like. (IgAN)
- Characteristic “ball in cup” basement membrane reaction first described in a South African biopsy series.
- Pt less likely to be black. Role of HAART in slowing progression is uncertain.
Co-existing diseases

- Hepatitis B
- Hepatitis C
- Syphilis
- Tuberculosis
Take home message:

1. The renal manifestations of HIV are diverse incorporating acute to chronic disease. Drug therapy may also be the culprit.

2. Not all kidney disease in HIV +ve patients is HIVAN.

3. Take the opportunity to screen the patient at every visit. Prevention is better that cure!!!

4. A renal biopsy should be considered in patients where the diagnosis in in doubt or if clinical therapy will be changed.

5. RRT is becoming a viable option in patients with controlled HIV infection and end stage renal disease.
Up to 30% of people living with HIV have abnormal kidney function. Untreated kidney problems can be fatal.
HIV can damage your kidneys; but this is extremely uncommon in people living with HIV who have a suppressed viral load.
The side effects of HIV medication can cause kidney disease. Work closely with healthcare providers to ensure your kidney’s health.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Reported nephrotoxicity</th>
<th>Risk factor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Crystal nephropathy</td>
<td>Infusion, volume depletion</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Tubular toxicity</td>
<td>CKD</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>ARF</td>
<td>CKD, critical illness</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>ARF, tubular toxicity</td>
<td>CKD, critical illness, prolonged illness</td>
</tr>
<tr>
<td>β-Lactams</td>
<td>Interstitial nephritis</td>
<td>β-Lactam allergy</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>ARF, tubular toxicity</td>
<td>CKD</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>ARF, tubular toxicity</td>
<td>CKD</td>
</tr>
<tr>
<td>Gancyclovir</td>
<td>ARF (rare)</td>
<td></td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Hyperkalemia, ARF</td>
<td>CKD</td>
</tr>
<tr>
<td>Sulfonamide</td>
<td>Interstitial nephritis, crystal nephropathy</td>
<td>Sulfa allergy</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Hyperkalemia, increased creatinine level</td>
<td>CKD, volume depletion</td>
</tr>
</tbody>
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**NOTE.** Adapted from Berns and Kasbekar [27]. ARF, acute renal failure; CKD, chronic kidney disease.
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<tr>
<td>Abacavir</td>
<td>Acute renal failure, interstitial nephritis (rare)</td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Case reports of nephrolithiasis, interstitial nephritis, reversible renal failure</td>
<td>Not established</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Tubular dysfunction (rare)</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Single report of hypersensitivity reaction</td>
<td></td>
</tr>
<tr>
<td>Enfvirtide</td>
<td>Single report of glomerulonephritis</td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>Nephrolithiasis, crystalluria, dysuria, papillary necrosis, acute renal failure</td>
<td>Concomitant treatment with low-dose ritonavir; for nephrolithiasis, urine pH $&gt;6$, low lean body mass, treatment with trimethoprim-sulfamethoxazole or acyclovir, chronic infection with hepatitis B or hepatitis C virus, warm environmental temperature, high indinavir concentration</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Tubular dysfunction (rare)</td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Reversible renal failure, but nephrotoxicity not definitely established</td>
<td>Concomitant treatment with nephrotoxic drugs, underlying renal pathology</td>
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<tr>
<td>Stavudine</td>
<td>Tubular dysfunction (rare)</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Tubular toxicity, Fanconi syndrome (rare), decreased glomerular filtration rate</td>
<td>Low body weight, impaired baseline renal function, concomitant treatment with potentially nephrotoxic drugs</td>
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