OVERVIEW OF HIV NEPHROPATHY

Emeritus Assoc Prof CR Swanepoel
University of Cape Town.
Disclosure of Interests

Consultancy and honoraria

- Company Roche
- Company Abbott
- Company Amgen

Medical Adviser for Fresenius Medical Care (South Africa).
Chimpanzees hunt and eat other primates.

Natural range of chimpanzee subspecies and location of SIVcpz isolation (adapted from reference 75).

According to UNAIDS – at the end of 2015.....

36.7 MILLION people worldwide are currently living with HIV/AIDS.

1.8 MILLION CHILDREN worldwide are living with HIV. Most of these children were infected by their HIV-positive mothers during pregnancy, childbirth or breastfeeding.

The vast majority of people living with HIV are in low- to middle-income countries, particularly in Sub-Saharan Africa.
People living with HIV in Western/Central Europe and North America, 2013

- United States of America: 56%
- France: 8%
- Spain: 6%
- United Kingdom: 5%
- Italy: 5%
- Canada: 4%
- Germany: 4%
- Portugal: 4%
- Poland: 4%
- Netherlands: 4%
- Rest of the region: 1%

Source: UNAIDS estimates, 2013
8 Countries Accounted for 57% of New HIV Infections in 2013

% of new HIV infections in 2013, by country

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<tr>
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<tbody>
<tr>
<td>South Africa</td>
<td>2,900,000</td>
<td>2,100,000</td>
<td>35,000,000</td>
<td>32,100,000</td>
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<tr>
<td>Nigeria</td>
<td></td>
<td></td>
<td>10%</td>
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<tr>
<td>Uganda</td>
<td></td>
<td></td>
<td>7%</td>
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<tr>
<td>India</td>
<td></td>
<td></td>
<td>6%</td>
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<tr>
<td>Mozambique</td>
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<td>5%</td>
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<tr>
<td>Kenya</td>
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<td>5%</td>
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<tr>
<td>Indonesia</td>
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<td></td>
<td>4%</td>
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<tr>
<td>Russia</td>
<td></td>
<td></td>
<td>4%</td>
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<tr>
<td>Rest of the World</td>
<td></td>
<td></td>
<td>43%</td>
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</tbody>
</table>

Source: UNAIDS
South Africa (2015)

7 million people living with HIV
19.2% adult HIV prevalence
380,000 new HIV infections
180,000 AIDS-related deaths
48% adults on antiretroviral treatment

HIV-associated nephropathy (HIVAN) is ranked as the third leading cause of ESRD among blacks aged 20 – 64 years in the USA, lagging behind diabetes and hypertension.

Very few studies on prevalence of HIV nephropathy from Africa. Prevalence low at approx 5%
How does one make the diagnosis?

Clinical impression, blood tests and ........

RENAL HISTOLOGY
HIV-associated renal disease – an overview

Nicola Wearne and Ikechi G. Okpechi

Division of Nephrology and Hypertension, University of Cape Town, Cape Town, South Africa
Figure 2. The biological pathways altered by HIV infection of renal epithelial cells, leading to progressive renal failure (adapted from Leventhal et al. [35] and Bruggeman et al. [36]).
Figure 2. The biological pathways altered by HIV infection of renal epithelial cells, leading to progressive renal failure (adapted from Leventhal et al. [35] and Bruggeman et al. [36]).
1st there was ..... MYH9

- **2008**: Identified a strong association of the gene **MYH9** (nonmuscle myosin heavy chain IIA - located on chromosome 22), with idiopathic and HIV-associated FSGS in African-Americans²

However some issues remained unsettled:

1/3 of African American Controls in the FSGS Genetic study were homozygous for MYH9

The majority of HIV-infected patients who are genetically at risk from MYH9 do not appear to develop severe kidney disease

Next came **APOL1**

- A **stronger association** with polymorphisms in the **APOL1 gene** were identified (encodes apolipoprotein L1)$^{3,4}$

**G1,G2** variants of **APOL1 gene** were strongly associated with the risk of **FSGS** as well as:

- **Only present among Africans** in the 1,000 Genomes project

- **Conclusions**: Kidney disease was explained by the presence of the **MYH9** risk haplotypes containing one of the **APOL1** risk alleles


The G1 and G2 genetic variants of the **APOL1** gene

**commonly found in individuals of recent African ancestry**

have also been associated with poor kidney outcomes for those with different kidney conditions from lupus to general CKD.
Growing evidence now indicates that both genes may independently contribute to kidney disease susceptibility.

APOL1 variation probably accounts for a majority of susceptibility to FSGS and HIVAN.

Hays T et Wyatt CM, KI (2012) 82, 259-260
Determined the role of APOL1 variants in 120 patients with HIV-associated nephropathy and CKD and 108 controls from a South African black population.

These results indicate HIV-positive, antiretroviral therapy-naïve South African blacks with two APOL1 risk alleles are at very high risk for developing HIV-associated nephropathy.
APOL1 genotype, blood pressure and survival in African Americans with non-diabetic nephropathy
Treatment and Outcomes

Social groups

cART

*Kidney toxicities

*Tenofovir

RRT – dialysis

Transplantation
ALL THESE VEGETABLES PREVENT THE ROLLOUT OF ANTIRETROVIRALS — TRUE OR FALSE?
AIDS council slammed for sidelining CEO

Respected head fails to have contract extended

The board of the South African National AIDS Council (Sanac) — which is responsible for overseeing donor funding for HIV/AIDS projects and coordinating the country’s response to the epidemic — has by

The workers of the board of Sanac on Friday warned that a leadership vacuum posed a reputational risk to Sanac, would demoralise staff and threaten funding.

“There is a risk of significant financial losses from donors who are considering investing in the trust. This could perhaps not do anything to compromise the recruitment process as Dr. Abdullah has also applied for the CEO position,” she said.

“The decision was then taken to look internally at senior management and appoint Dr. Kpanakga as acting CEO. Applications were being shortlisted.

Sanac’s nine-member board is chaired by Gwen Ramokgopa, who was appointed Gauteng health MEC after Qedani Mahlangu resigned on Tuesday in the wake of the scandal over the deaths of at least 94 mentally ill at the Wonderkop mental health facility."
cART – now freely available

Dialysis – accepted onto programs
 KDIGO

HIVAN

Figure 3. Without combined antiretroviral therapy (cART), HIV-associated nephropathy (HIVAN) remains an important cause of end-stage renal disease and death in Cape Town South Africa. Time to renal death over a 24-month period [16].

Table 1 | HAART-associated kidney disease

<table>
<thead>
<tr>
<th>Renal syndrome</th>
<th>Medication</th>
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<tbody>
<tr>
<td><strong>Acute kidney injury</strong></td>
<td></td>
</tr>
<tr>
<td>Toxic acute tubular necrosis</td>
<td>Tenofovir, ritonavir, didanosine</td>
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<tr>
<td>Acute interstitial nephritis</td>
<td>Atazanavir, abacavir, indinavir</td>
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<tr>
<td>Crystal nephropathy</td>
<td>Indinavir, atazanavir</td>
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<tr>
<td><strong>Tubulopathies</strong></td>
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<tr>
<td>Fanconi’s syndrome</td>
<td>Tenofovir, didanosine, ritonavir</td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
<td>Lamivudine, stavudine</td>
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<tr>
<td>Nephrogenic diabetes insipidus</td>
<td>Tenofovir, didanosine, indinavir</td>
</tr>
<tr>
<td><strong>Nephrolithiasis</strong></td>
<td>Indinavir, atazanavir, nelfinavir, amprenavir, saquinavir, efavirenz</td>
</tr>
<tr>
<td><strong>Chronic kidney disease</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic interstitial nephritis</td>
<td>Indinavir, tenofovir</td>
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<tr>
<td>Post-AKI kidney disease</td>
<td>Several HAART drugs</td>
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</table>
TENOFOVIR AND ITS EFFECTS ON THE KIDNEY
Tenofovir

- Nucleotide reverse transcriptase inhibitor
- Anti- HIV and anti- Hep B virus activity
- It is a weak inhibitor of mitochondrial DNA $\gamma$-polymerase
The proximal tubular cell is the main target of tenofovir toxicity due to its complement of cell membrane transporters.

A number of drugs interact with these transporters and may cause excessive entry or reduced outflow favouring proximal tubular cell accumulation and toxicity.
Drug treatment of HIV/HIVAN.

Perazella MA. Kidney Int. 2010, 78, 1060 – 1063
<table>
<thead>
<tr>
<th>Transporter</th>
<th>Drug interaction</th>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>hOAT1</td>
<td>Probenecid inhibits hOAT1; NSAIDs inhibit hOAT1</td>
<td>Probenecid decreases the incidence of renal toxicity by cidofovir, might for tenofovir [28]</td>
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<td>Acyclovir; DDI competes with tenofovir</td>
<td>Acyclovir increases serum concentrations of tenofovir; Tenofovir increases DDI levels [29]</td>
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<tr>
<td>MRP-4</td>
<td>Inhibition of MRP-4: probenecid, dipyridamole, NSAIDs [30]</td>
<td>Acyclovir increase serum concentrations of tenofovir; NSAIDs associated with tenofovir nephrotoxicity [30, 31]</td>
</tr>
<tr>
<td></td>
<td>Cidofovir, acyclovir, valaciclovir, ganciclovir, and valganciclovir</td>
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<tr>
<td>MRP-2</td>
<td>Ritonavir is transported by MRP-2</td>
<td>Ritonavir increases tenofovir concentration and has been associated with tenofovir nephrotoxicity</td>
</tr>
</tbody>
</table>
110 participants were enrolled (55 to each arm).

A randomised double blind placebo-controlled trial of prednisone 1.5mg/kg/day for 2 weeks then 0.75mg/kg/day for 2 weeks. Patients with immediately life-threatening TB-IRIS manifestations were excluded.

SYMPTOM SCORE

WEEK 2

p = 0.001

% PATIENTS

PLACEBO ARM (n=51)  PREDNISONE ARM (n=55)

- DETERIORATED
- NO CHANGE
- IMPROVED OR RESOLVED
WEEK 4

p = 0.03

% PATIENTS

PLACEBO ARM (n=48)  PREDNISONE ARM (n=54)

OPEN LABEL OR DIED WITHIN 2 WEEKS
Figure 3. Without combined antiretroviral therapy (cART), HIV-associated nephropathy (HIVAN) remains an important cause of end-stage renal disease and death in Cape Town South Africa. Time to renal death over a 24-month period [16].

HIV-Positive-to-HIV-Positive Kidney Transplantation — Results at 3 to 5 Years

Elmi Muller, M.B., Ch.B., M.Med., Zunaid Barday, M.B., Ch.B., Marc Mendelson, M.D., Ph.D., and Delawir Kahn, M.B., Ch.B., Ch.M.


Slides courtesy Mignon McCulloch x 3
Patient outcomes

- Alive and well: 29
- Alive and on dialysis: 6
- Died: 8
Patient Survival

1 Year 89.1% (95% CI 73.4-95.8)
Graft Survival

1 year graft survival 95.12% (95% CI 81.9-98.8)
Address poverty, HIV to stem TB

THE rise of incurable tuberculosis (TB) underscores the need to address poverty, overcrowding and the HIV epidemic in Africa, experts say.
INCREASE IN INCURABLE TB

Address poverty, HIV to stem TB

Lisa Isaacs

THE rise of incurable tuberculosis (TB) underscores the need to address poverty, overcrowding and the HIV epidemic in Africa, experts say.

A study which tracked more than 275 patients with extensively drug-resistant TB (XDR-TB) and incurable TB in two Western and Northern Cape hospitals over a period of six years found that of the two thirds of patients who were discharged from the hospital, most of these patients ended up with poor outcomes.

UCT Professor of Medicine Dr Keeran Dheda said more than half of patients with XDR-TB remained alive at the end of only 16 months.

"These high-risk patients were the downsteam of further cases of TB," Dheda said.

The study, sequencing of drug-resistant TB refers to a drug-resistant strain which has been found in several countries including South Africa.

The study, sequencing of drug-resistant TB refers to a drug-resistant strain which has been found in several countries including South Africa. Resistance to TB antibiotics regimen, while XDR-TB presents resistance to four key TB antibiotics.

Incurable TB cases have now been documented in several countries including South Africa. Resistance to TB antibiotics regimen, while XDR-TB presents resistance to four key TB antibiotics.

"This emphasises the need for appropriate containment strategies that will curb transmission," she added.

In 2014 there were almost 500,000 cases of MDR TB globally, with 18,734 reported cases of rifampicin-resistant or MDR TB in South Africa, of which roughly 8% were thought to be extensively or totally drug-resistant.

Estimates from Africa, Russia, India and China suggest that treatment fails to cure 30-75% of patients with extensively or totally drug-resistant tuberculosis.
Vaccines....
WHO 2016
Education is the most powerful weapon which you can use to change the world.

Nelson Mandela