



OVERVIEW OF HIV NEPHROPATHY

Emeritus Assoc Prof CR Swanepoel
University of Cape Town.

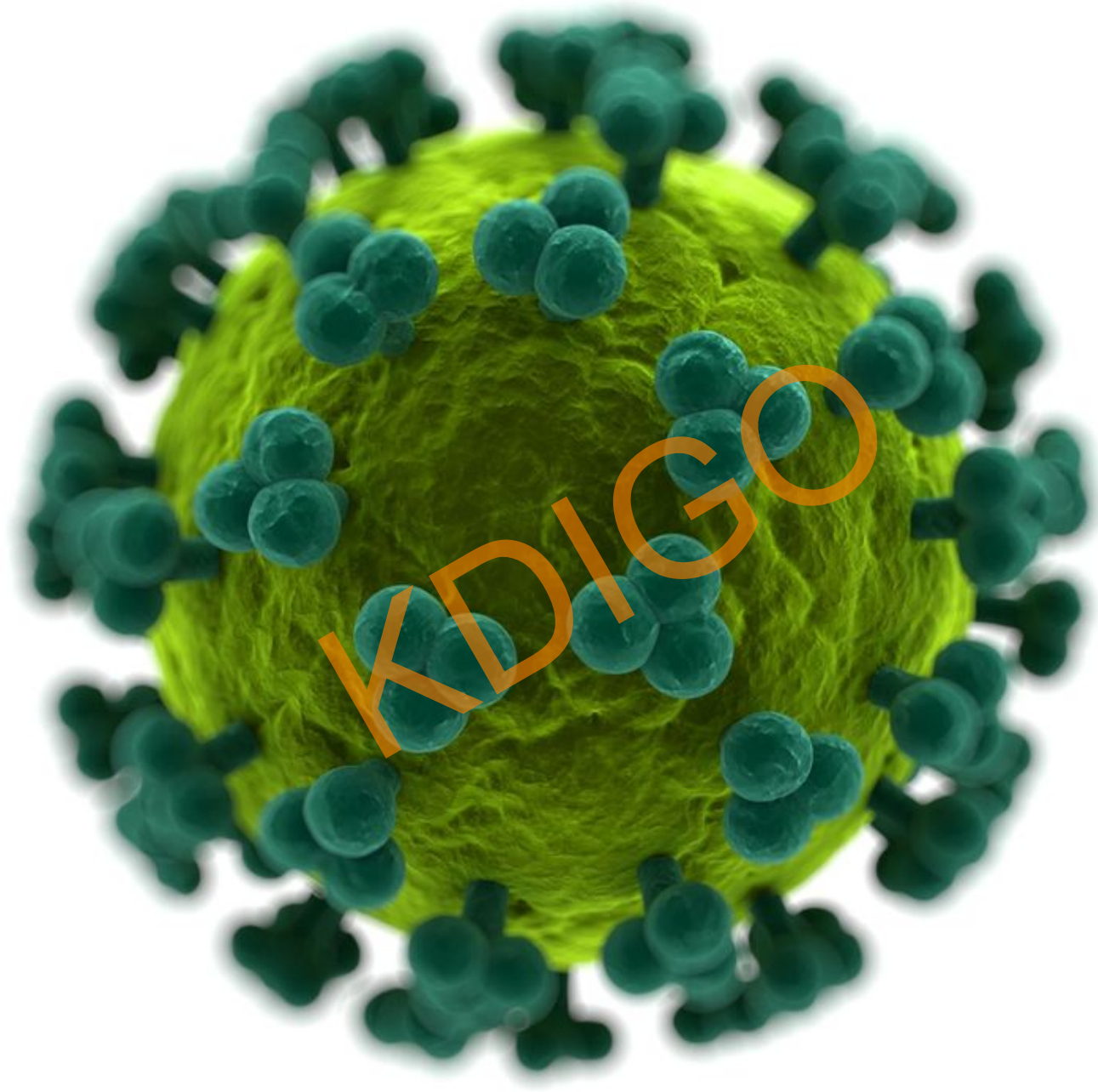
Disclosure of Interests

Consultancy and honoraria

- Company Roche
- Company Abbott
- Company Amgen

Medical Adviser for Fresenius Medical Care (South Africa).







Guinea-Bissau

Cameroon

KDIGO



Keele BF, Van Heuverswyn F, Li Y, et al. Chimpanzee reservoirs of pandemic and nonpandemic HIV-1. *Science*. 2006;313(5786):523-526.



Keele BF, Van Heuverswyn F, Li Y, et al. Chimpanzee reservoirs of pandemic and nonpandemic HIV-1. *Science*. 2006;313(5786):523-526.

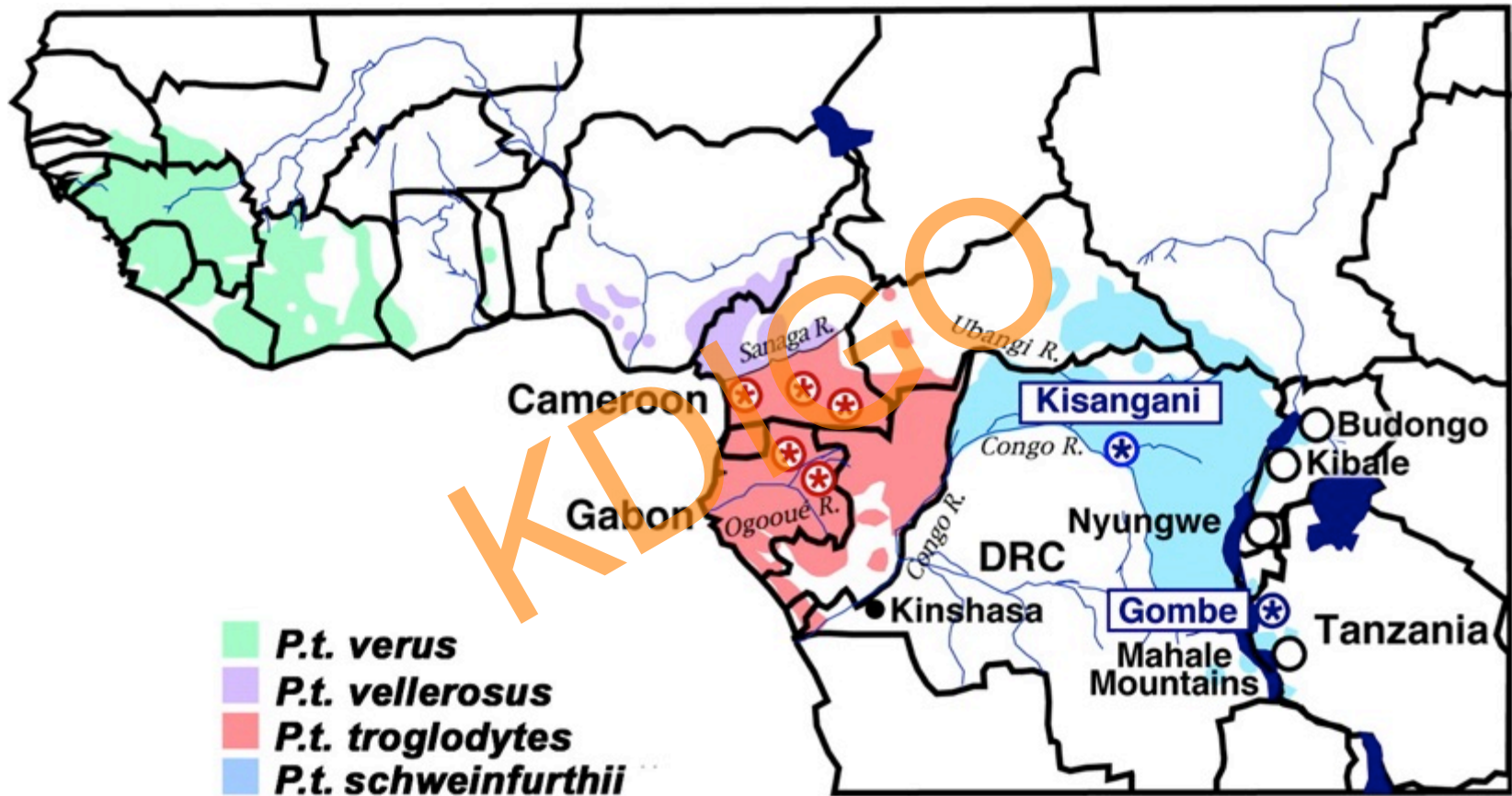
Chimpanzees hunt and eat other primates.



Paul M. Sharp et al. *J. Virol.* 2005;79:3891-3902

Journal of Virology

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



Paul M. Sharp et al. J. Virol. 2005;79:3891-3902

Journal of Virology

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



36.7 MILLION

people worldwide are currently living with HIV/AIDS.

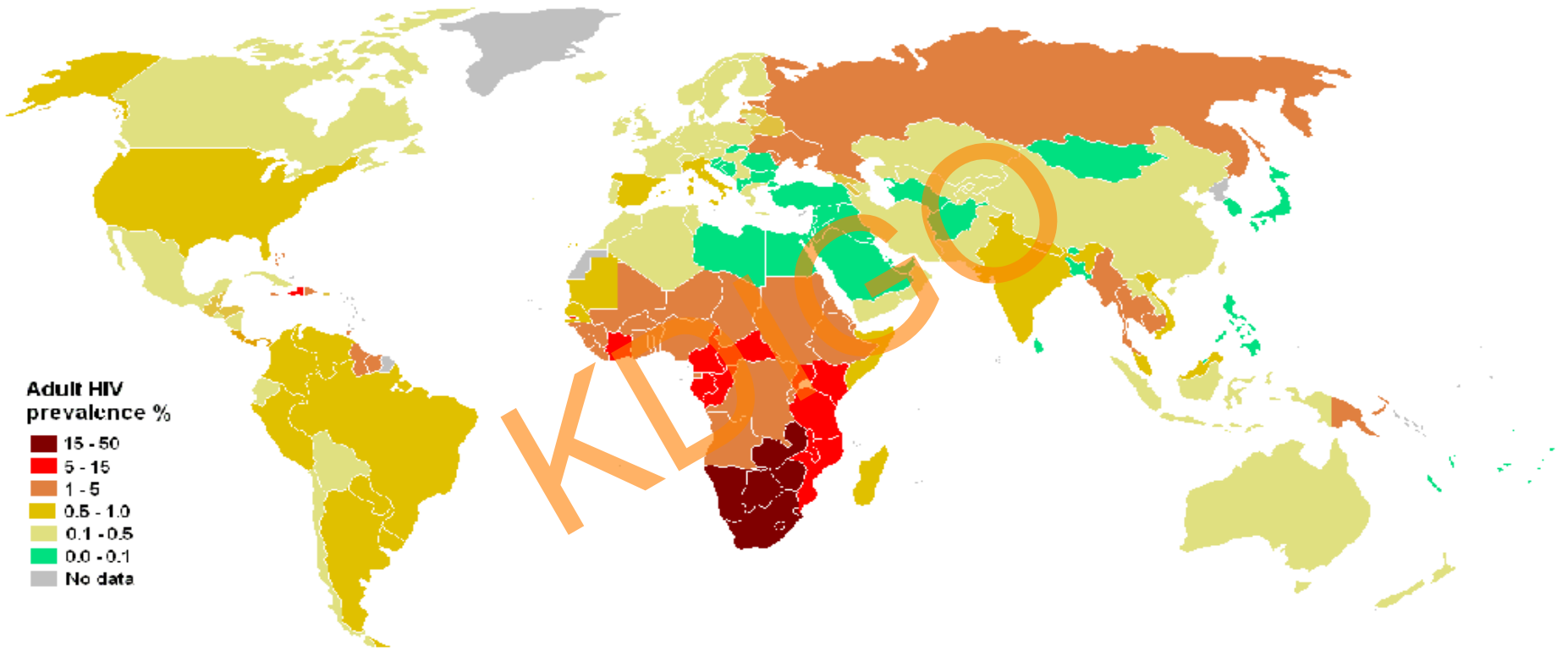
The vast majority of people living with HIV are in low- to middle-income countries, particularly in Sub-Saharan Africa.



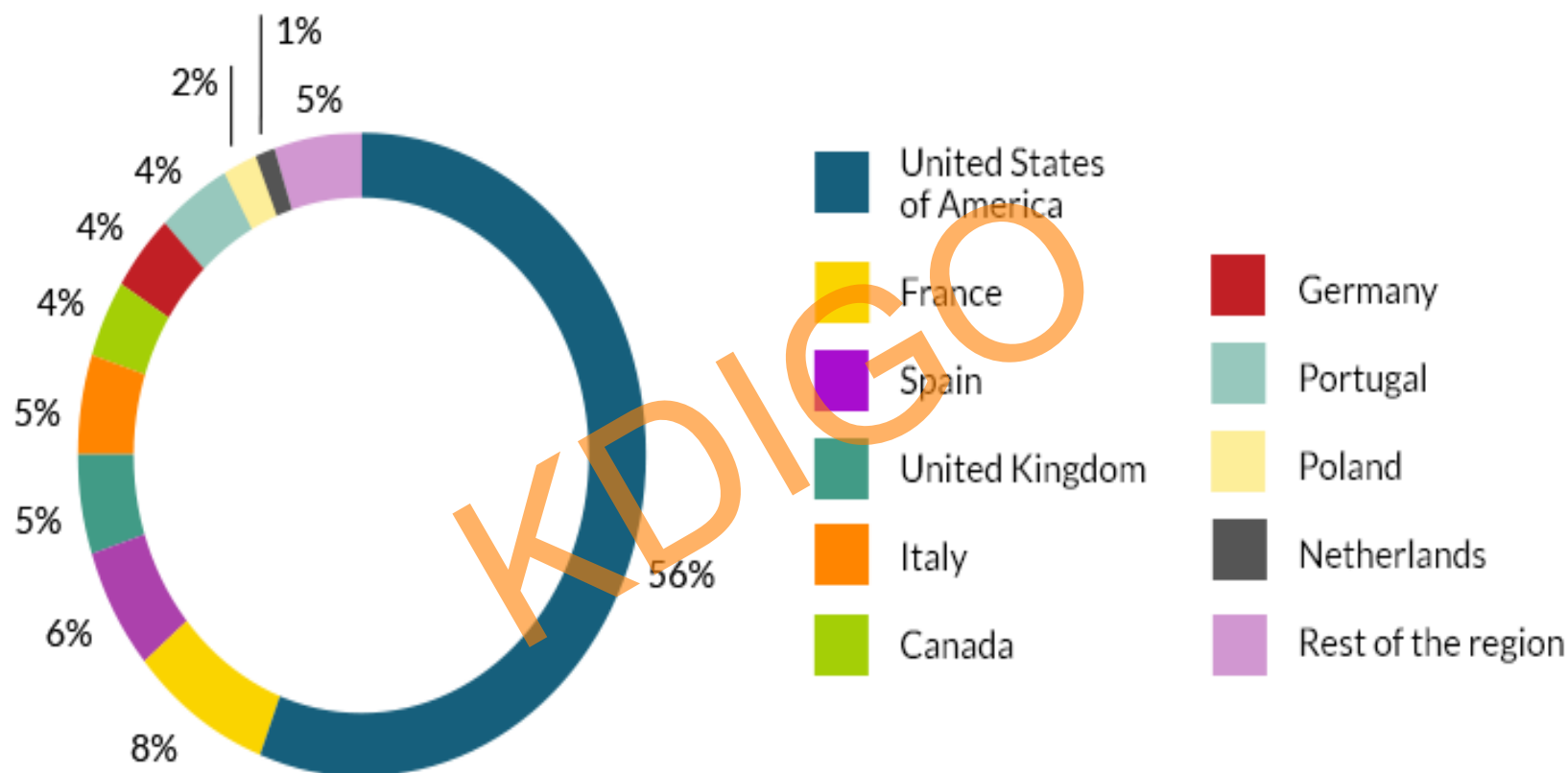
1.8 MILLION CHILDREN

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





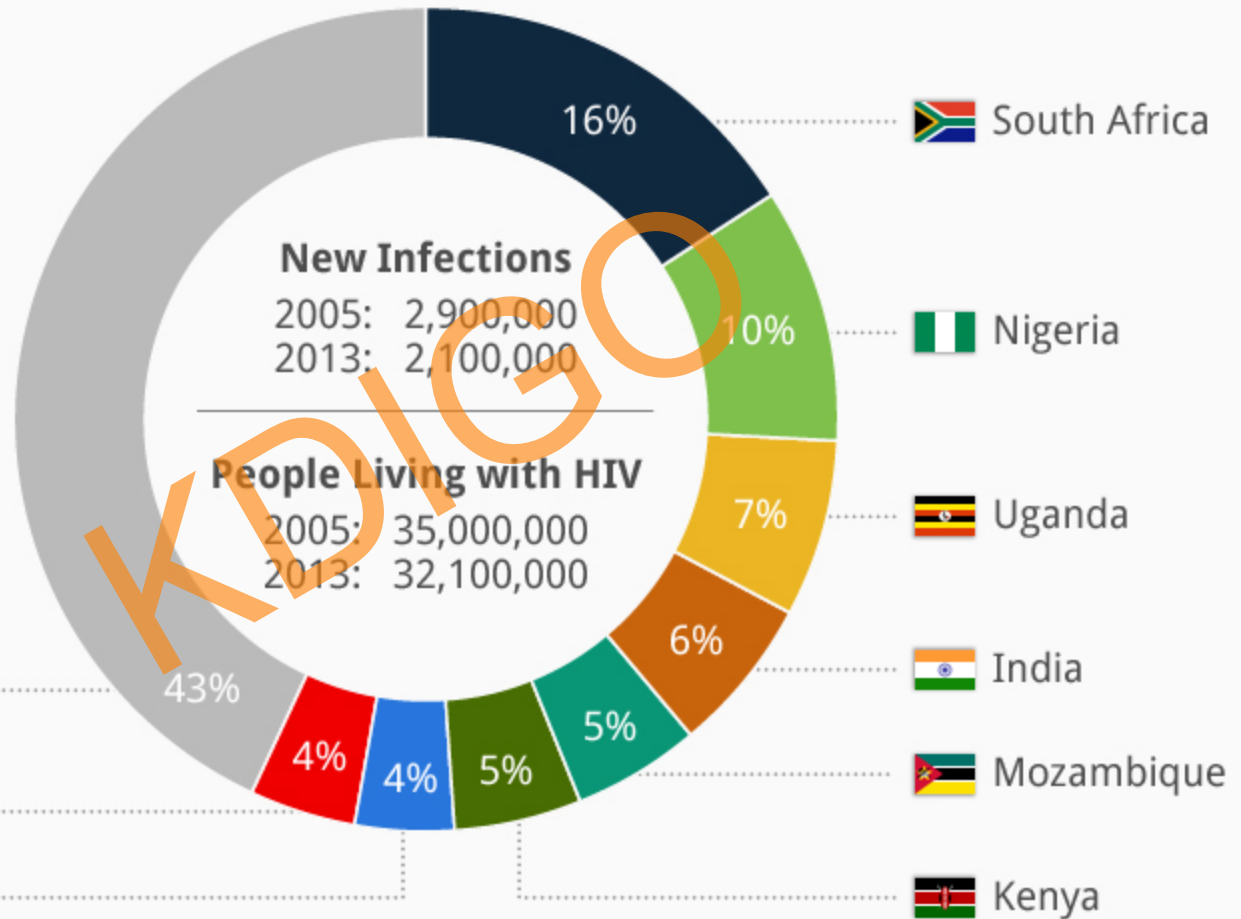
People living with HIV in Western/Central Europe and North America, 2013



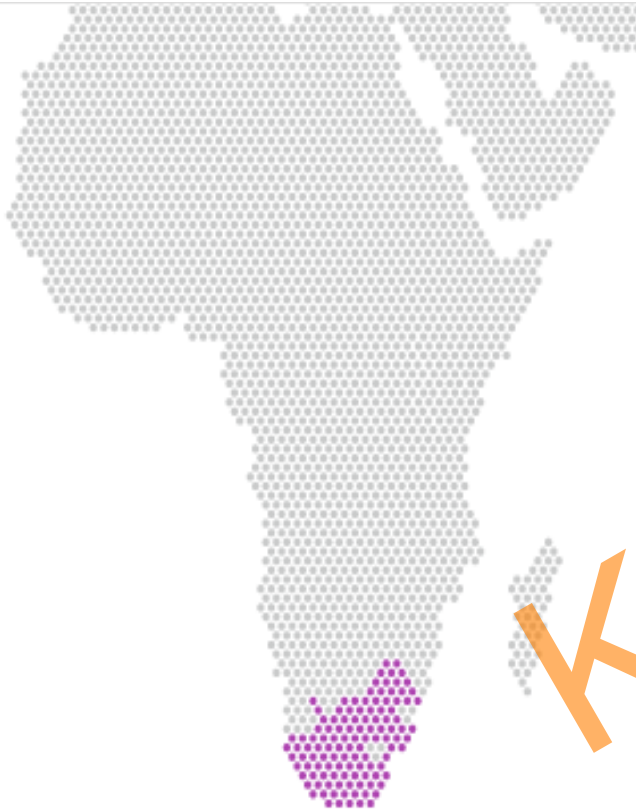
Source: UNAIDS estimates, 2013

8 Countries Accounted for 57% of New HIV Infections in 2013

% of new HIV infections in 2013, by country



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

Source: UNAIDS Gap Report 2016

Ross MJ, Klotman PE. Recent progress in HIV associated nephropathy. J Am Soc Nephrol. 2002; 13:2997-3004

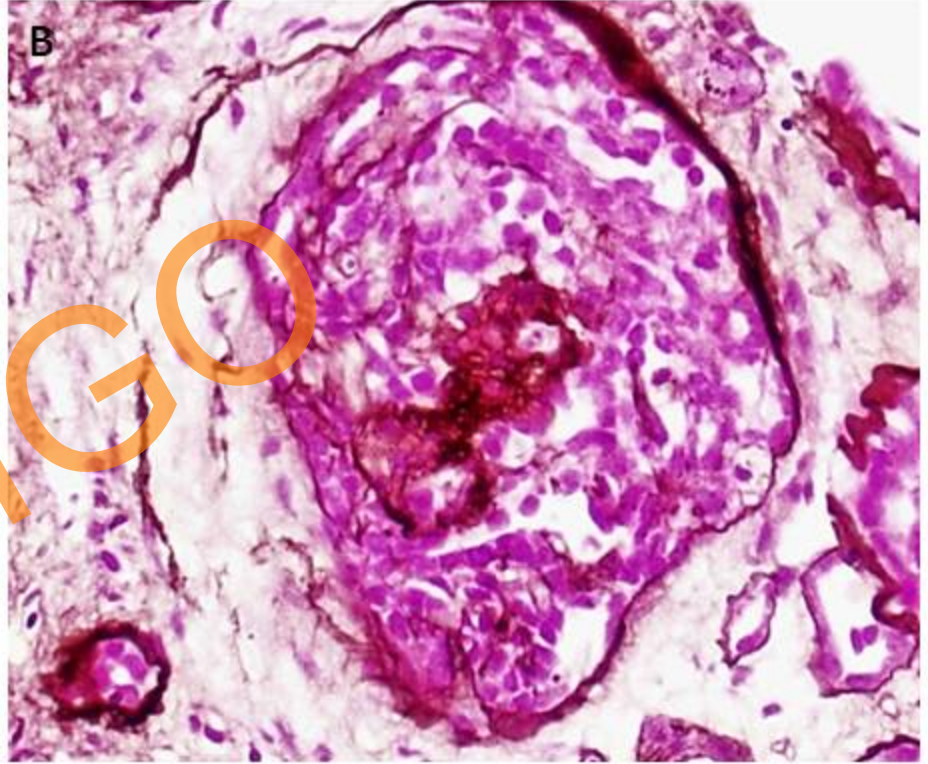
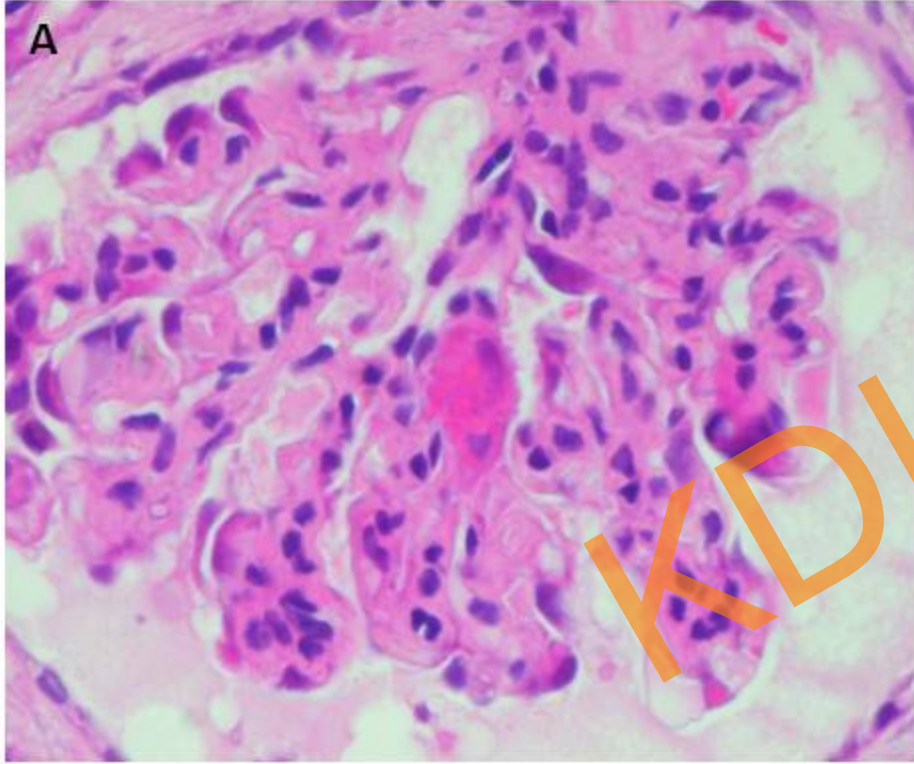
HIV-associated nephropathy (HIVAN) is ranked as the third leading cause of ESRD among blacks aged 20 – 64 years in the USA, lagging behind diabetes and hypertension

Very few studies on prevalence of HIV nephropathy from Africa. Prevalence low at approx 5%

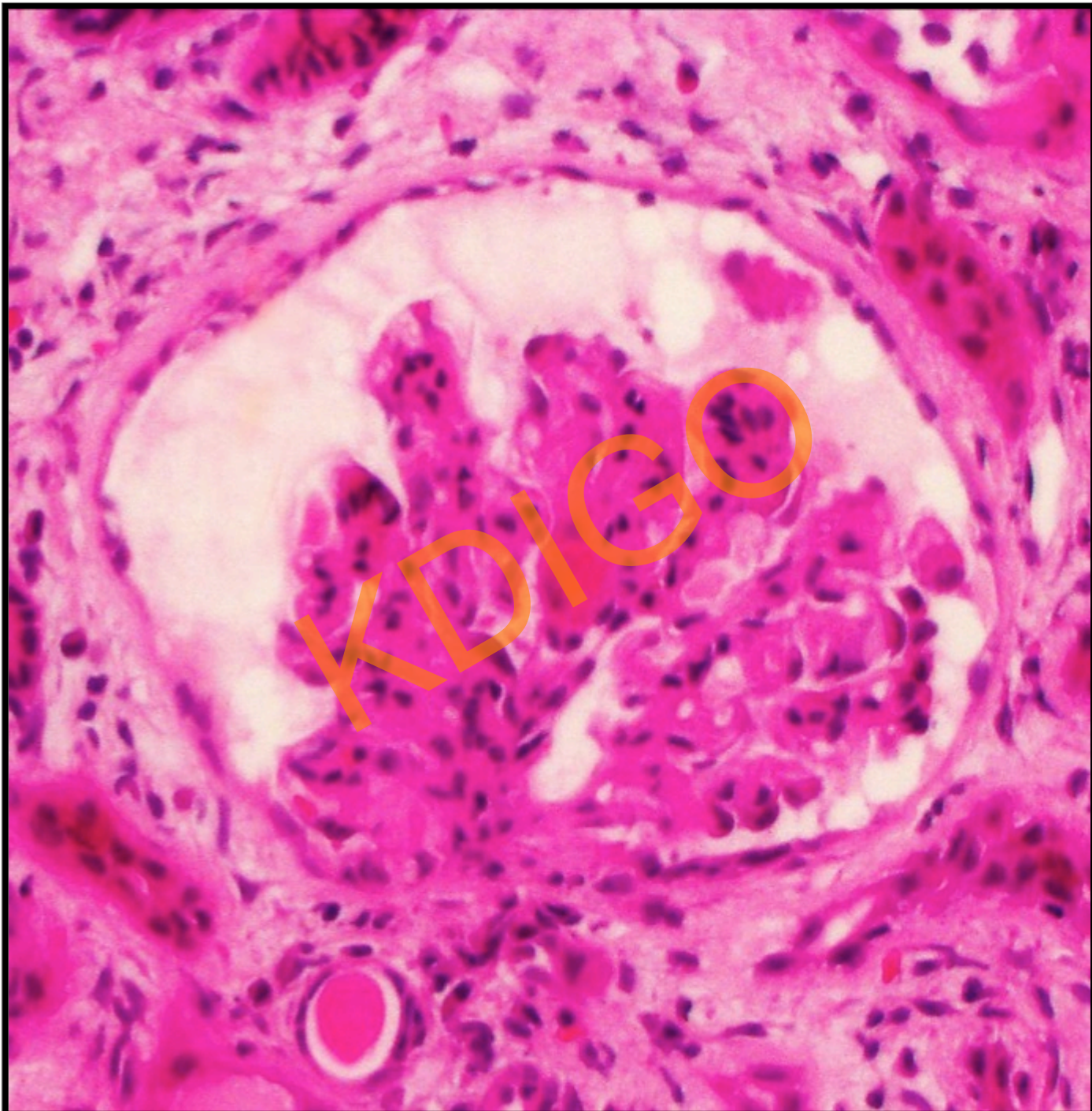
How does one make the diagnosis?

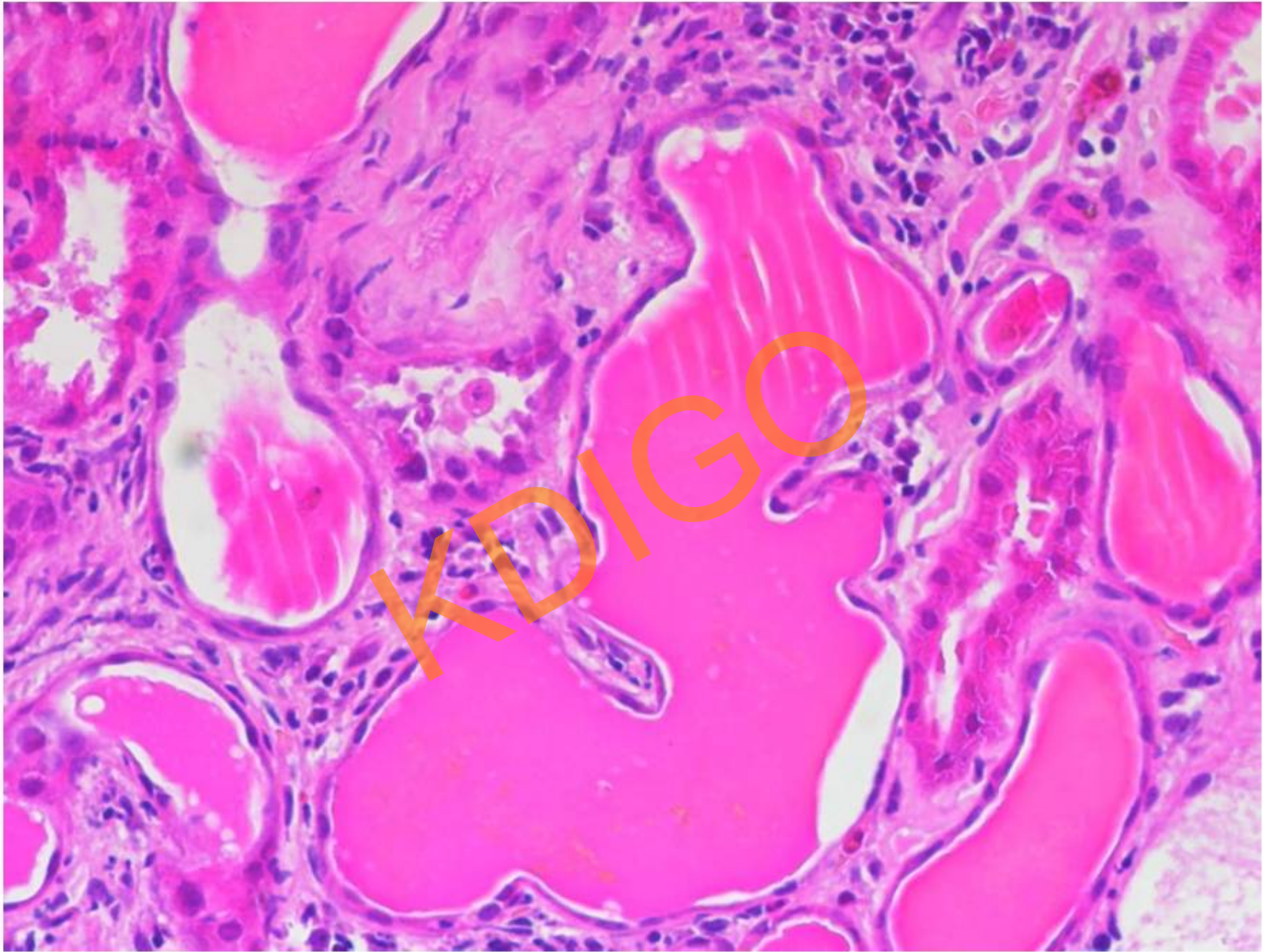
Clinical impression, blood tests and

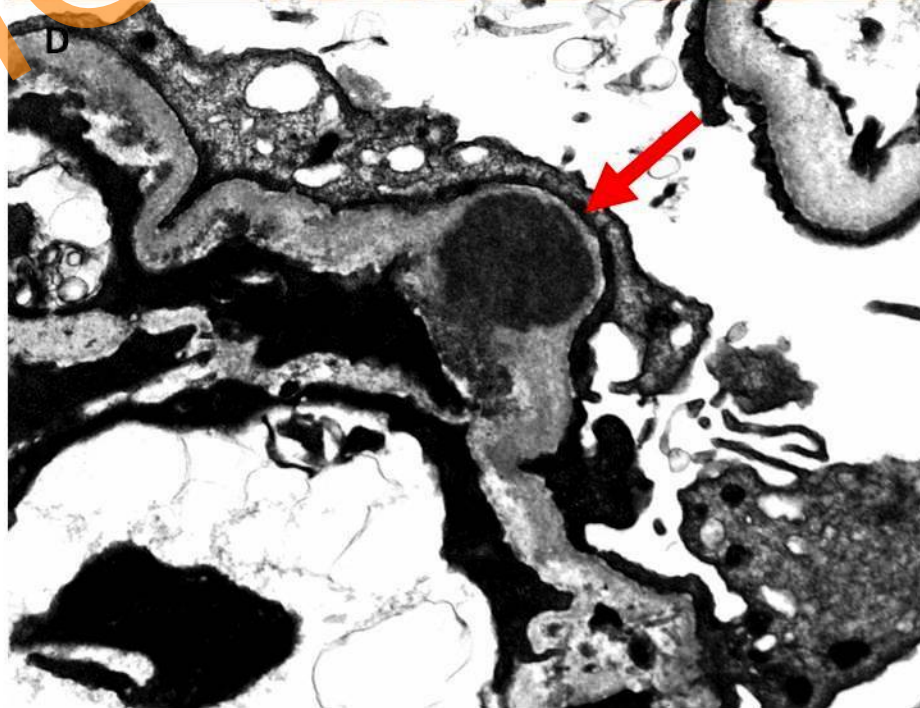
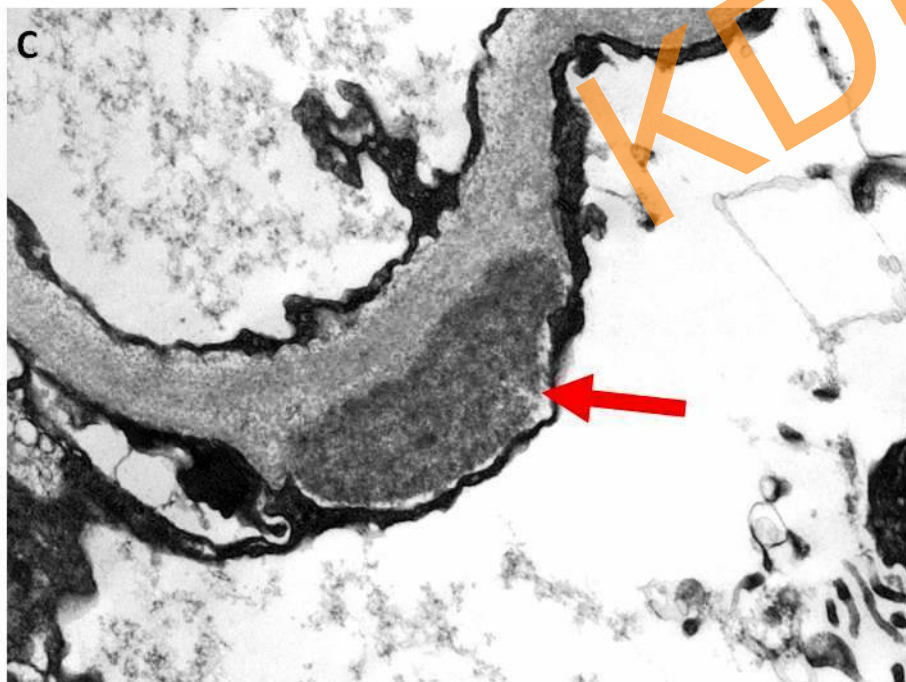
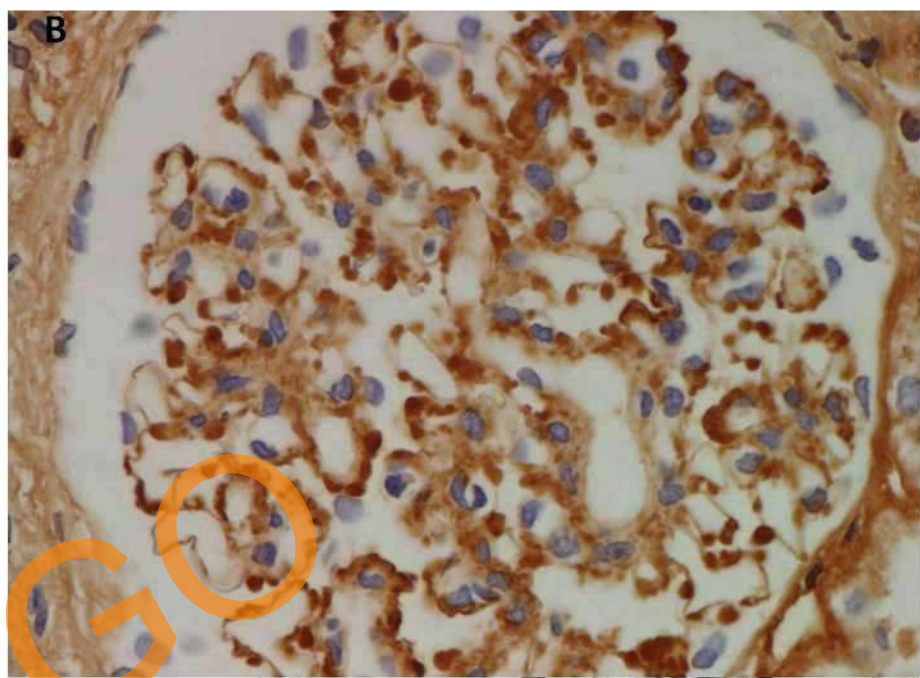
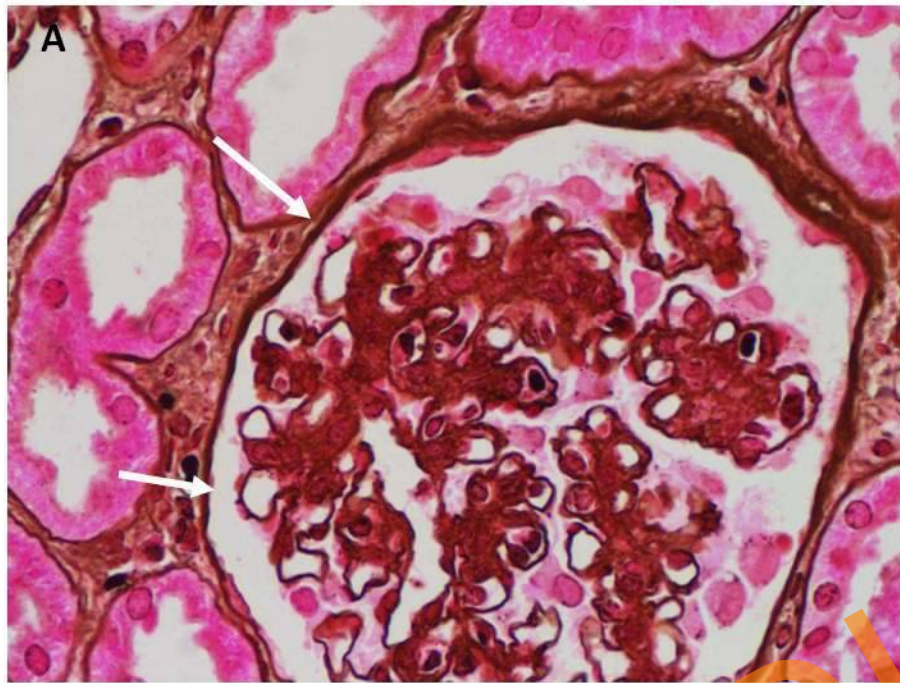
RENAL HISTOLOGY



KDIGO







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

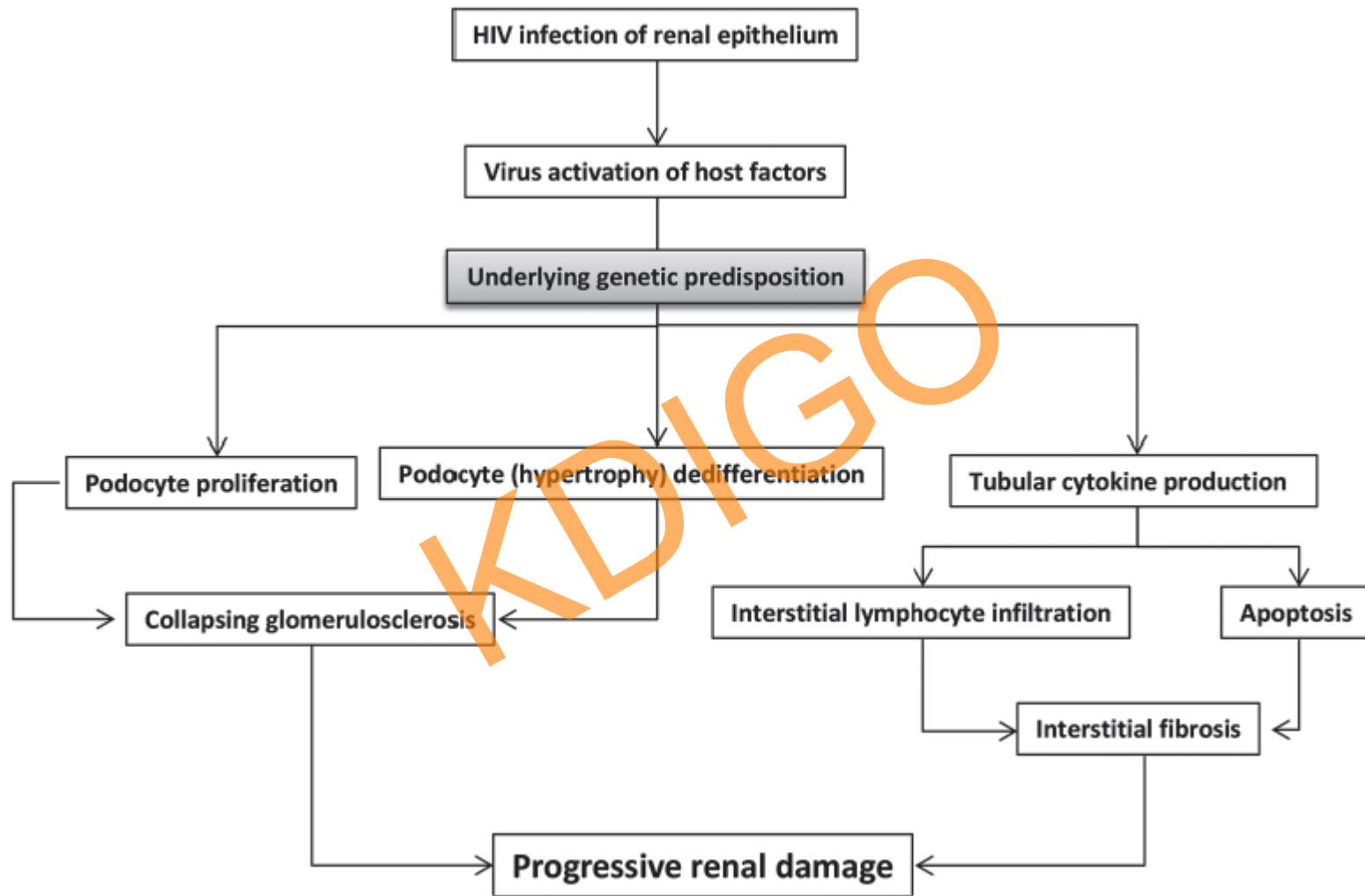


Figure 2. The biological pathways altered by HIV infection of renal epithelial cells, leading to progressive renal failure (adapted from Leventhal et al. [35] and Bruggeman et al. [36]).

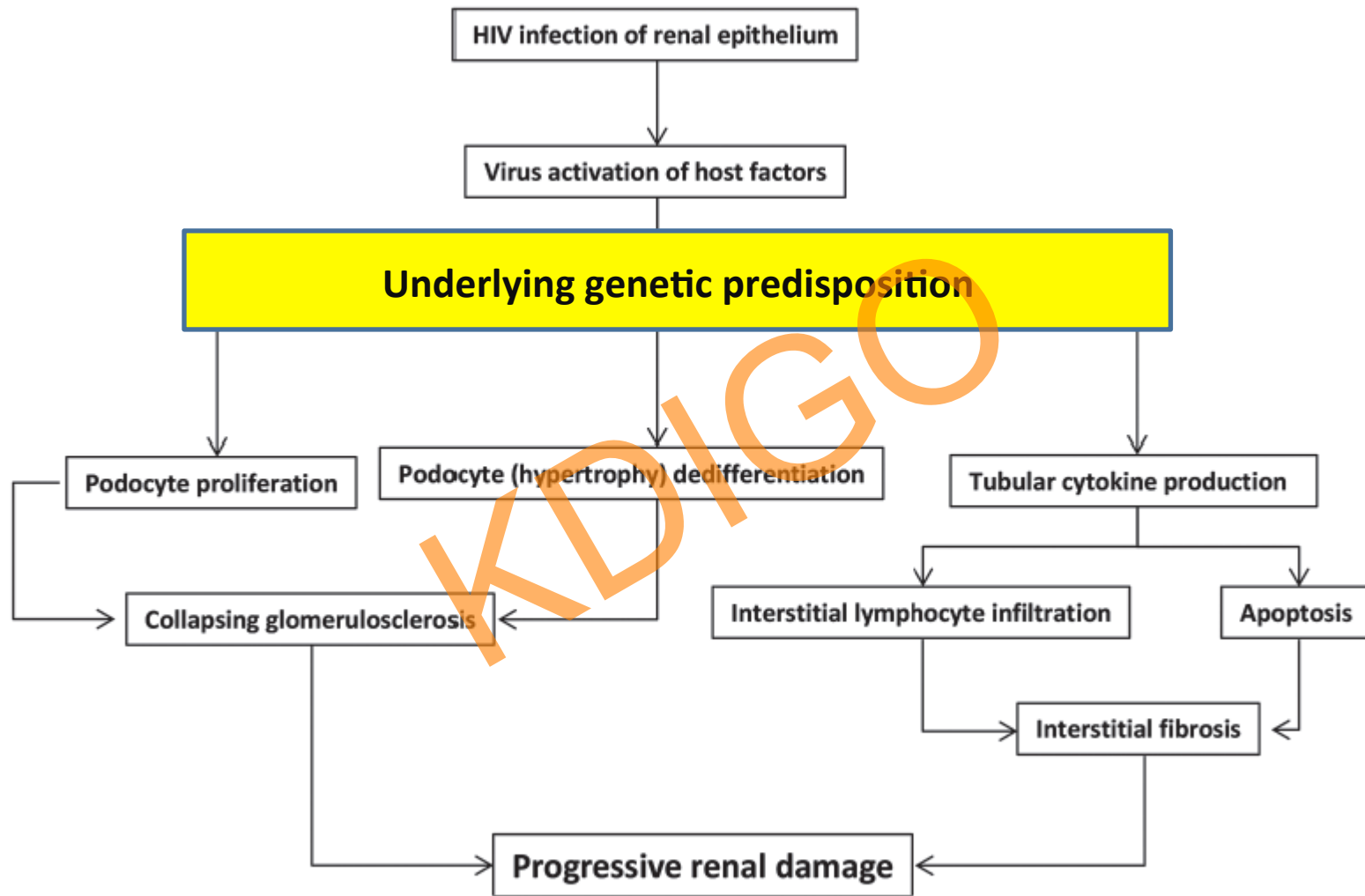
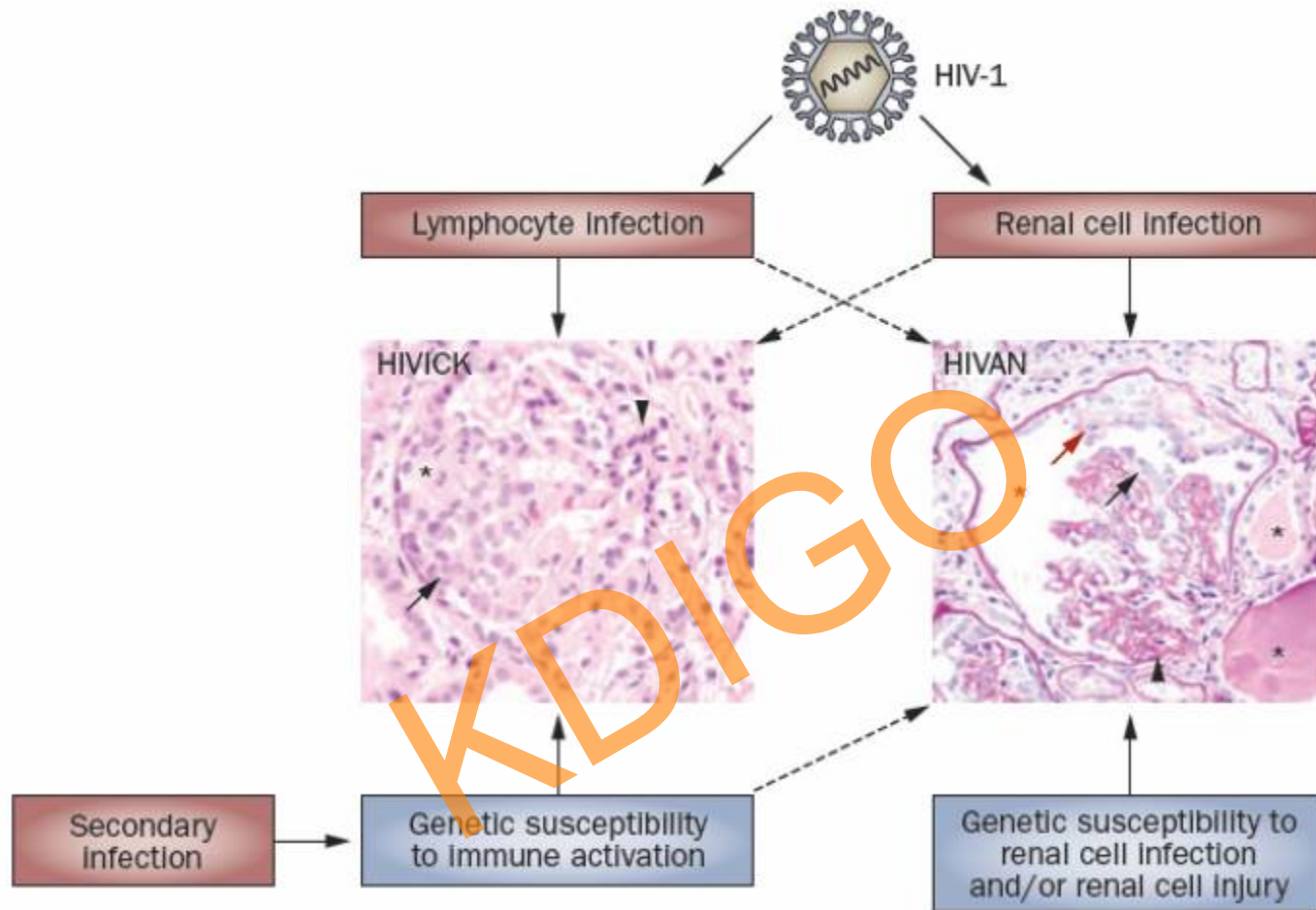


Figure 2. The biological pathways altered by HIV infection of renal epithelial cells, leading to progressive renal failure (adapted from Leventhal et al. [35] and Bruggeman et al. [36]).



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

Kopp JB et al. 2008. *MYH9* is a major-effect risk gene for focal segmental glomerulosclerosis. *Nat. Genet.* 40(10):1175-84

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

Genovese G, et al. 2010. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 329(5993):841-45

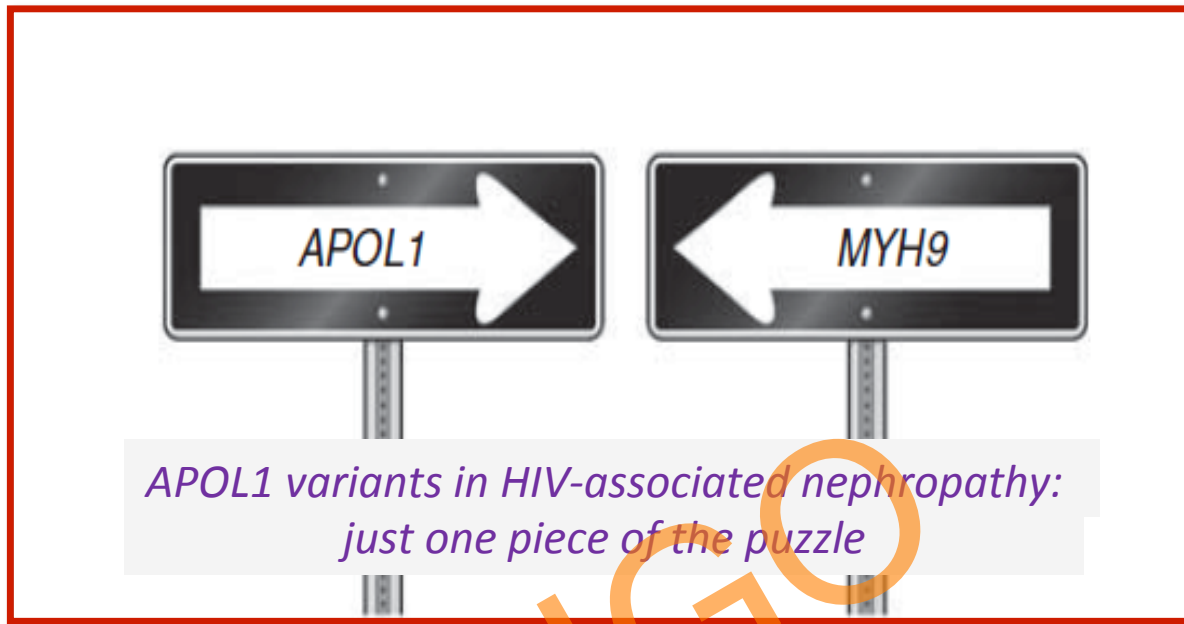
Kopp JB , e t al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV associated nephropathy . *J Am Soc Nephrol* **2011**; **22**: 2129 – 2137

Of great interest.....

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

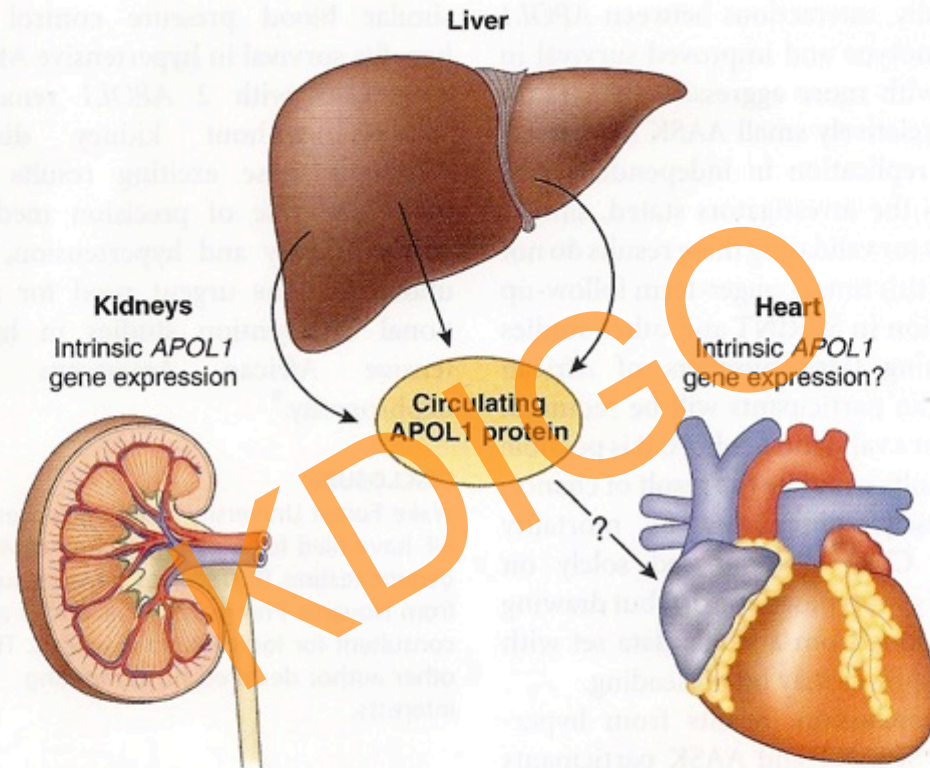
APOL1 Risk Variants Are Strongly Associated with HIV-Associated Nephropathy in Black South Africans

APOL1 variants are associated with HIV-associated nephropathy and FSGS in African Americans

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



- Nephropathy progression
- 40% ESKD in African Americans
- *APOL1* expressed in glomerular endothelial cells, podocytes, and renal tubule cells

- Possible effects on atherosclerosis and coronary artery calcium
- Does blood pressure control modify *APOL1* gene effect?
- *APOL1* expressed in the vasculature

Figure 1 | Potential apolipoprotein L1 gene (*APOL1*) renal-risk variant effects on kidney and cardiovascular disease. ESKD, end-stage kidney disease.

Treatment and Outcomes

Social groups

cART

- *Kidney toxicities

- *Tenofovir

RRT – dialysis

Transplantation



ALL THESE VEGETABLES PREVENT THE ROLLOUT
OF ANTIRETROVIRALS — TRUE OR FALSE ?



AFRICAN
POTATO



BEETROOT



LEMON



GARLIC



MANTO

Zapiro
© 2008. All rights reserved. Reproduction prohibited.

AIDS council slammed for sidelining CEO

● Respected head fails to have contract extended

Ta
Sc

Th
Ni
w
se
Hi
or
re
fal
its

ob
cr

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

entry
r the
AIDS,
see-
016-
cated
three

anya
end-
ould
isad-
want

renewing contract, ending his five-year tenure.

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

he wrote to Ramokgopa last Friday warning 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 exceed

to 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 Kganakga as acting CEO." Applications were being shortlisted

cART – now freely available

Dialysis – accepted onto programs

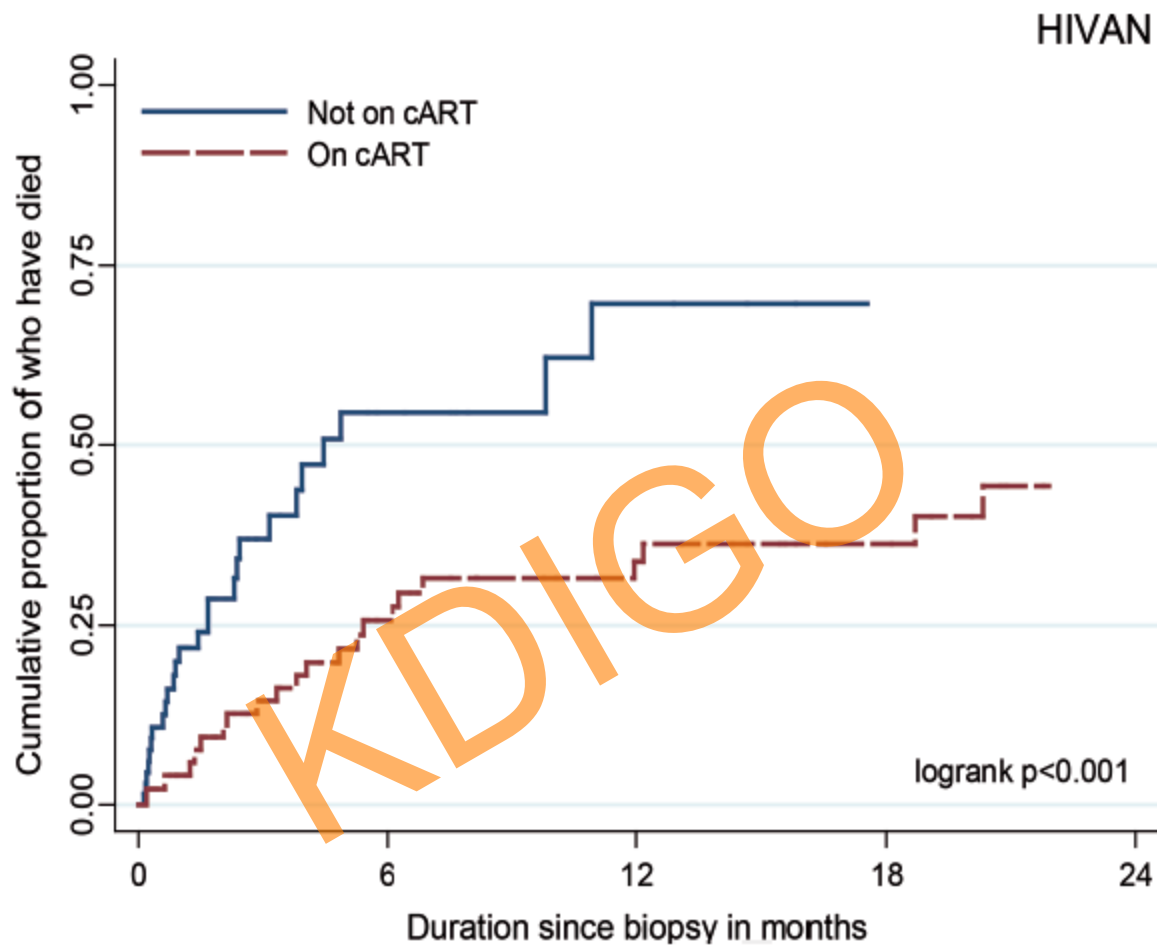


Figure 3. Without combined antiretroviral therapy (cART), HIV-associated nephropathy (HIVAN) remains an important cause of end-stage renal disease and death in Cape Town South Africa. Time to renal death over a 24-month period [16].

Wearne N, Swanepoel CR, Boulle A, Duffield MS, Rayner BL. The spectrum of renal histologies seen in HIV with outcomes, prognostic indicators and clinical correlations. *Nephrol Dial Transplant.* 2012; 27: 4109-4118. [CrossRef PubMed](#)

Table 1 | HAART-associated kidney disease

Renal syndrome	Medication
<i>Acute kidney injury</i>	
Toxic acute tubular necrosis	Tenofovir, ritonavir, didanosine
Acute interstitial nephritis	Atazanavir, abacavir, indinavir
Crystal nephropathy	Indinavir, atazanavir
<i>Tubulopathies</i>	
Fanconi's syndrome	Tenofovir, didanosine, ritonavir
Renal tubular acidosis	Lamivudine, stavudine
Nephrogenic diabetes insipidus	Tenofovir, didanosine, indinavir
<i>Nephrolithiasis</i>	Indinavir, atazanavir, nelfinavir, amprenavir, saquinavir, efavirenz
<i>Chronic kidney disease</i>	
Chronic interstitial nephritis	Indinavir, tenofovir
Post-AKI kidney disease	Several HAART drugs

TENOFOVIR AND ITS EFFECTS
ON THE KIDNEY

KIDNIGO

Tenofovir

- Nucleotide reverse transcriptase inhibitor
- Anti- HIV and anti- Hep B virus activity
- It is a weak inhibitor of mitochondrial DNA γ -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

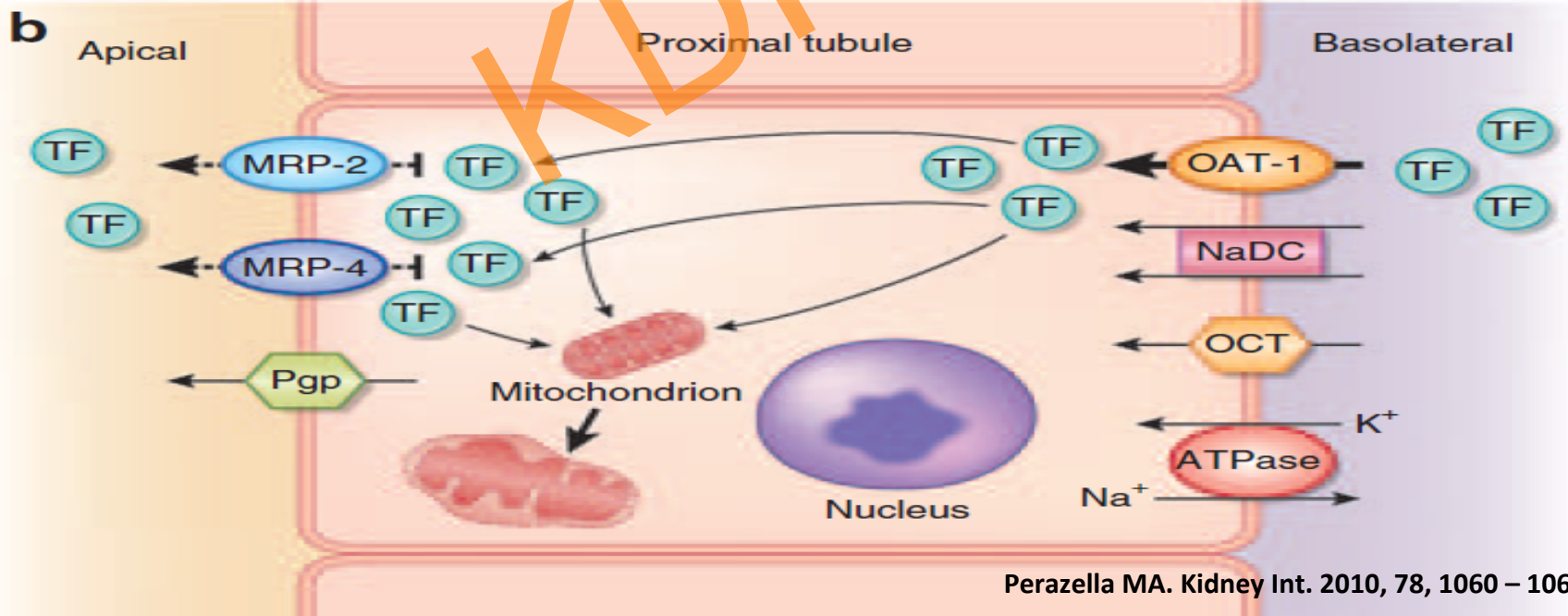
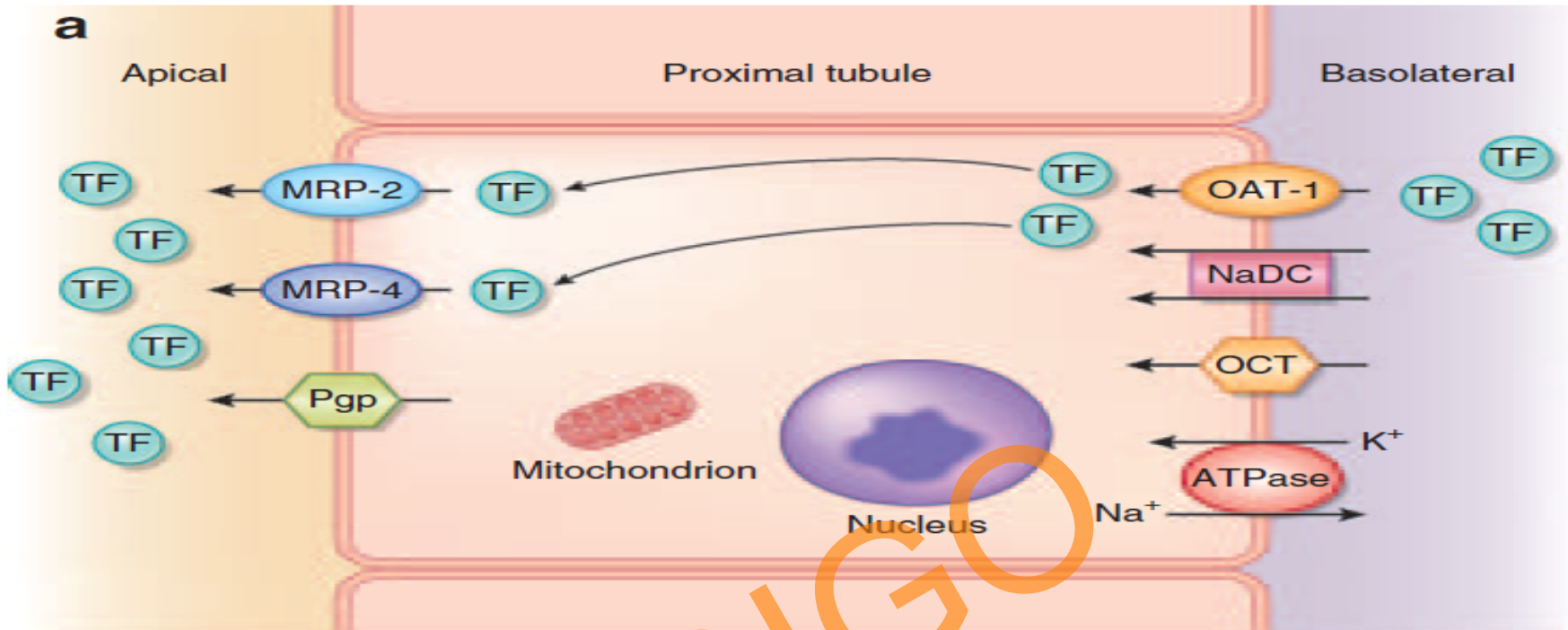


TABLE 1: Drugs interfering with proximal tubular tenofovir transporters.

Transporter	Drug interaction	Effect
hOAT1	<p>Probenecid inhibits hOAT1</p> <p>NSAIDs inhibit hOAT1</p> <p>Acyclovir</p> <p>DDI competes with tenofovir</p>	<p>Probenecid decreases the incidence of renal toxicity by cidofovir, might for tenofovir [28]</p> <p>Acyclovir increases serum concentrations of tenofovir</p> <p>Tenofovir increases DDI levels [29]</p>
MRP-4	<p>Inhibition of MRP-4: probenecid, dipyridamole, NSAIDs [30]</p> <p>Cidofovir, acyclovir, valaciclovir, ganciclovir, and valganciclovir</p>	<p>Acyclovir increase serum concentrations of tenofovir</p> <p>NSAIDs associated with tenofovir nephrotoxicity [30, 31]</p>
MRP-2	<p>Ritonavir is transported by MRP-2</p>	<p>Ritonavir increases tenofovir concentration and has been associated with tenofovir nephrotoxicity</p>

Randomized placebo-controlled trial of prednisone for paradoxical TB-associated immune reconstitution inflammatory syndrome

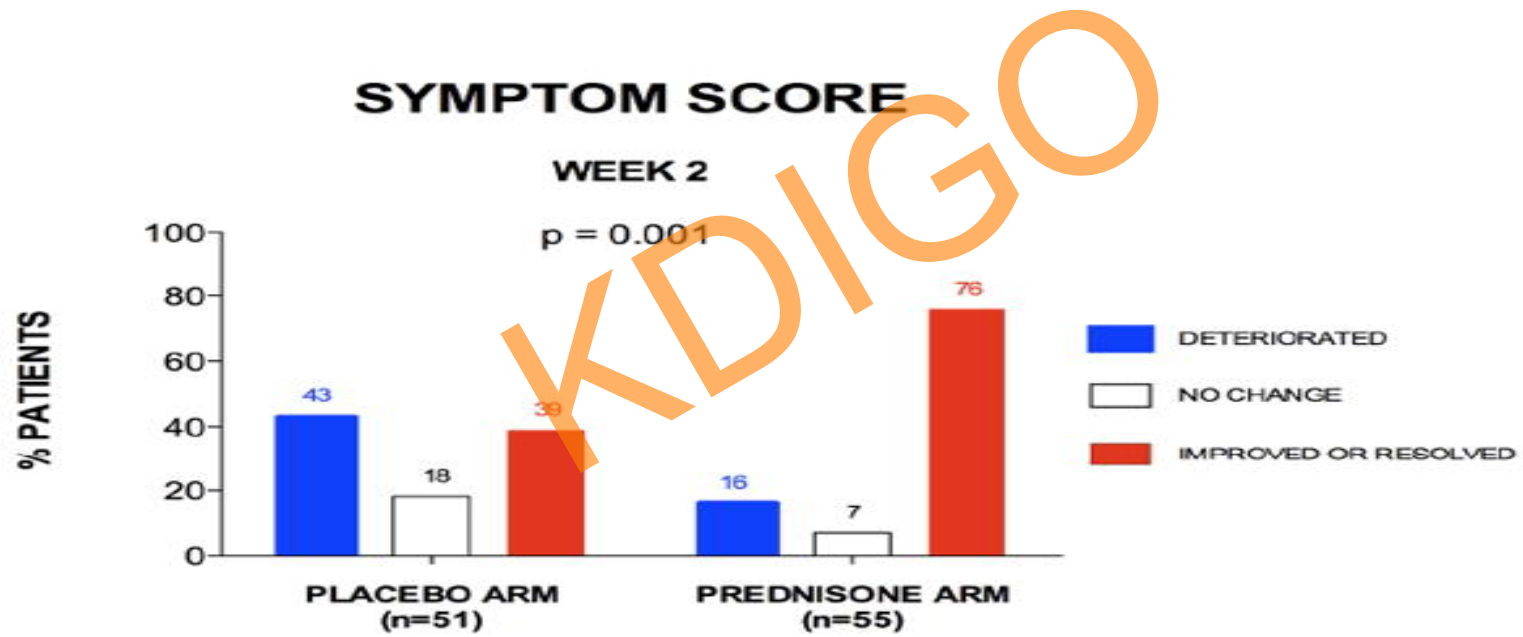
110 participants were enrolled (55 to each arm).

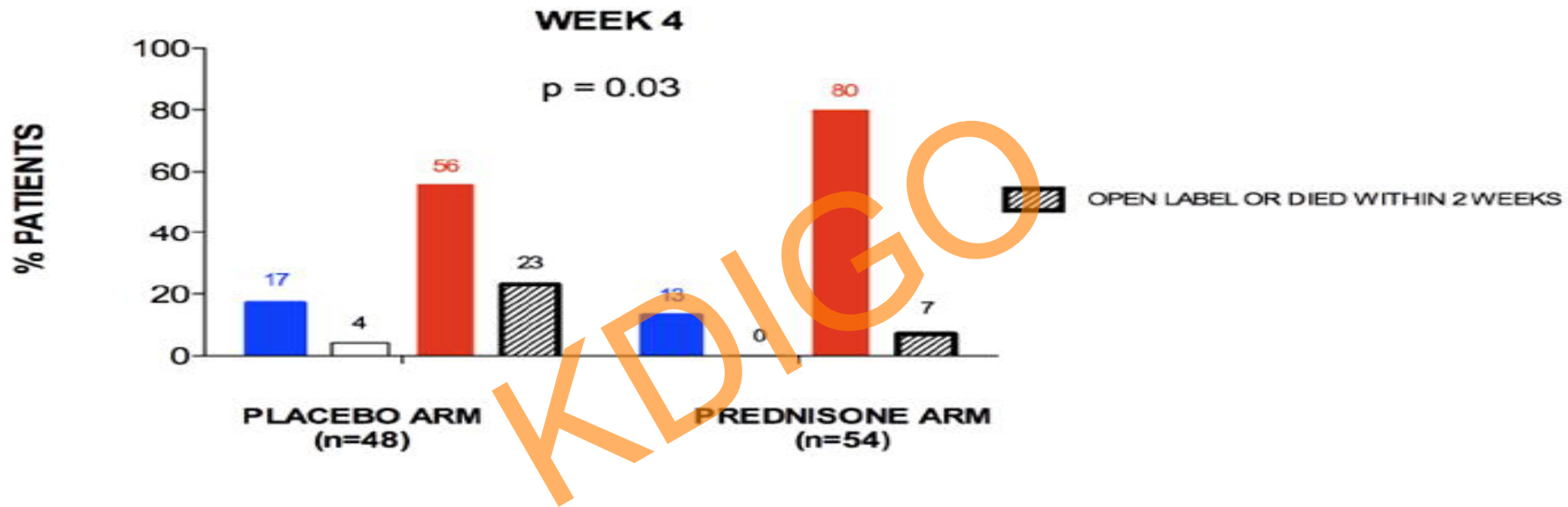
A randomised double blind placebo-controlled trial of prednisone 1.5mg/kg/day for 2 weeks then 0.75mg/kg/day for 2 weeks.

Patients with immediately life-threatening TB-IRIS manifestations were excluded.

110 participants

a





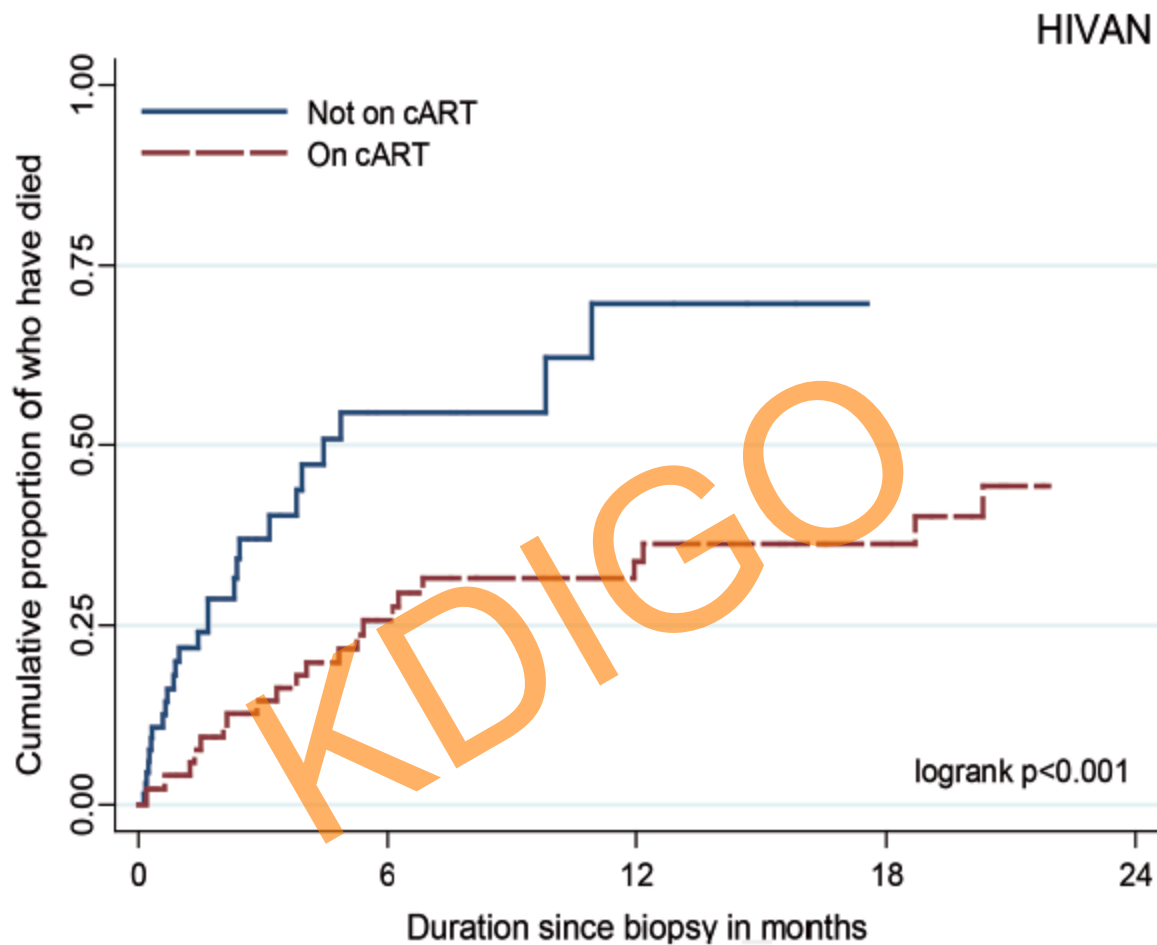


Figure 3. Without combined antiretroviral therapy (cART), HIV-associated nephropathy (HIVAN) remains an important cause of end-stage renal disease and death in Cape Town South Africa. Time to renal death over a 24-month period [16].

Wearne N, Swanepoel CR, Boulle A, Duffield MS, Rayner BL. The spectrum of renal histologies seen in HIV with outcomes, prognostic indicators and clinical correlations. *Nephrol Dial Transplant.* 2012; 27: 4109-4118. [CrossRef PubMed](#)



The NEW ENGLAND JOURNAL of MEDICINE

HOME

ARTICLES & MULTIMEDIA ▾

ISSUES ▾

SPECIALTIES & TOPICS ▾

FOR AUTHORS ▾

CME >

ORIGINAL ARTICLE

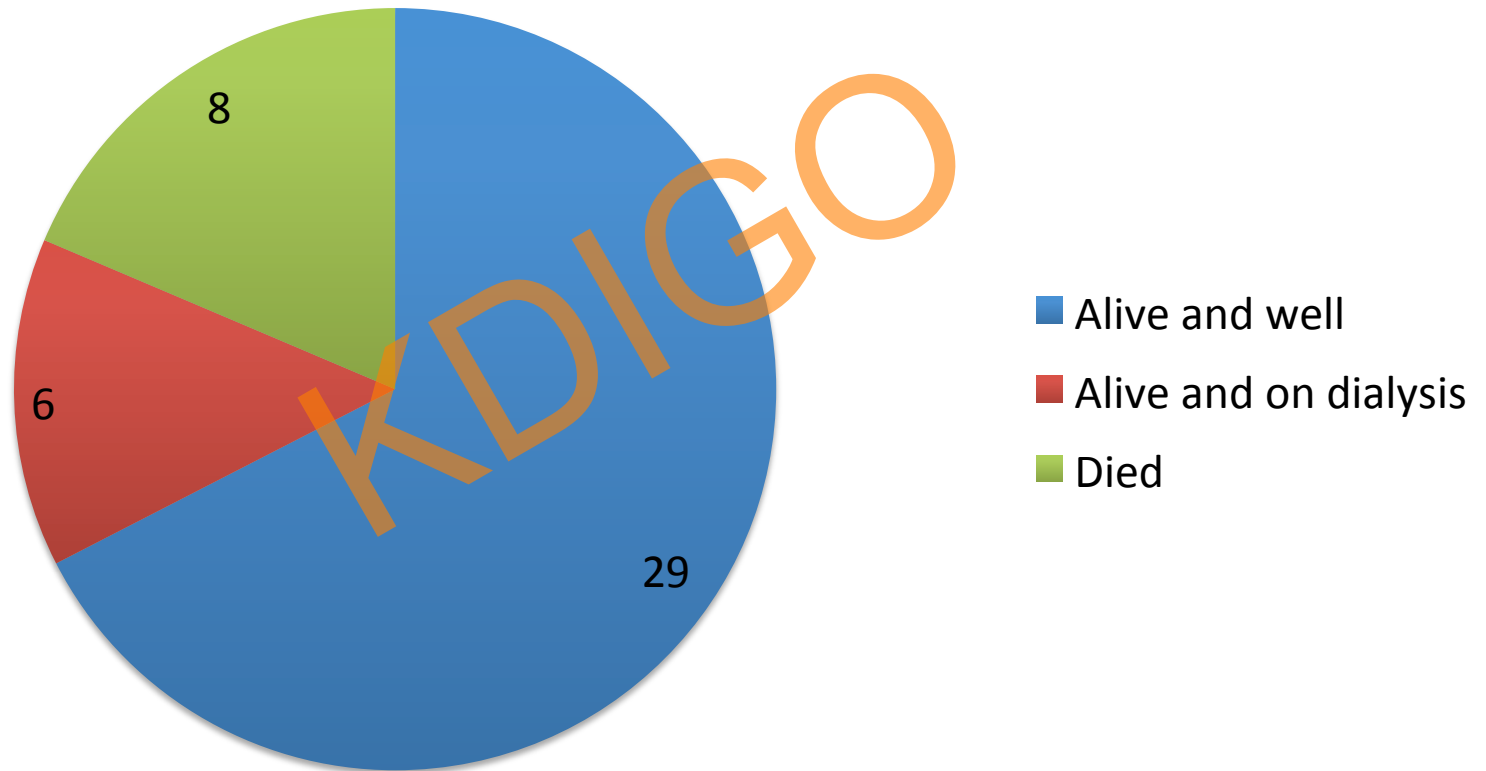
HIV-Positive-to-HIV-Positive Kidney Transplantation — Results at 3 to 5 Years

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.

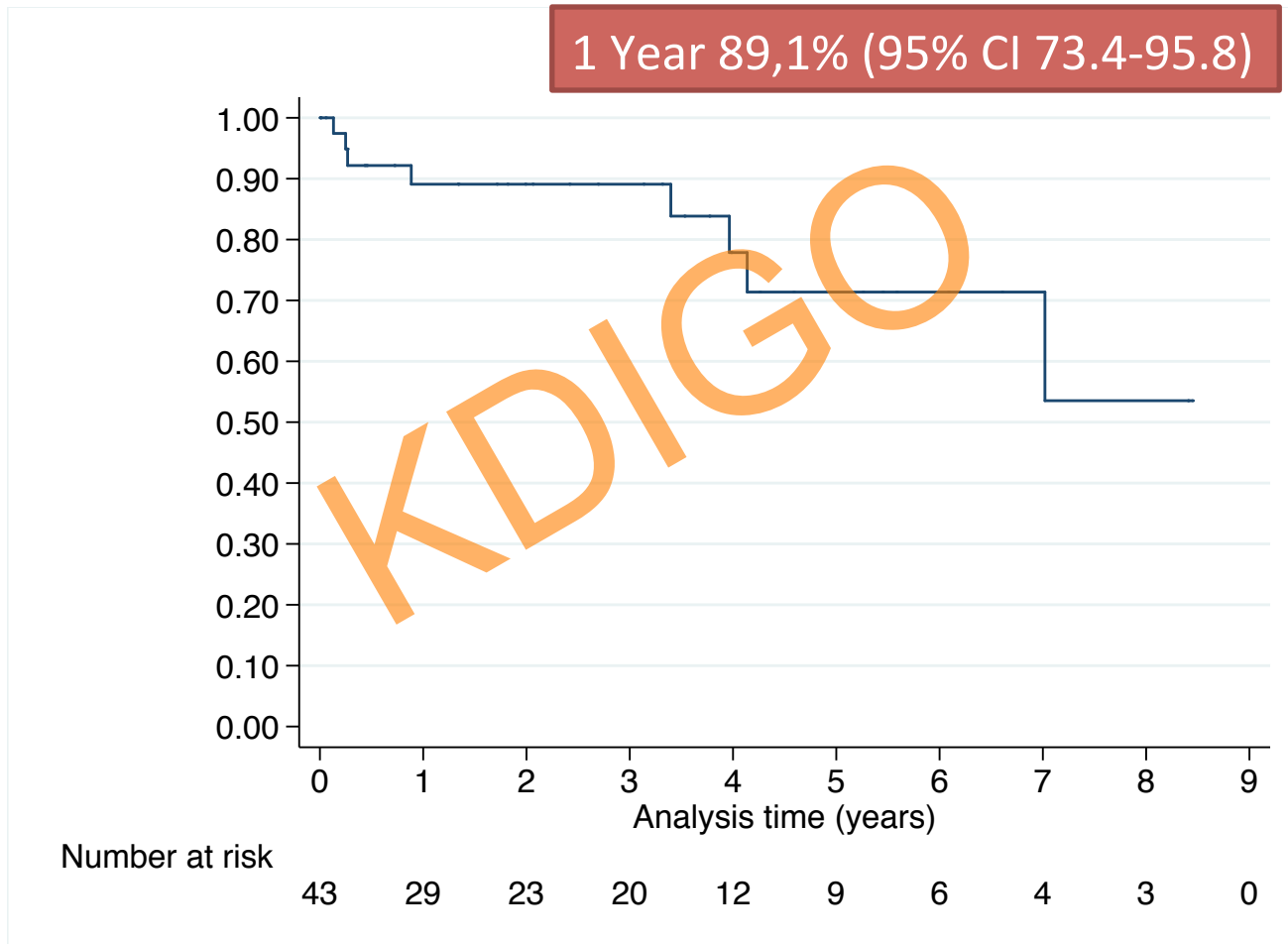
N Engl J Med 2015; 372:613-620 | [February 12, 2015](#) | DOI: 10.1056/NEJMoa1408896

Slides courtesy Mignon McCulloch x 3 →

Patient outcomes

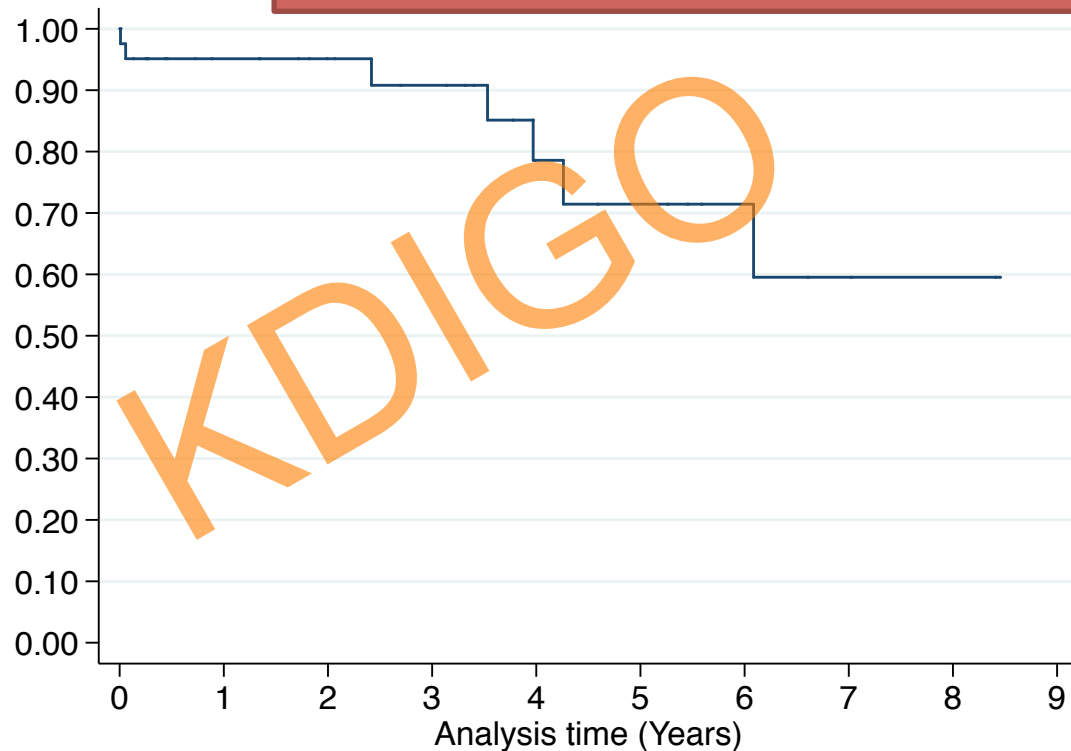


Patient Survival



Graft Survival

1 year graft survival 95,12% (95% CI 81.9-98.8)



Number at risk

43 29 23 20 11 9 6 4 3 0

MONDAY 30/1/17

INCREASE IN INCURABLE TB

Address poverty, HIV to stem TB

Lisa Isaacs

Research Council president

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

ve Professor
d: "The rise
and TB in
res the need
overcrowd-
epidemic in
ly.
ises the need
containment
ll curb trans-
led.
were almost
t MDR TB
734 reported
cin-resistant
outh Africa,
ly 8% were
tensively or
stant.

more than half the discharged patients with incurable TB remained alive for an average of only 16 months.

"These highly infectious patients were associated with the downstream generation of further cases of incurable TB," Dheda said.

The study utilised DNA sequencing and aerosol sampling technology. Incurable TB refers to an almost totally drug-resistant type of TB, which has begun to supplant existing multidrug-resistant tuberculosis (MDR TB) and XDR-TB. MDR-TB refers to resistance to the two main TB antibiotics in the TB treatment regimen, while XDR-TB presents resistance to four key TB antibiotics.

Incurable TB cases have now been documented in several countries including

Further resistance to the drugs used to treat extensively drug-resistant disease has resulted in patients for whom a treatment regimen cannot be constructed with the drugs available in the national programme. And who thus have programmatically untreatable tuberculosis.

Estimates from Africa, Russia, India and China suggest that treatment fails to cure 30-75% of patients with extensively or totally drug-resistant tuberculosis.

TB researchers suggest that urgent action, including rapid diagnosis, wider access to newer and repurposed drugs, and bolstering home-based care and building long-term community stay facilities for patients are pivotal to address the rising transmission and infection rates of

MONDAY 30/1/17

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 273 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 Keertan Dheda said

more than half of patients with TB remained alive after only 16 months.

"These high mortality rates are the downstream result of further cases of TB," Dheda said.

The study used DNA sequencing and genotyping technology. TB refers to a disease caused by drug-resistant TB which has been an existing multiple drug-resistant tuberculosis (MDR-TB, XDR-TB, MDR-TB).

Resistance to TB antibiotics is a major problem. The standard treatment regimen, while XDR-TB presents resistance to four key TB antibiotics.

Incurable TB cases have now been documented in several countries including

Research Council president and chief executive Professor Glenda Gray said: "The rise of incurable TB, and TB in general, underscores the need to address poverty, overcrowding and the HIV epidemic in Africa and globally.

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

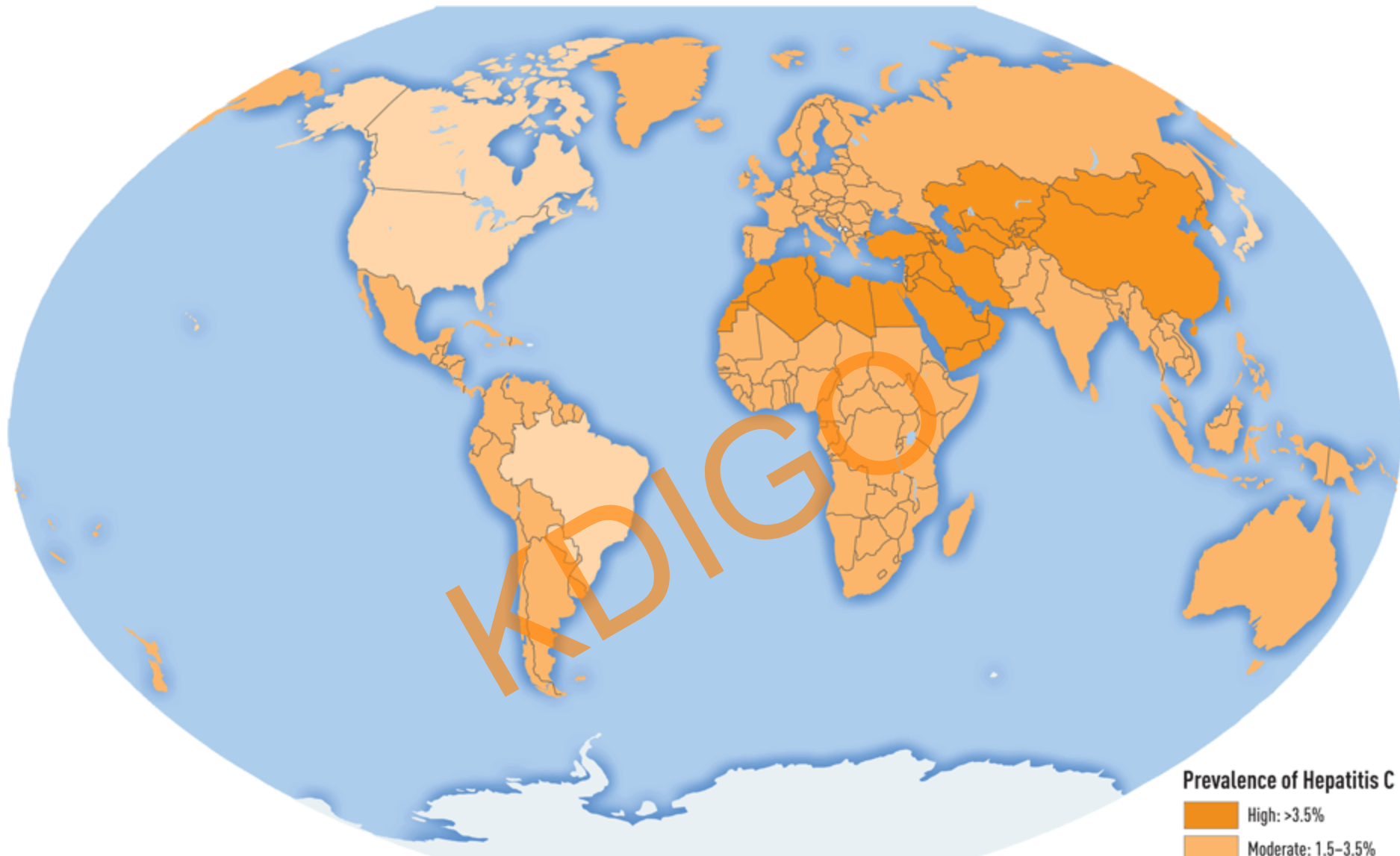
In 2014 there were almost 500 000 cases of MDR TB globally, with 18 734 reported cases of rifampicin-resistant or MDR TB in South Africa, of which roughly 8% were thought to be extensively or totally drug resistant.

Estimates from Africa, Russia, India and China suggest that treatment fails to cure 30-75% of patients with extensively or totally drug-resistant tuberculosis.

drugs, and bolstering home-based care and building long-term community stay facilities for patients are pivotal to address the rising transmission and infection rates of

Vaccines....

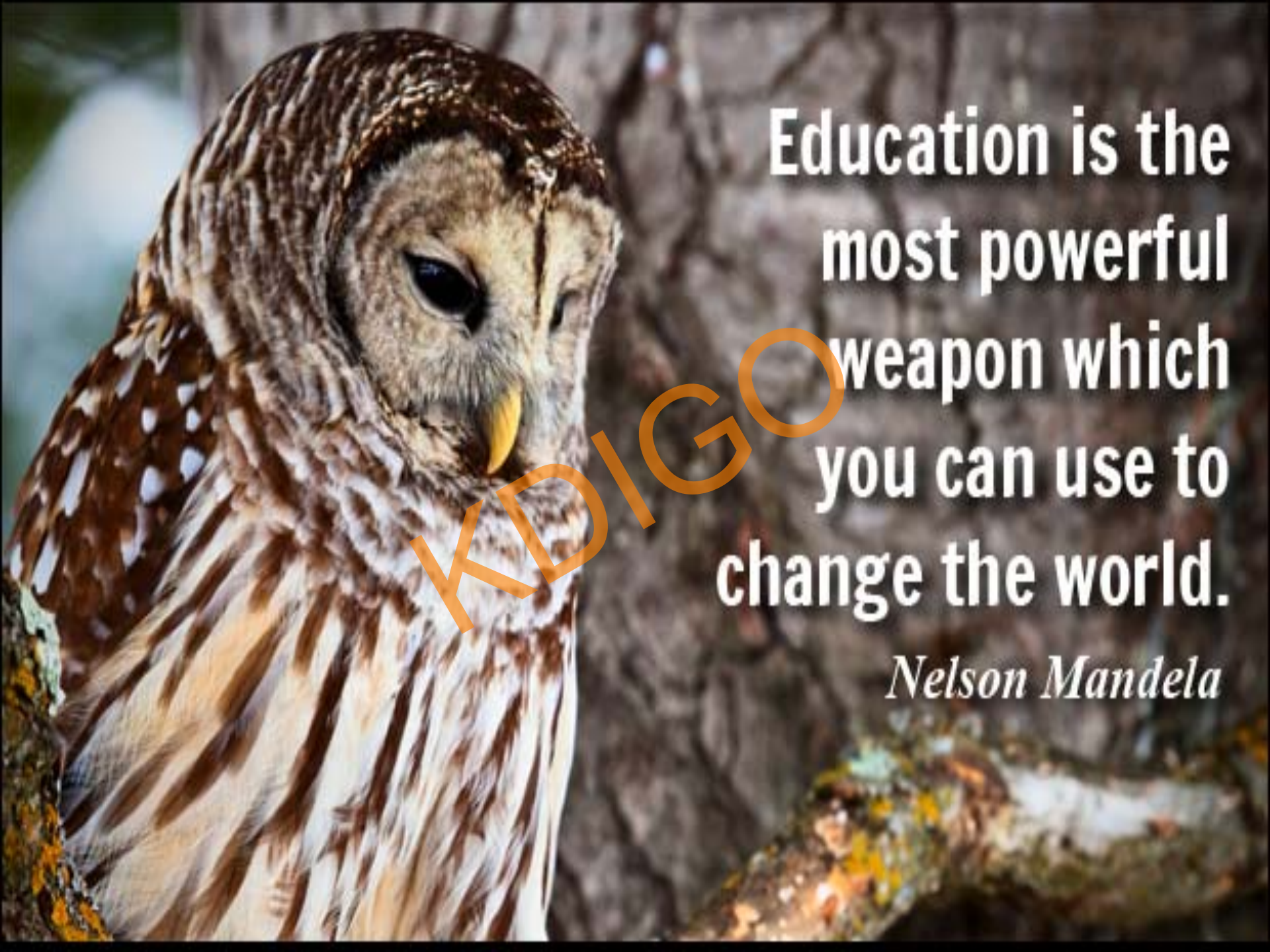
KIDIGO



Prevalence of Hepatitis C

- High: >3.5%
- Moderate: 1.5-3.5%
- Low: <1.5%
- No Data

WHO 2016



**Education is the
most powerful
weapon which
you can use to
change the world.**

Nelson Mandela