HIV and CKD: 2021 Update

Meghan Sise, MD, MS
Renal Associates, MGH

HOPE conference
July 13, 2021

Financial Disclosures

- None related to the material in this talk

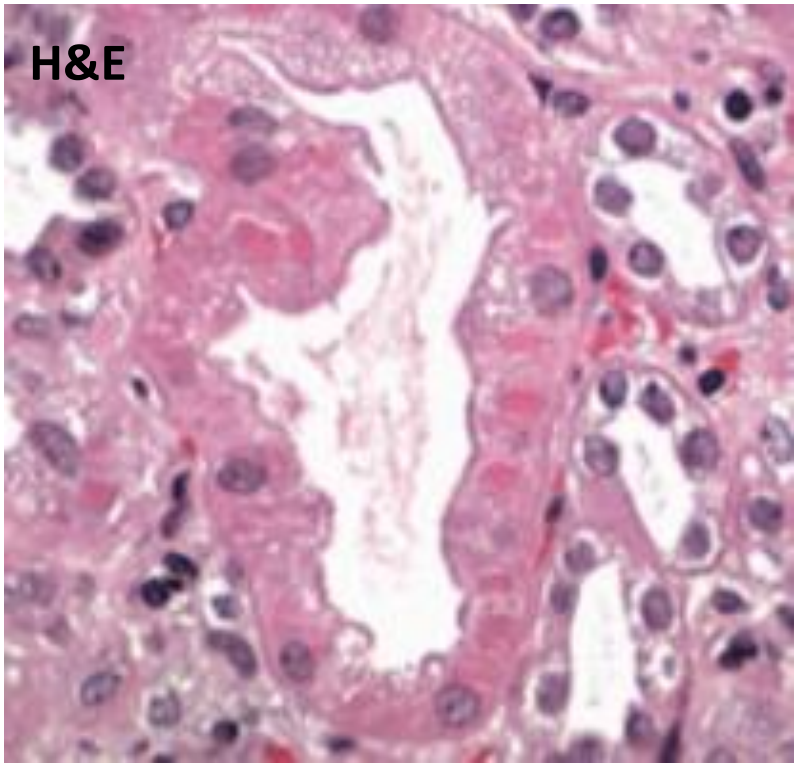
Case 1: Should I stop the tenofovir?

- 67 yo M with CAD, Crohn's disease diagnosed with acute HIV in 2014 (presented with febrile illness, CMV viremia and acute HIV diagnosed) immediately began ARVs and has been well controlled referred for evaluation of proteinuria.
  - Minimal symptoms, slight weight gain, low energy
- TDF/FTC/DRV/r until October 2016 → TAF/FTC/RPV
- Creatinine 1.3 (stable)
- UPC 8 grams, Alb/Cr 5.6 grams
- Albumin 2.7

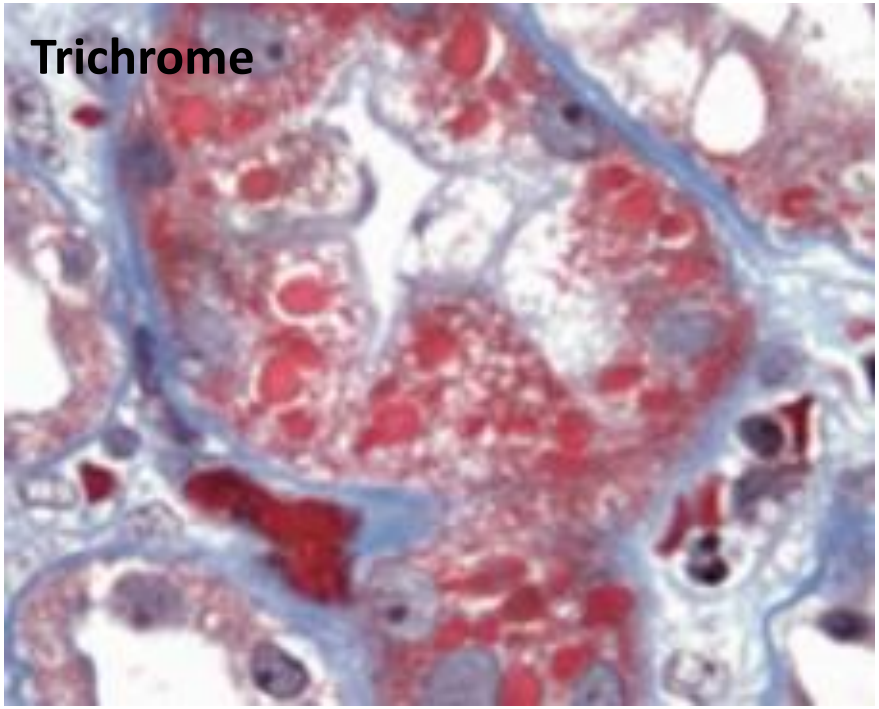
Case 2: Should I stop the tenofovir?

Tenofovir nephrotoxicity - Pathology

- prominent eosinophilic intracytoplasmic inclusions – Giant mitochondria - within PTE cells



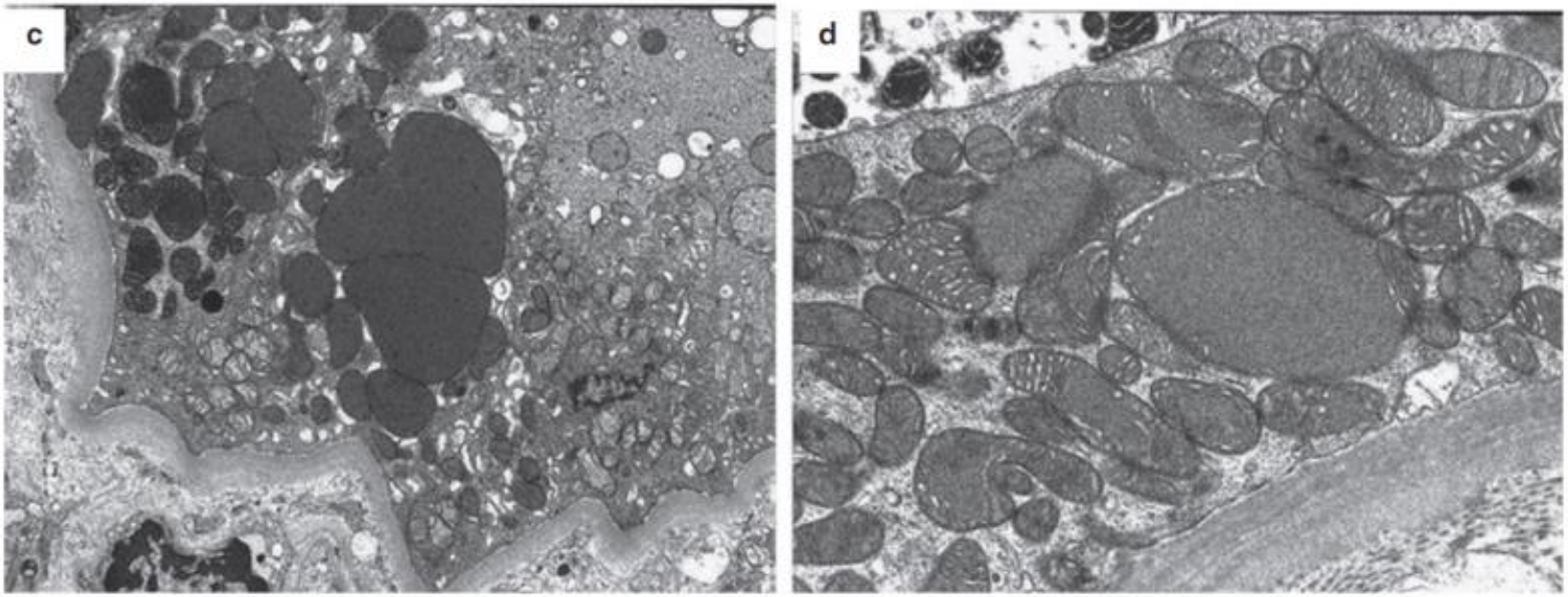
Herlitz L. KI. 2010



PAS and Silver stain normal

Tenofovir

- Inhibitor of mitochondrial DNA *γ*-polymerase
- Changes in mitochondria size and shape, clumping, loss/disorientation of cristae, mitochondrial depletion



Herlitz L. KI. 2010

Tenofovir

- When injured proximal tubular cells fail
  - reabsorbing low-molecular-weight proteins
    - vitamin D-binding protein (DBP)
    - *β*2-microglobulin
  - reabsorbing glucose through the Na/gluc cotransporter 2
  - Reabsorbing aminoacids, phosphate, uric acid
  - mitochondrial 1α-hydroxylase
  - Decreased ammoniagenesis
  - reabsorbing low-molecular-weight proteins

Proteinuria in Tenofovir toxicity

- Glomerular proteinuria
  - Loss of filtration barrier
  - Protein composition mirrors the plasma composition
  - Predominantly albumin > 67%

- Tubular proteinuria
  - Low molecular weight proteins
  - Retinol binding protein, n-acetyl-glucosaminidase, B-2-microglobulin, a-1-microglobulin
  - Typically unmeasured proteins

Proteinuria in Tenofovir toxicity

Urine albumin to total protein ratio (UAPR)

- Normally ~0.67
- Glomerular etiology > 0.4
- Tubular etiology < 0.4
- Sensitive 88% and specific 99% for tubular etiology

– Typically unmeasured proteins

Smith ER. *Nephrol Dial Transplant* 2012,**27**:1534-1541

Proteinuria in Tenofovir toxicity

Urine albumin to total protein ratio (UAPR)

- Normally ~0.67
- Glomerular etiology > 0.4
- Tubular etiology < 0.4
- Sensitive 88% and specific 99% for tubular etiology

Urine albumin-to-protein ratio (UAPR) - 0.18 (0.14-0.19)

– Typically unmeasured proteins

Sise ME. *AIDS.* 2015

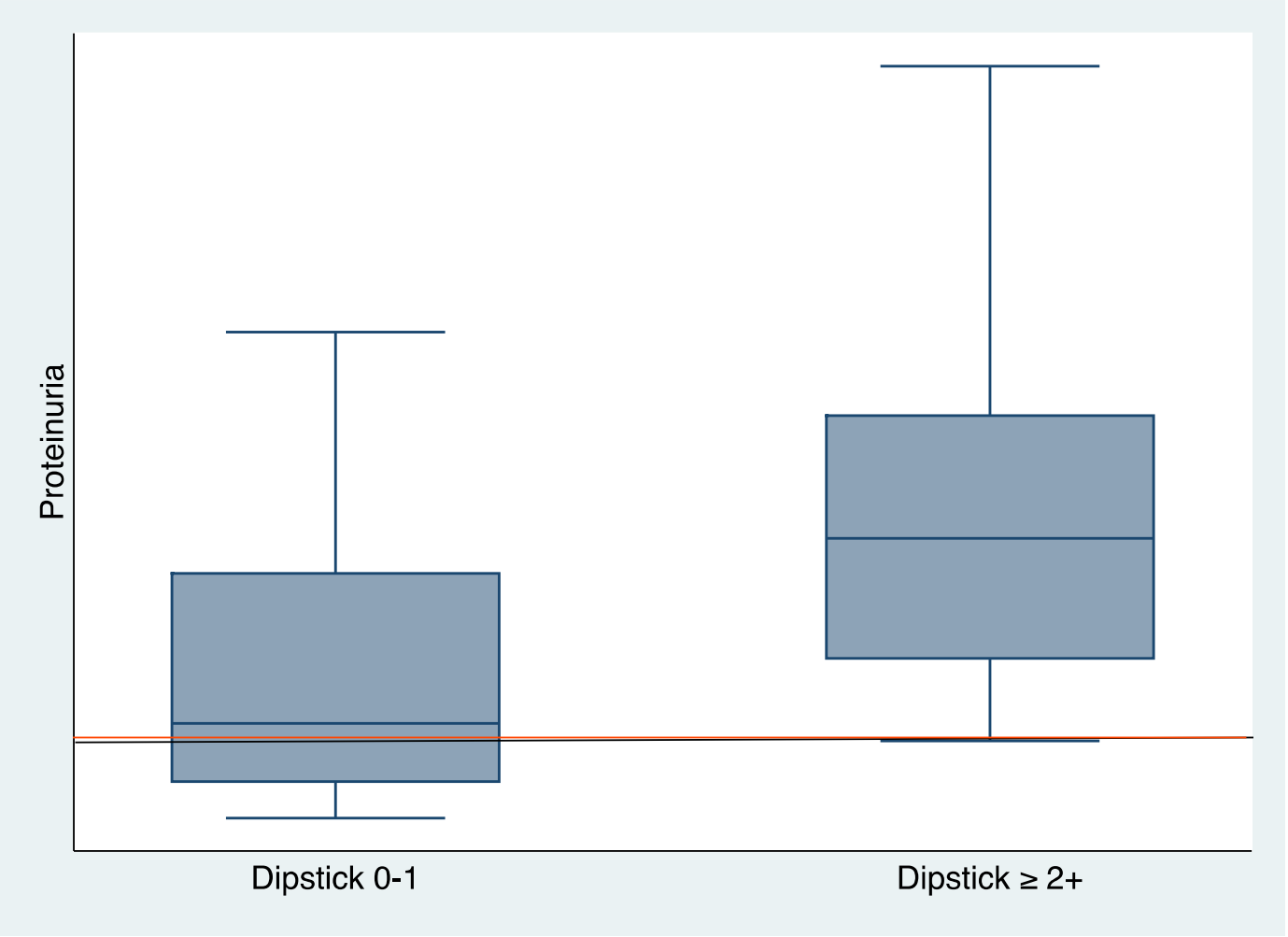
Proteinuria in Tenofovir toxicity

Parameter	Median (IQR) or %
Urinary Findings Urine dipstick (n = 37) 0-trace 1+ 2+ 3+ or greater Hematuria	 8% 32% 35% 24% 53%
Urine protein quantification 24 hour measurement (n=17) Spot protein-to-creatinine ratio (n=15)	 1742mg (1200-2000) 1667mg/g Creatinine (851 – 2301)
Urine albumin quantification (n=10) **	235mg/gCr (136-299)

Urine albumin-to-protein ratio (UAPR) - 0.18 (0.14-0.19)

Insensitivity of Urinary Dipstick

- 1000mg/g



113mg/millimole

Take Home Point

- Tenofovir causes tubular damage this will lead to tubular proteinuria that may be missed by dipstick
- Consider sending quantitative spot urine ratio
  - Urine protein
  - Urine albumin
  - Urine creatinine
- A low Urine Albumin/Total Protein ratio (<0.4) in the presence of high total urine protein suggests potential for significant tubular damage
- Where to set the proteinuria cutoff?
  - No data to guide this decision
  - >200-300mg/g (30mg/millimole) may be too conservative?

Tenofovir toxicity – risk factors

Table 3: Predictors of significant renal function decline.

Preexisting renal impairment
Older age
Advanced HIV disease
Vasculometabolic disease
Concomitant use of nephrotoxic drugs or protease inhibitors
Low body weight
ABCC2 gene (encoding the outward tenofovir transporter MRP-2) polymorphisms

TDF nephrotoxicity - PREP

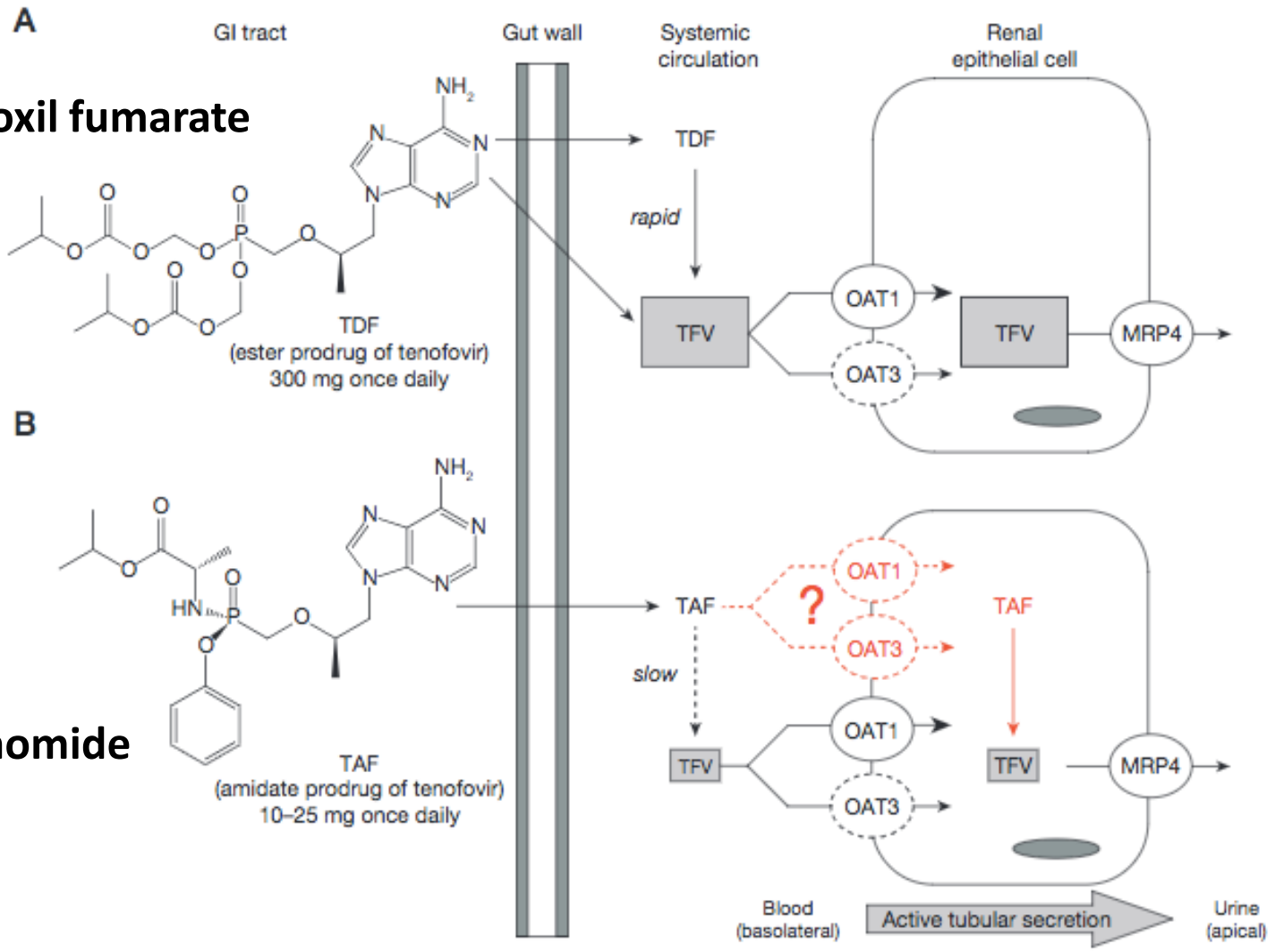
- Small, but significant change in eGFR (~2-4%)
- TDF-based PrEP resulted in a small change fro baseline that was nonprogressive for 36 months and not accompanied by a significant increase in the likelihood of a clinically relevant change in eGFR (ie, ≥25%) (<2% at 12 mo)
- Kidney injury biomarkers at 12 months did not correlate with clinical outcomes

Mugwanya Jama Intern Med 2015. Nickolas AIDS 2021

TDF vs. TAF

Tenofovir disoproxil fumarate

Tenofovir alafenomide



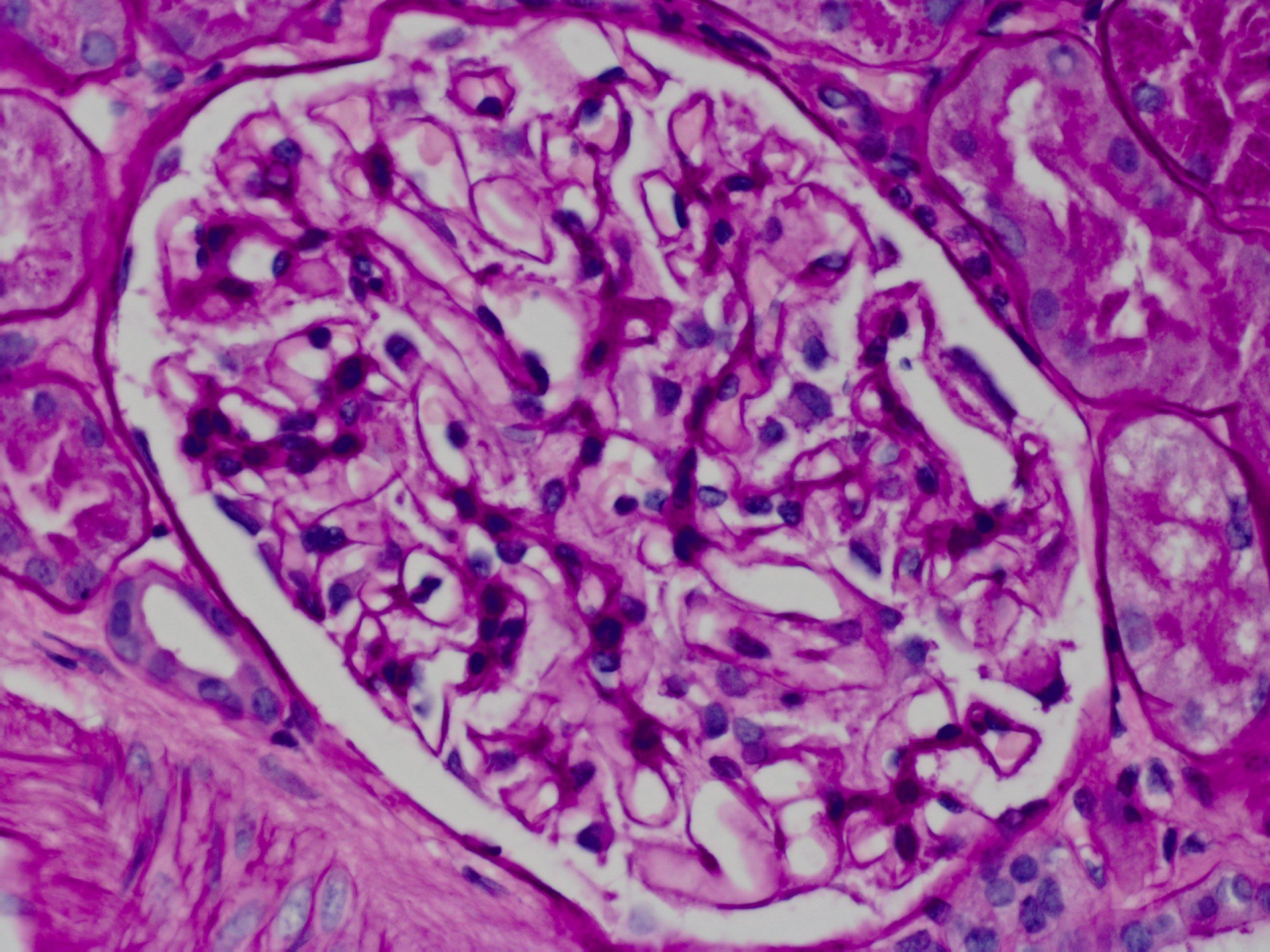
Bam R, et al. Antivir Ther. 2014;19(7):687-92

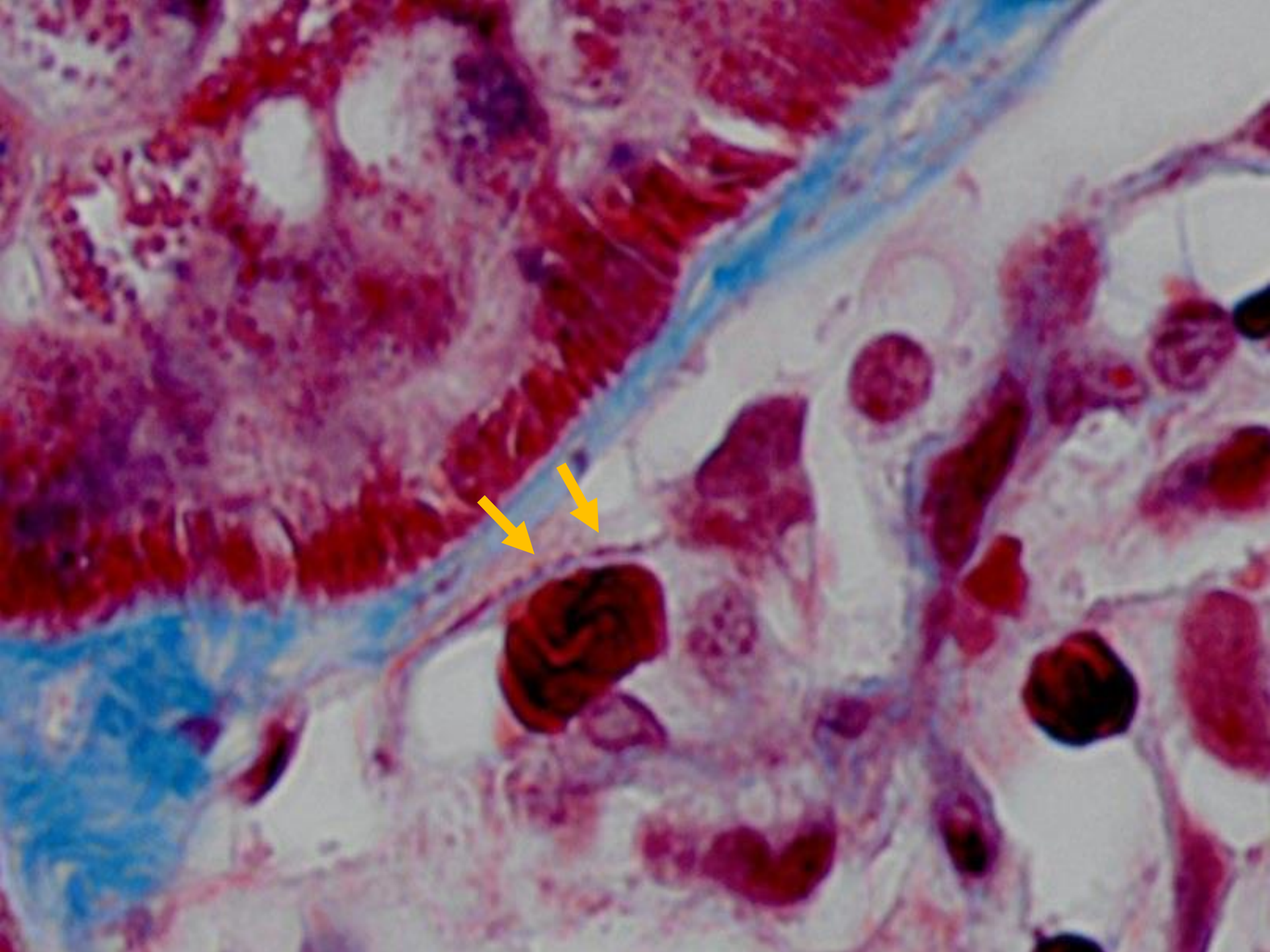
TAF in CKD

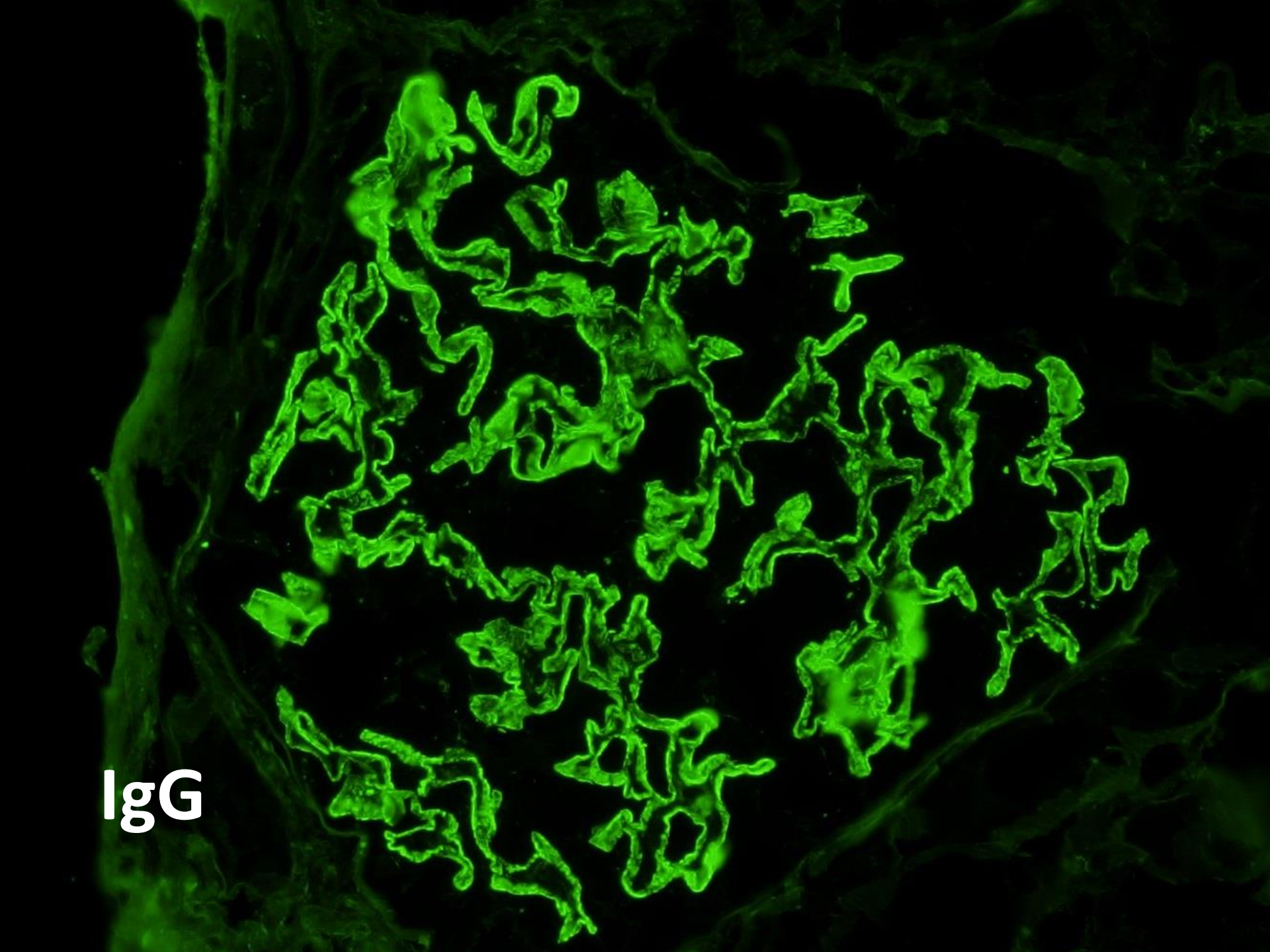
- Data seems to be safe for GFR 30-59
- Below 30, pharmacokinetic data suggests that tenofovir levels are similar to those seen in patients getting TDF
- No data for situations like the case presented...
  - Two risk factors for high TFV exposure: 1) Low GFR 2) Boosted PI
- My experience:
  - The majority have full resolution of proteinuria.
  - Some with low baseline GFR and boosted PI may not improve

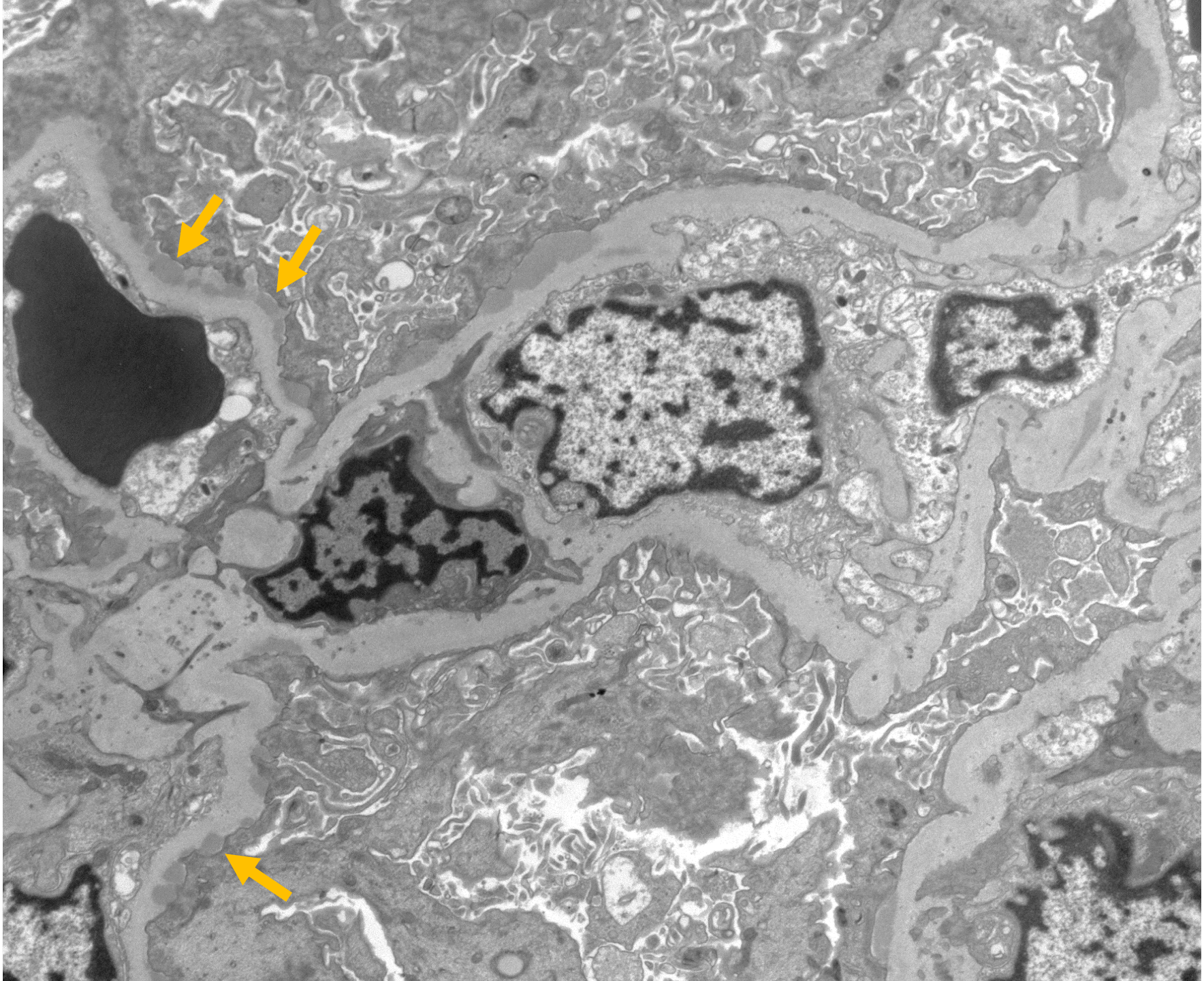
Back to our case

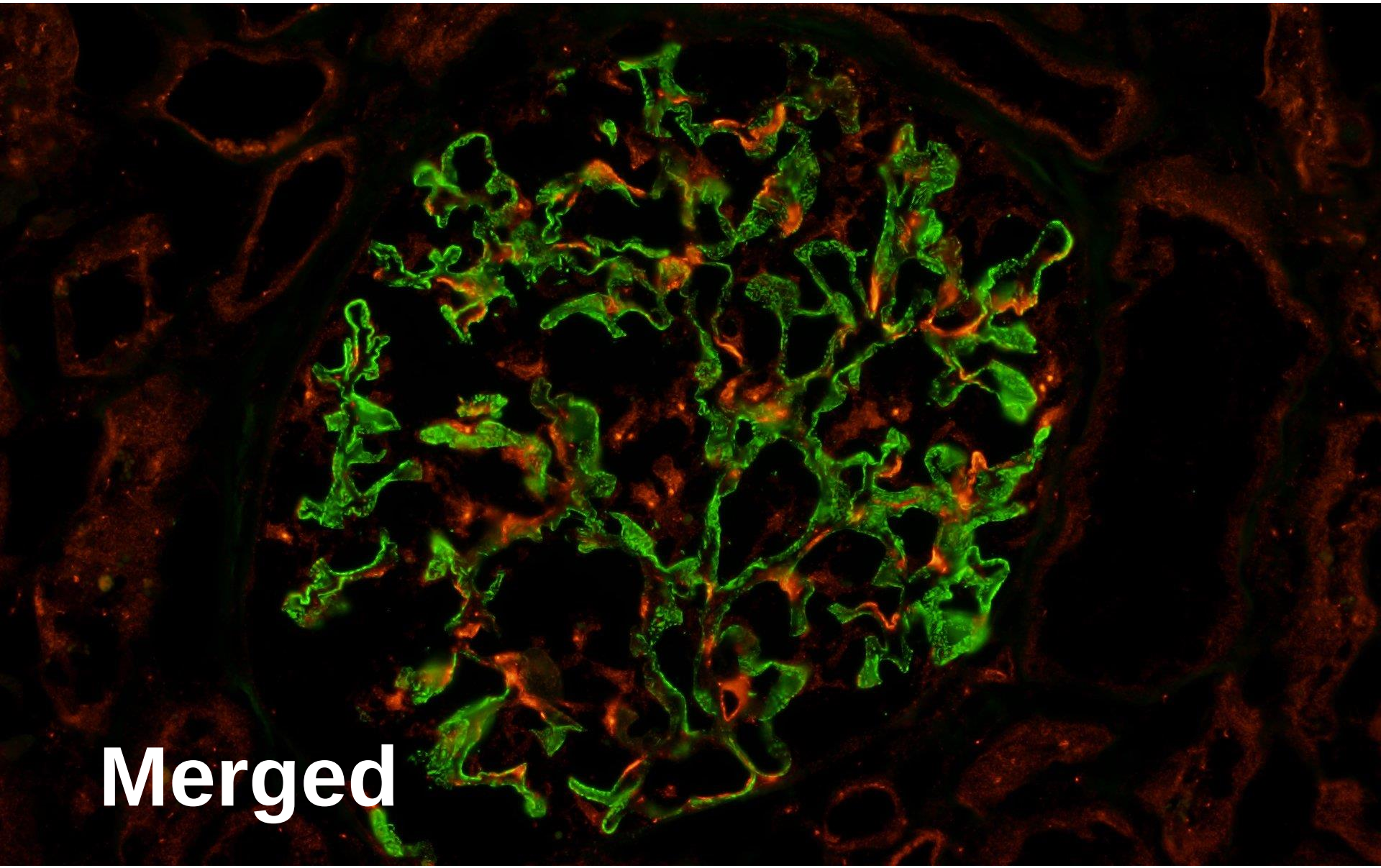
- Nephrotic syndrome






IgG




Merged

Diagnosis

Non-PLA2R type Membranous glomerulopathy,

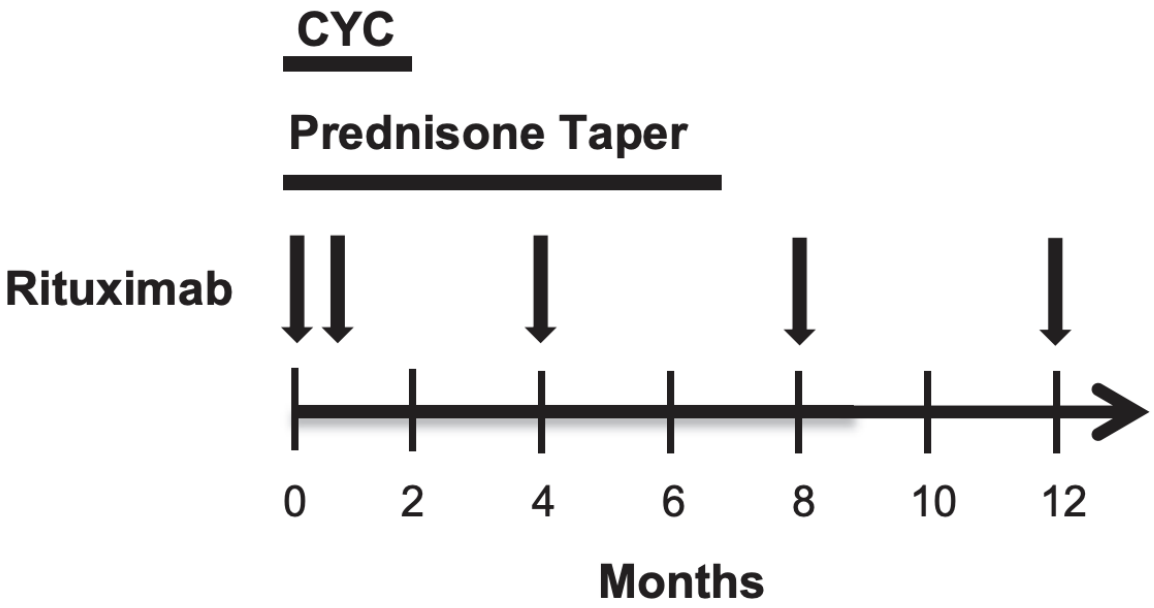
Arteriosclerosis

- 19% global sclerosis (5/27)
- 5% interstitial fibrosis and tubular atrophy

Case List

Case 1: Treatment of Membranous nephropathy in HIV

- Membranous nephropathy



  - Full remission within 3 months
  - Current creatinine 1.4, UPC 0.09

Immune complex diseases in HIV

- IGAN → Immunosuppression (per standard criteria)
- Lupus-like nephritis → Immunosuppression (Prednisone and MMF)
- Lupus nephritis → Immunosuppression (Prednisone and MMF)
- Membranous nephropathy in the setting of HIV
  - Evaluate for HBV
  - Check PLA2R status → Immunosuppression (Rituximab-based)
  - Exclude secondary causes → Malignancy resection (if detected)
- MPGN
  - Evaluated if HCV-related and treat → DAAs
- Infection-related GN
  - Post strep or staph associated → Antimicrobials, surgery
- Immunotactoid
  - Look for paraprotein related disease → Chemotherapy

Case 2

- 71 yo Hispanic man with a history AIDS dx 1999, now well controlled on ARVs, HTN, diabetes, gout and stage 3 CKD was was referred to me due to progressive renal failure.

- ROS: two weeks of worsening R flank pain

Case 2

- Past medical history:
  - Hypertension
  - Gout
  - Hypercholesterolemia
  - AIDS – dx w CD4 41, no OI
  - Obesity
  - Diabetes - > 15 years
  - CKD – creatinine 1.7-2.0 as far back as 1999, 700mg of albuminuria two years prior

Case 2

- Past medical history:
  - Hypertension
  - Gout
  - Hypercholesterolemia
  - AIDS – dx w CD4 41, no OI
  - Obesity
  - Diabetes - > 15 years
  - CKD – creatinine 1.7-2.0 as far back as 1999, 700mg of albuminuria two years prior

Taking a detour

- Renal disease in a diabetic

Taking a detour

- Renal disease in a diabetic
  - Diabetes is common
  - Sharma et al. 2500 kidney biopsies
  - 25% of all kidney biopsies are done in diabetics
    - 1/3 DN alone
    - 1/3 Other kidney disease
    - 1/3 DN + Other

- Clin J Am Soc Nephrol 8: 1718

Taking a detour

- Renal disease in a diabetic
  - Clinical syndrome that often prompts a biopsy in a diabetic
    - Sudden onset of proteinuria
    - AKI
    - Short duration of DM
  - Clinical syndrome that does NOT predict finding an alternate dx
    - Nephrotic range proteinuria
    - Hematuria

Taking a detour

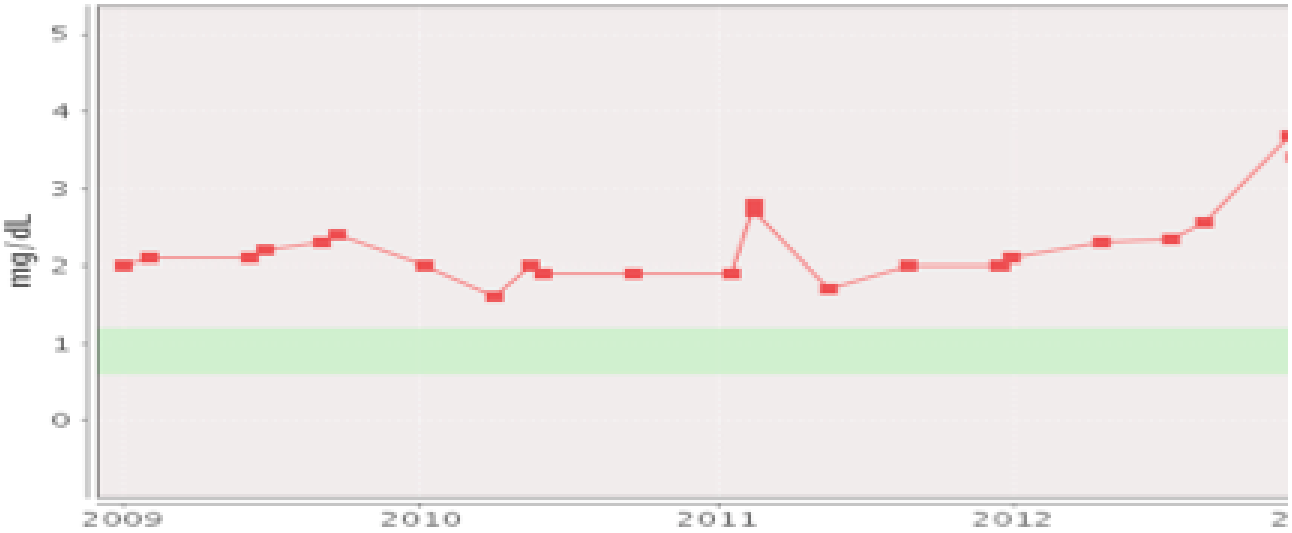
- Renal disease in a diabetic
  - "Other diagnosis"
    - ATN - ~30%
    - HTN nephrosclerosis – 18%
    - Secondary FSGS (hypertension, obesity) – 16%
    - Treatable stuff – 30%
  - DM ≥ 12 years was the best predictor of finding DN alone

History

- Allergies: ASA, PCN, Sulfadiazine
- Medications
  - Metoprolol 50mg BID
  - Rosuvasatin 20mg daily
  - Allopurinol 200mg daily
  - Fenofibrate 134mg daily
  - Abacavir 600
  - Lamivudine 300 one daily
  - Atazanvir 300mg daily
  - Ritonavir 100mg daily
  - Lisinopril 30mg daily
- Family: no family hx of renal failure

Labs

- August 2012 BUN/Cr 25/2.3, microalbumin 700mg/gm creatinine



- Dec 2012 – BUN/Cr -- 46/ 3.68
  -- UPC 89mg/dl/58mg/dl = ~1.5g/day
  -- no RBC or WBC on UA

Differential Diagnosis

- Progression of Diabetic Nephropathy
- ATN
- “Treatable alternative diagnosis”
  - I do a serologic workup in anyone with > 1G proteinuria

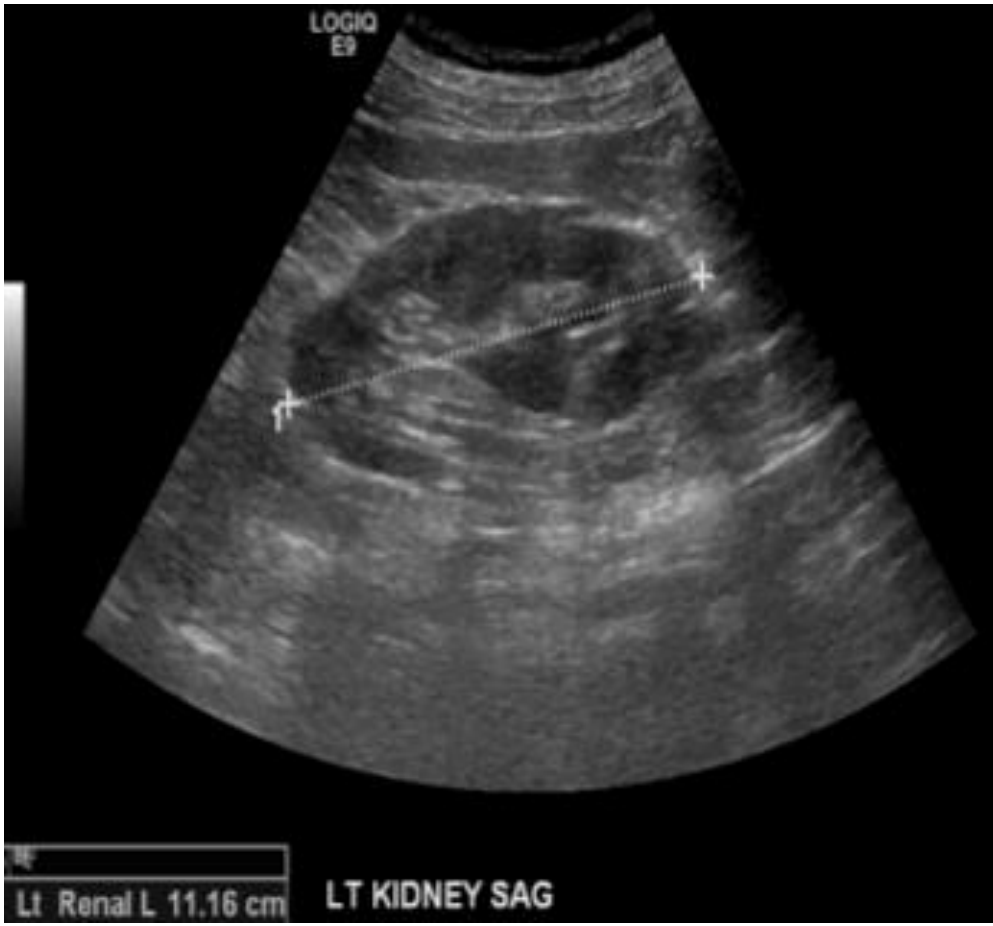
Differential Diagnosis

- Progression of Diabetic Nephropathy
- ATN
- “Treatable alternative diagnosis”
  - I do a serologic workup in anyone with > 1G proteinuria

- Right sided flank pain

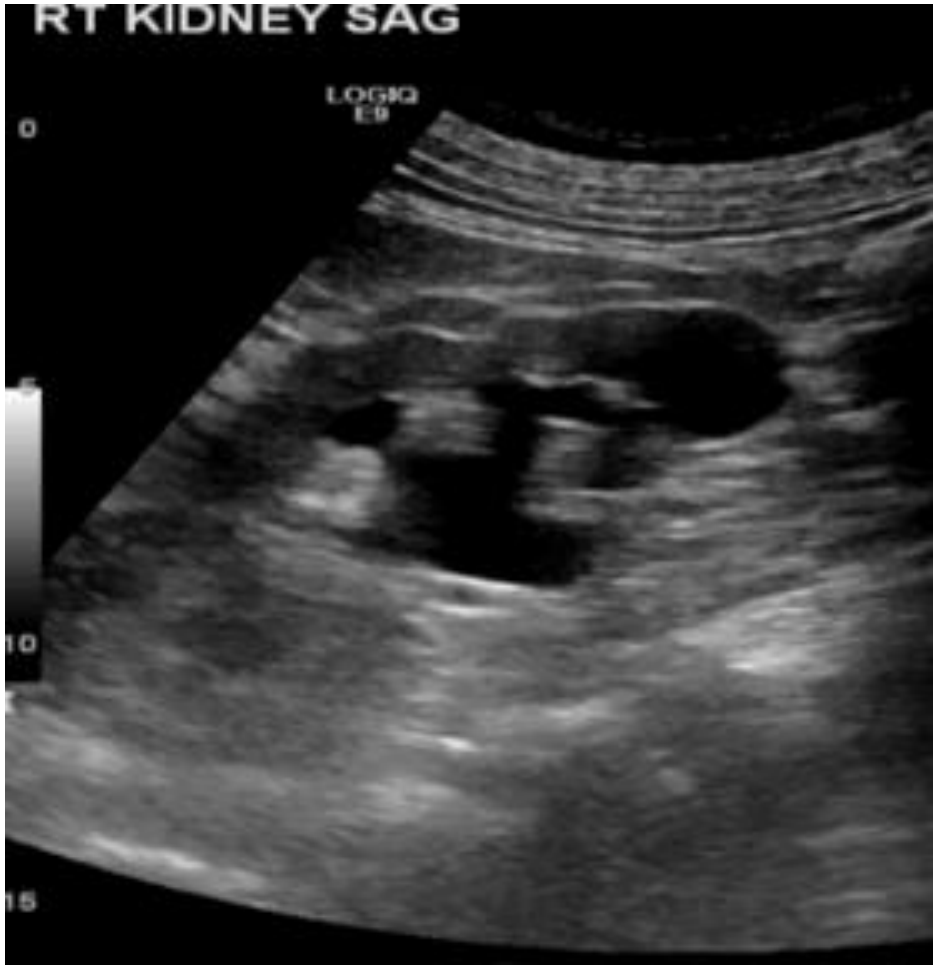
Imaging

- LEFT KIDNEY:
  - 11.6 cm in length.
  - mild cortical thinning
  - No hydronephrosis



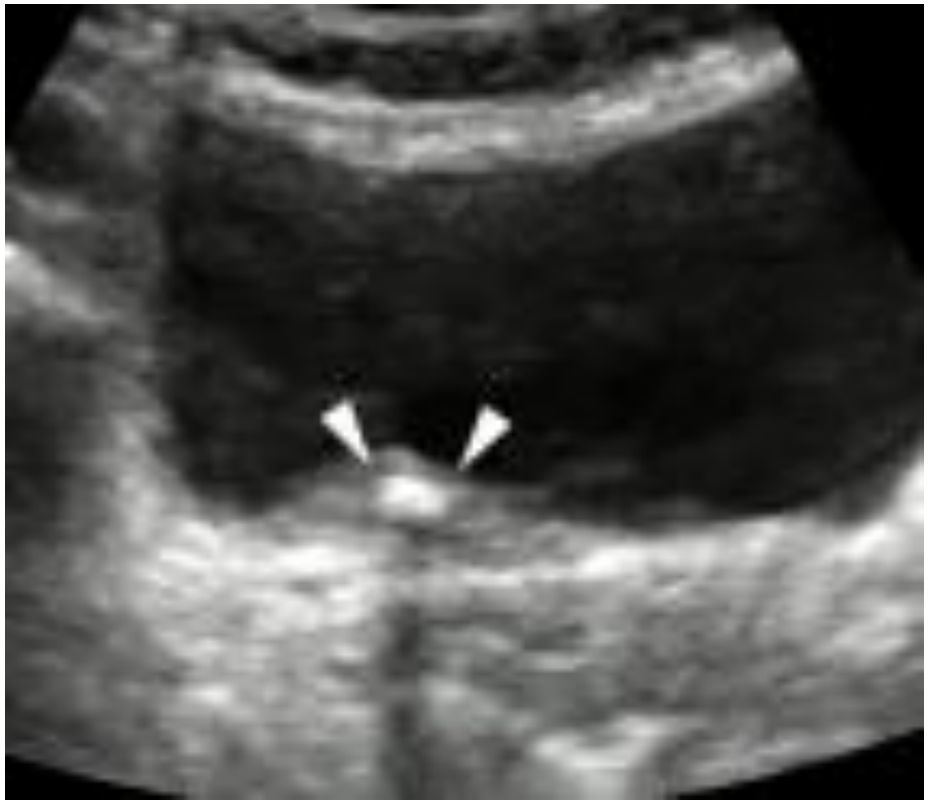
Imaging

- RIGHT KIDNEY:
  - 10.8 cm in length.
  - Mild-Mod hydronephrosis.
  - Right hydroureter
  - No calculus seen



No calculus seen?

Calcium based stone



Followup

- Urgent referral to Urology
- Two stage procedure
  - First just a stent

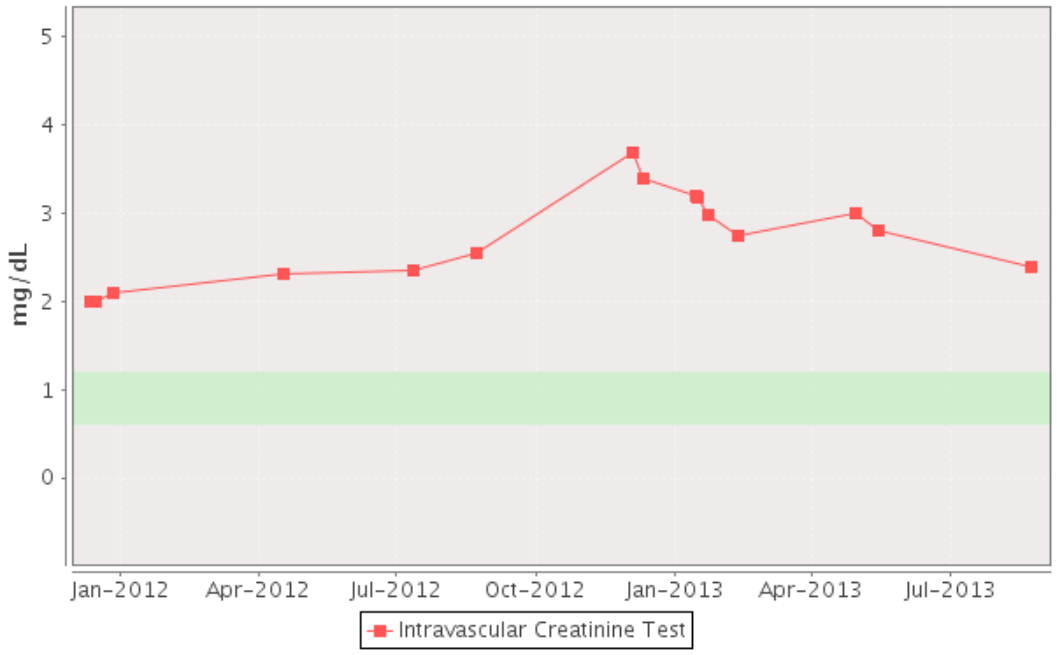
  10 days later
  - 4 stones removed from the ureter
  - Numerous small stones in the renal pelvis, aggreate over 2cm worth of stone
  - Dilation of UPJ stricture

- Stone composition: 100% Atazanavir

- Atazanavir changed to darunavir

Followup

- April 2013 – BUN/CR 37/2.9 UPC ratio 0.8
- August 2013 – BUN/CR 35/2.4



Indinavir vs. Atazanavir

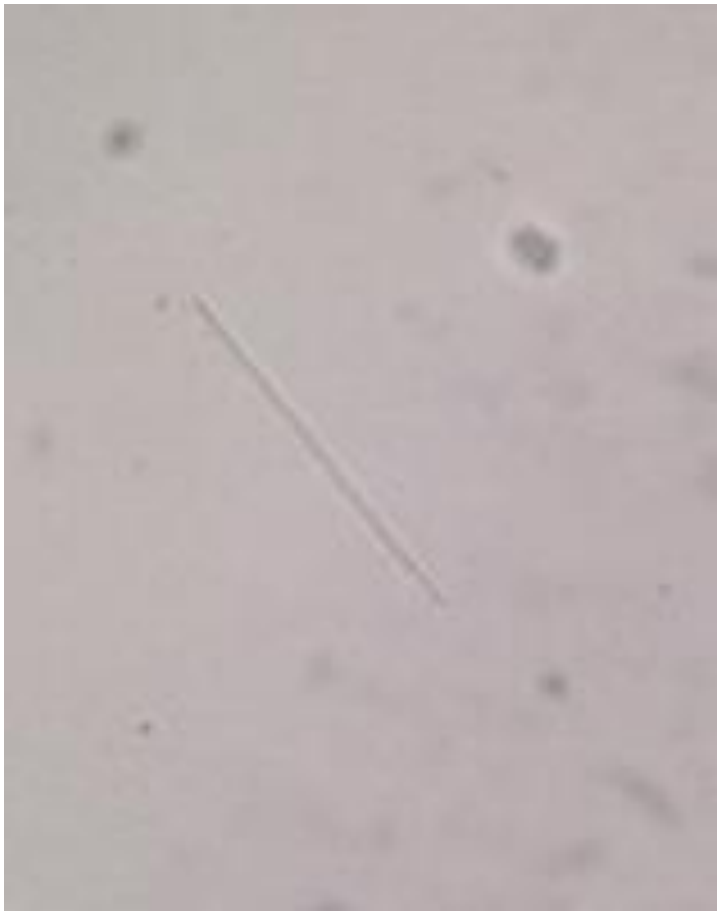
- Indinavir
  - 19% excreted unchanged in the urine
  - More soluble in acid urine
  - Renal colic in 8% of patients (Kopp Ann Intern Med 1997)

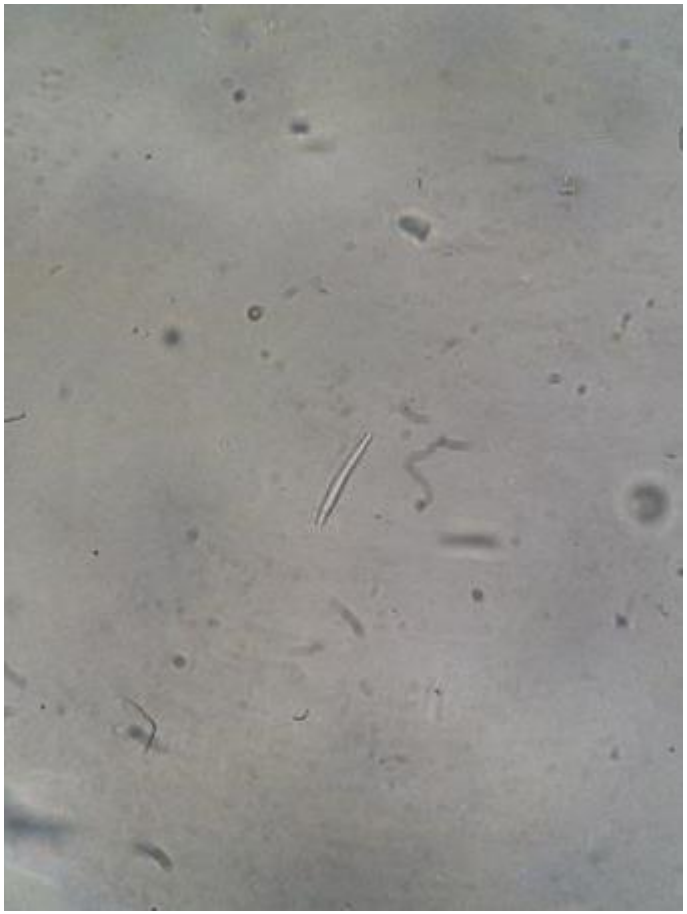
- Atazanavir
  - Approximately 7% is excreted unchanged in the urine
  - Solubility increases in acidic urine
  - Renal stones affect 1-2% of users (Rockwood AIDS 2011)
    - 4-fold increased risk compared to patients on other regimens

Atazanavir and Nephrolithiasis

- Atazanavir crystals
  - needle shaped
  - birefringent

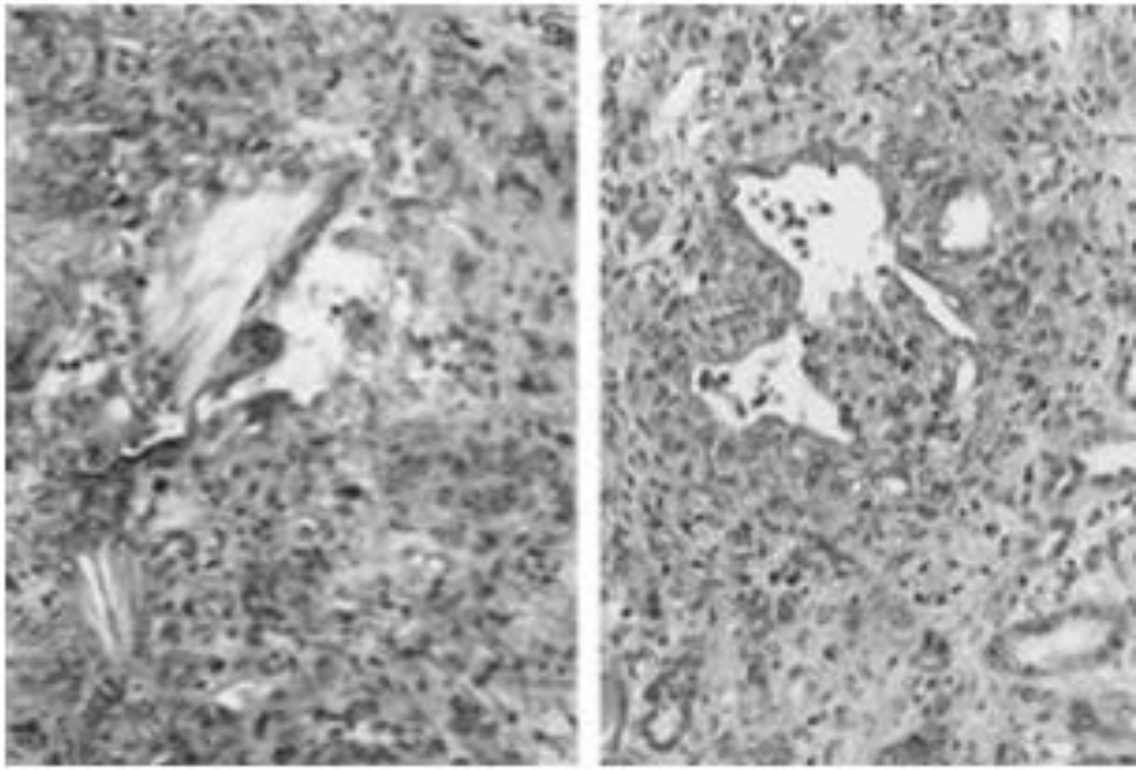
Patients Urine





Atazanavir and Nephrolithiasis

- Intra-tubular crystal precipitation has been confirmed by biopsy



Atazanavir and Nephrolithiasis

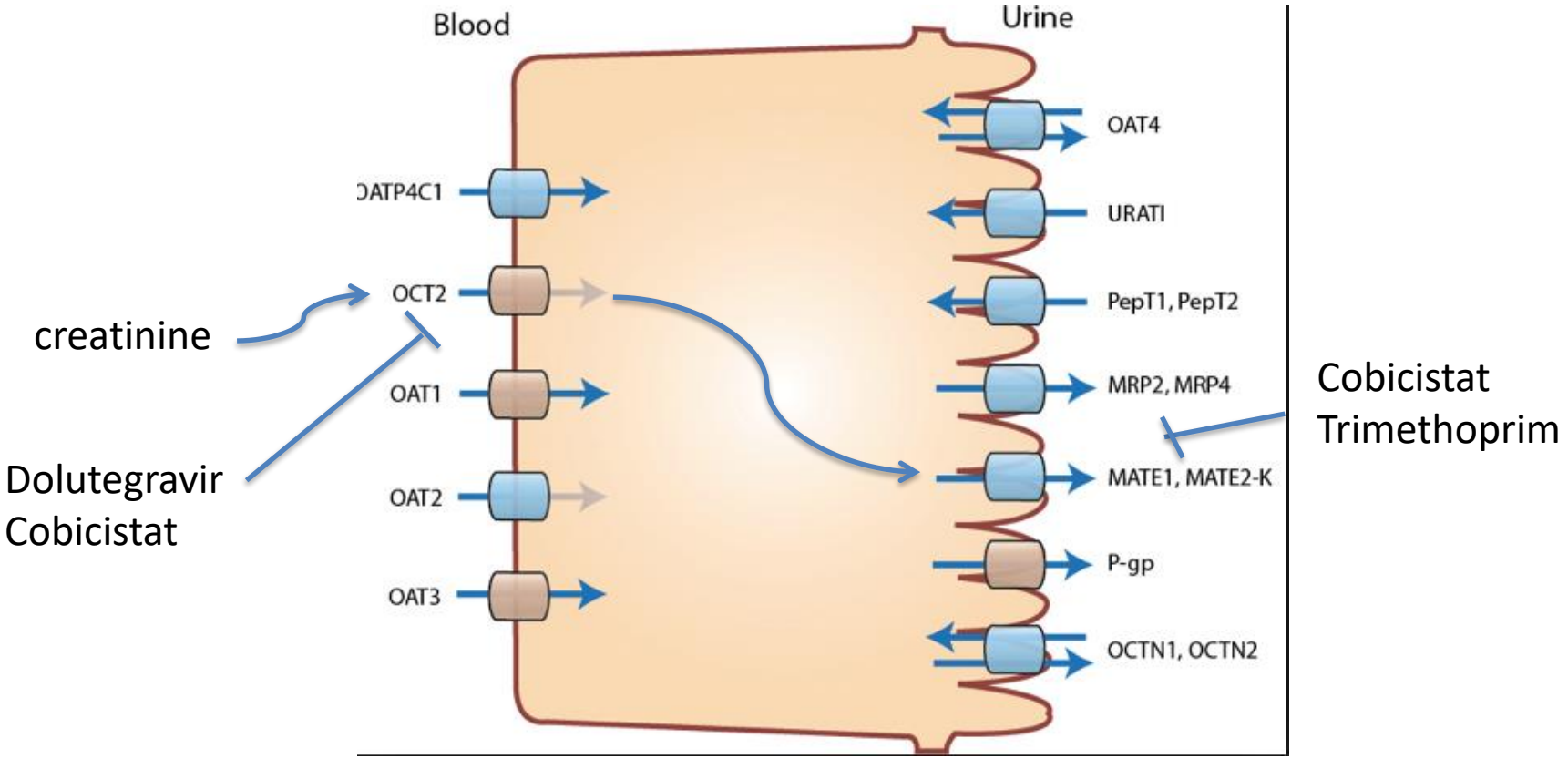
- Rockwood AIDS 2011 – England
  - Patients on ATZ/r (n=1206) vs. EFV/LPV/r followed 45 mo (n=4449)
  - 7.3 per 1000 patient yrs vs. 1.9
  - Stone diagnosis made only on radiologic basis (likely underestimated)
- Median time to stone = 30 months
- Some patients had stones even after ATZ d/c
- CKD and prior stones are most important RF
- Significantly increase Total Bili level - ? Predisposition to slower metabolism and higher drug levels

Atazanavir and Nephrolithiasis

- Hamada et al CID 2012 – single Japanese center
  - stones dx in 31 patients (23.7 cases per 1000 person-years) in the ATV/r group vs. 4 in patients (2.2 cases per 1000 person-years) in the other PIs group (n = 775).
  - adjusted hazard ratio, 10.44; P < .001)
  - 33% had recurrent stones if continuing ATV
  - No recurrent stones in patients discontinuing ATV

ARVs can affect creatinine secretion

- Cobicistat and Dolutegravir



MATE = Multidrug and Toxin Extrusion MRP = multidrug resistance protein

Cystatin C based eGFR

Cystatin C	Creatinine
Produced by all nucleated cells	Produced by muscle cells
Filtered then metabolized by tubules	Filtered but also secreted
Levels independent of muscle mass or diet	Levels depend on muscle mass and diet
Levels affected by hyper and hypo-thyroidism	Unaffected by thyroid activity
Levels increased by inflammation	Levels not increased by inflammation
More expensive	Cheap

Changing epidemiology of CKD

- CKD is common in HIV infected adults ~15-20% in US

- Its associated with significantly higher mortality

Multiple comorbidities

- 2854 HIV infected adults on ARV, case control

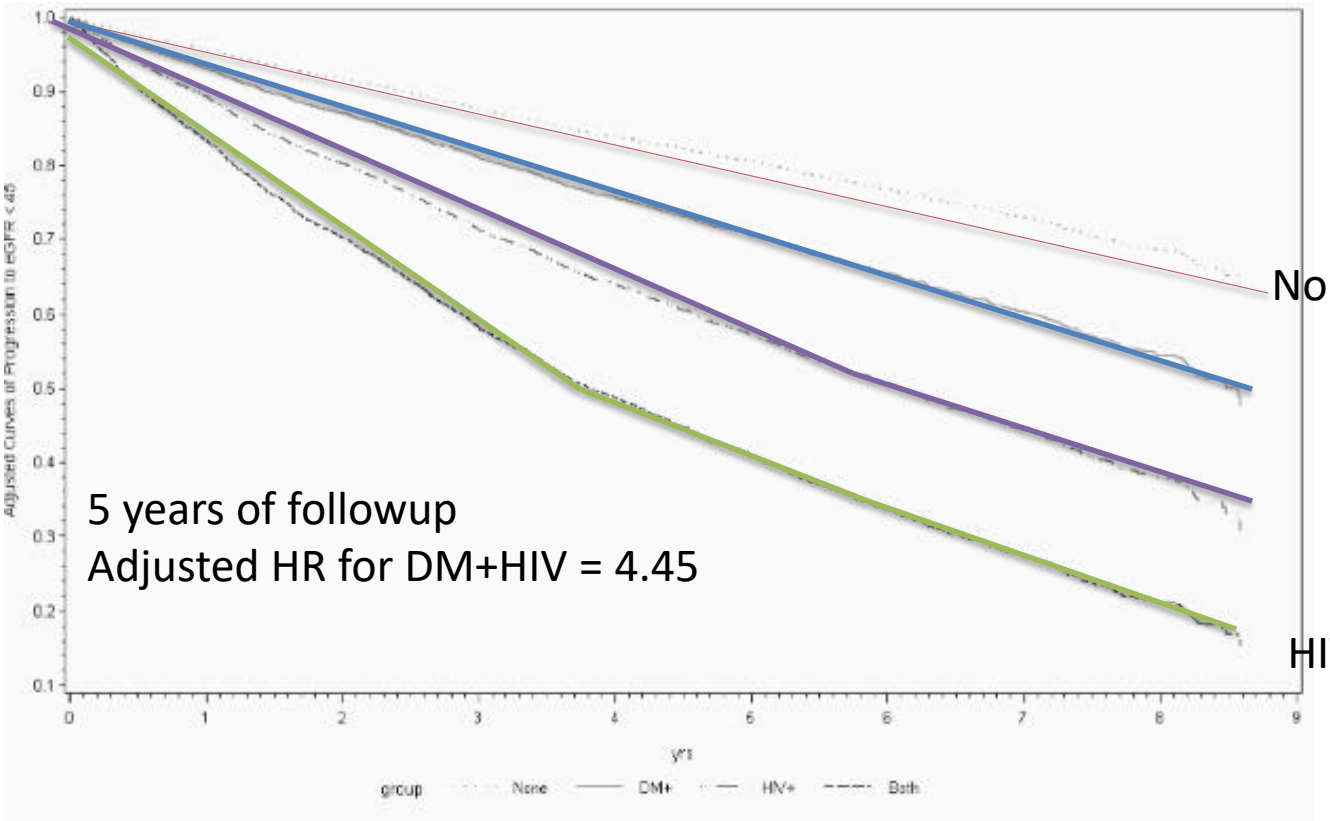
NICM, by age	HIV-infected patients (n = 2854)	HIV-uninfected controls (n = 8562)	*P* value
Renal failure			
≤40 years	18 (3.28%)	1 (0.06%)	<.001
41–50 years	90 (5.22%)	8 (0.15%)	<.001
51–60 years	41 (9.07%)	4 (0.29%)	<.001
>60 years	33 (24.26%)	2 (0.49%)	<.001

- 40-year-old HIV-infected patient had the same risk as a 55-year-old HIV-uninfected person of having multiple chronic medical conditions

Guaraldi G. Clin Infect Dis 2011;53:1120-6

Diabetes and HIV

31,000 veterans, 45% Black, progression to eGFR < 45



Medapalli JAIDS.2012 60(4): 393

HIV and Diabetes

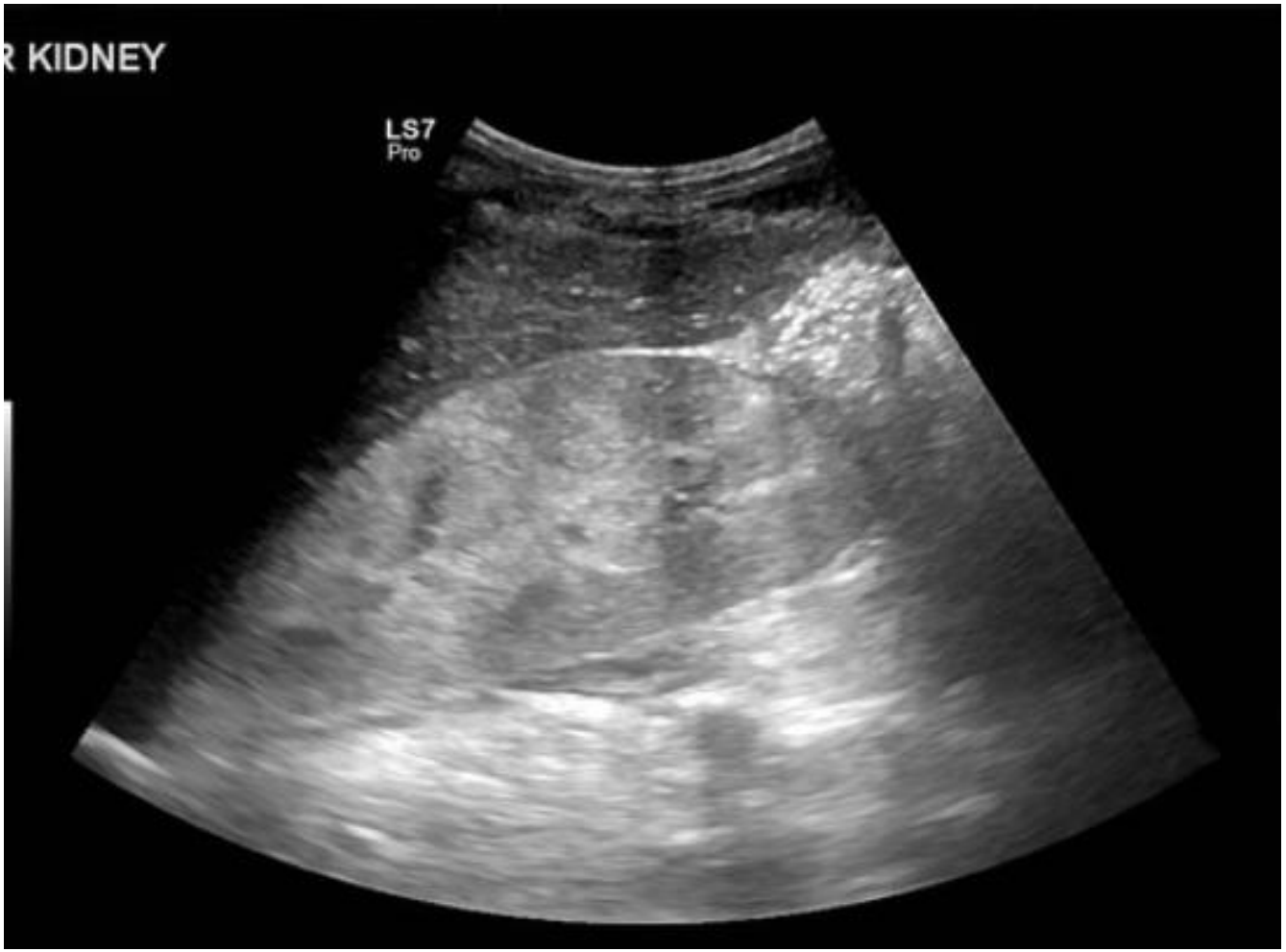
- B6 mice demonstrated that the HIV transgene worsened glomerular injury in mice with streptozotocin-induced diabetes mellitus.

- Increased expression of proinflammatory genes

- Current theory: HIV can exacerbate the course diabetic kidney disease, possibly by potentiating inflammatory renal injury.

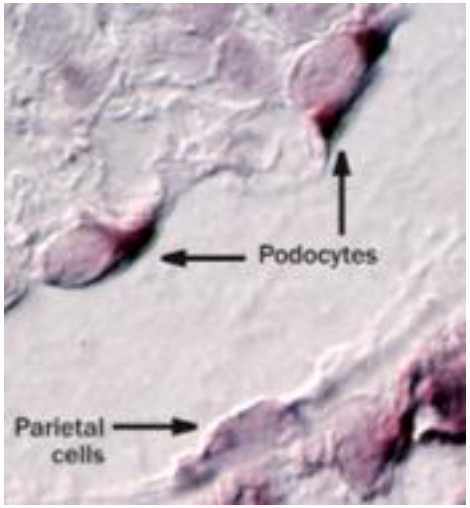
Mallipattu SK. Kidney Int 2013; 83: 626–634.

HIVAN

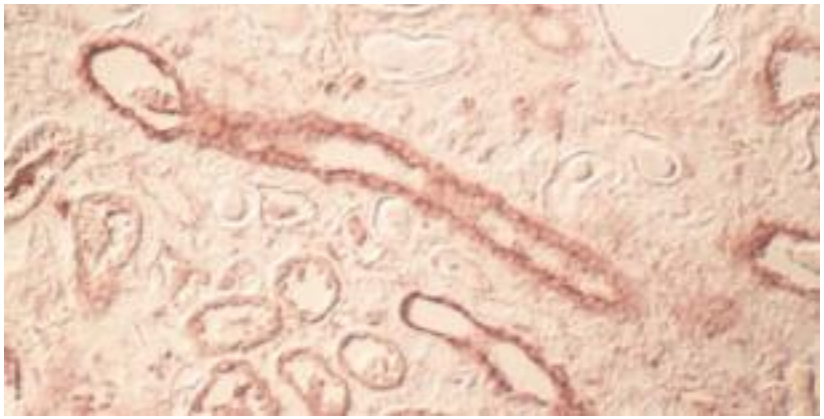


HIVAN Pathophysiology

- Viral genes expressed in the kidney
- Genetically susceptible host
- Leads to de-differentiation of podocyte and proliferation of tubular cells



In situ hybridization



Bruggeman. *Nat. Rev. Nephrol*. 2009. Marras Nat Med 2002;

Clinical Presentation of HIVAN

- Proteinuria
  - Microalbuminuria to nephrotic range
- Hematuria
  - Microscopic to gross hematuria
- Edema or nonedematous
- Normal or Hypertensive
- Ultrasound: large, echogenic kidneys
- Rapid progression to ESRD if untreated

HIVAN predominantly affects Blacks

- 18-50X increased risk of HIVAN in those of West African descent
- OR for ESRD in Black vs. Caucasian = 6:1
- Blacks make up over 80% of HIV infected population on dialysis
- APOL1: Requires homozygosity or compound heterozygosity to confer increased risk
  - OR 28 for HIVAN
  - HIV-positive homozygotes have a 50% lifetime risk of developing HIVAN without ARVs

Kopp JB. J Am Soc Nephrol 2011; 22: 2129–2137.

Treatment of HIVAN

Combination antiviral therapy

ACEi or ARB

Non-HIVAN FSGS

- Glomerular findings without tubulointerstitial changes
- Partially treated HIVAN?
- Genetically susceptible individuals
- cART attenuates but does not ‘cure’ HIVAN, it may convert HIVAN into an insidious disease with minimal-to-mild proteinuria and slow loss of glomerular filtration rate

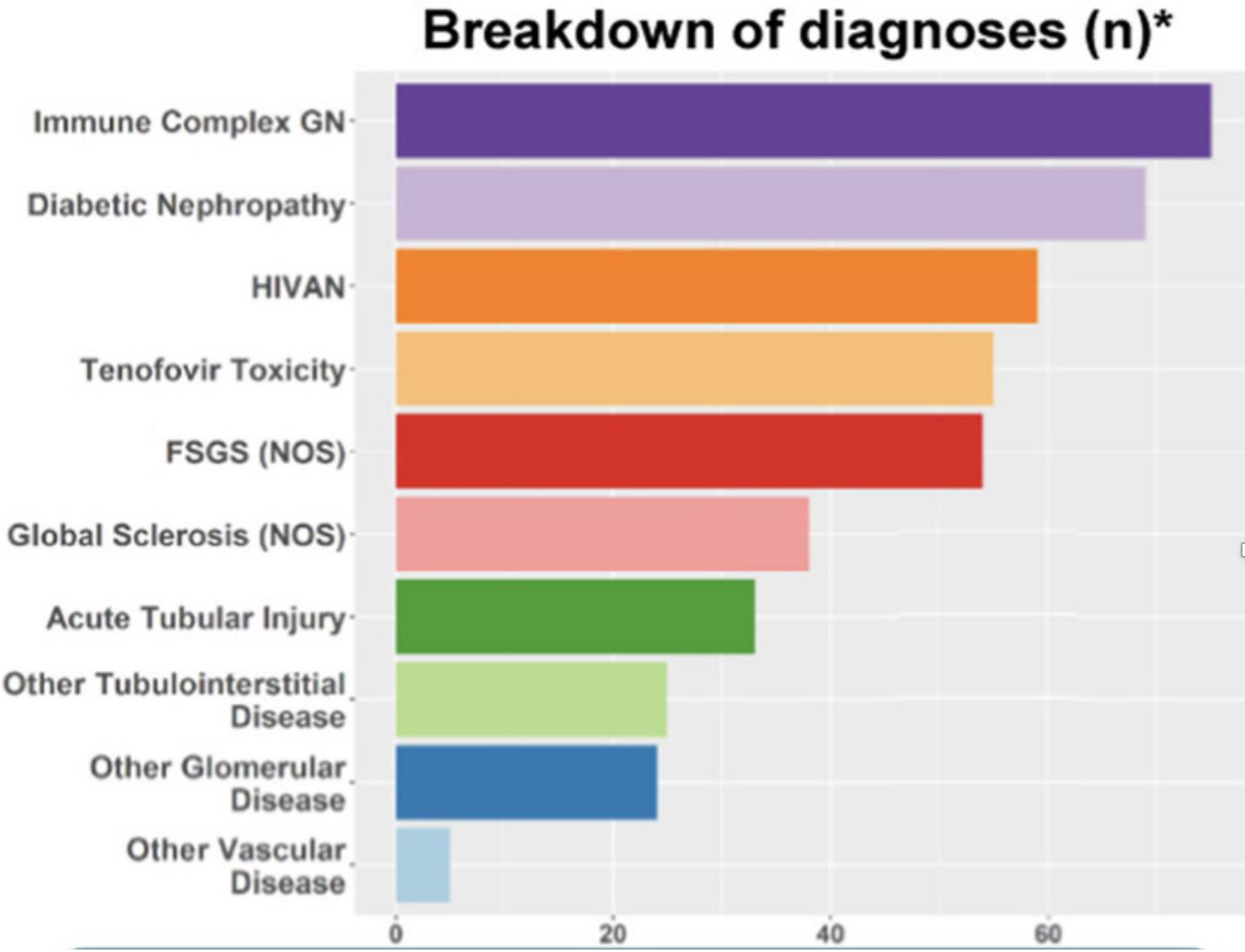
Berliner AR. Am J Nephrol 2008; 28: 478–486, Ross MJ Kidney Int. 86(2):266. 2014 .

The Spectrum of Kidney Biopsy Findings in HIV-infected Patients in the Modern Era

Kidney biopsies

26,737 native biopsies from 2010 – 2018 retrospectively reviewed

*Dual diagnoses were present in 17% of cases



Kudose *KI* 2019

Treatment of HIVAN

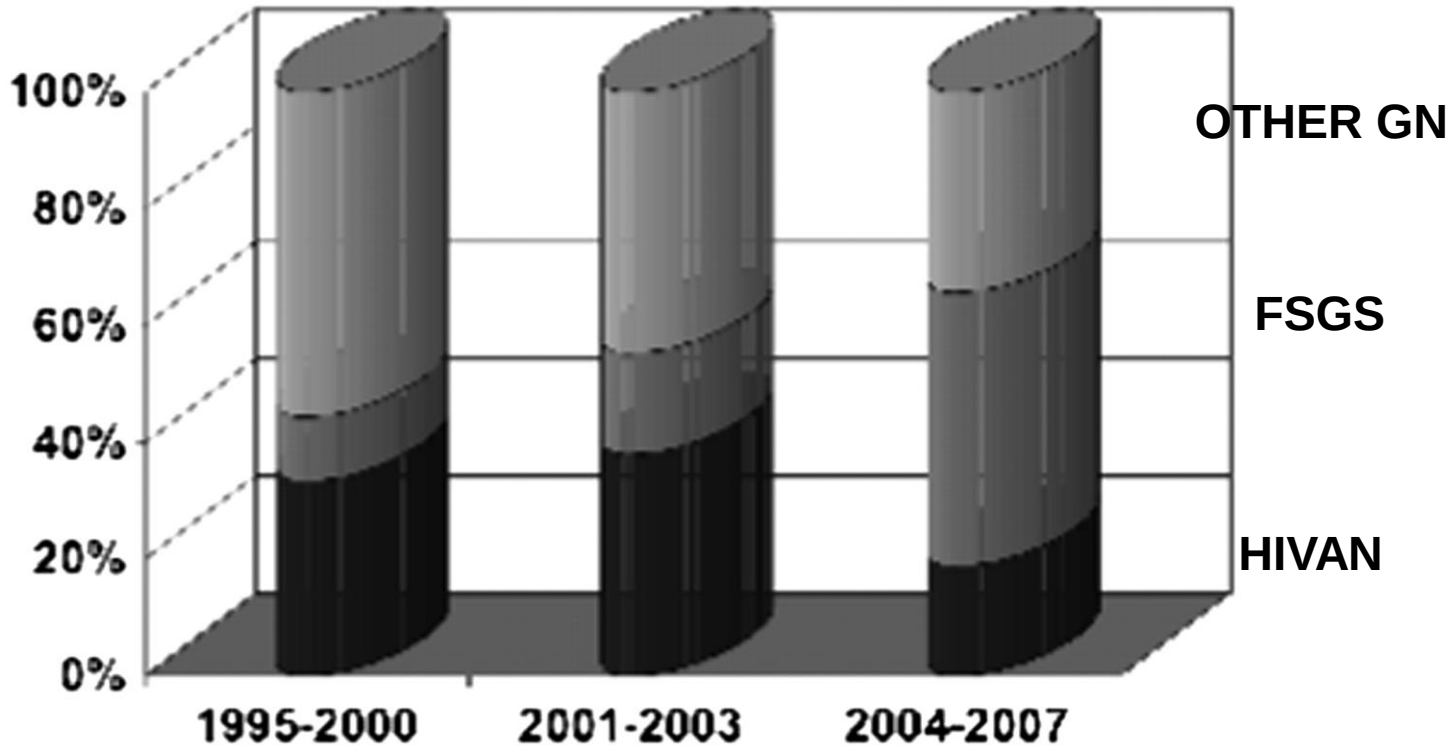
Even with ARVs progression to ESKD is extremely high in patients with HIVAN

Slightly inferior dialysis outcomes among non-white patients

HIV+ transplantation

Sawinski D. *KI*. 2018

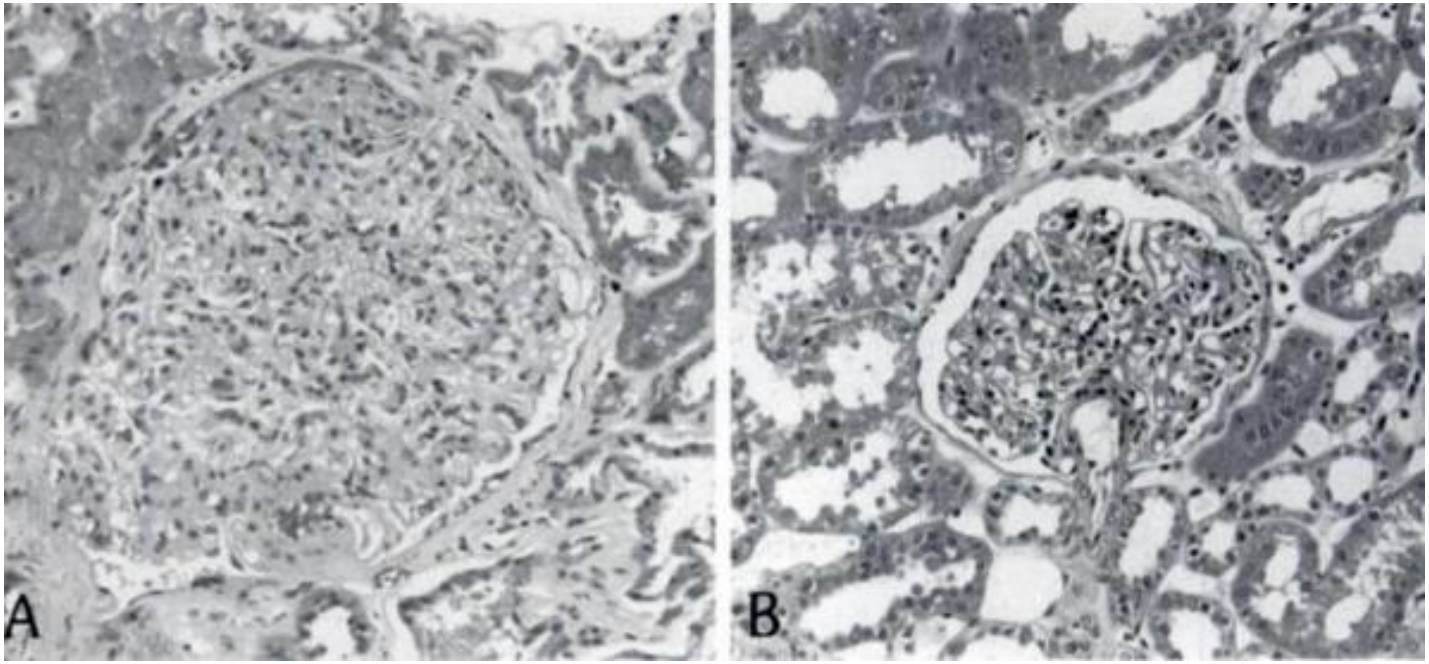
Biopsy findings in HIV over time



Lescure F et al. Nephrol. Dial. Transplant. 2012

Other forms of FSGS

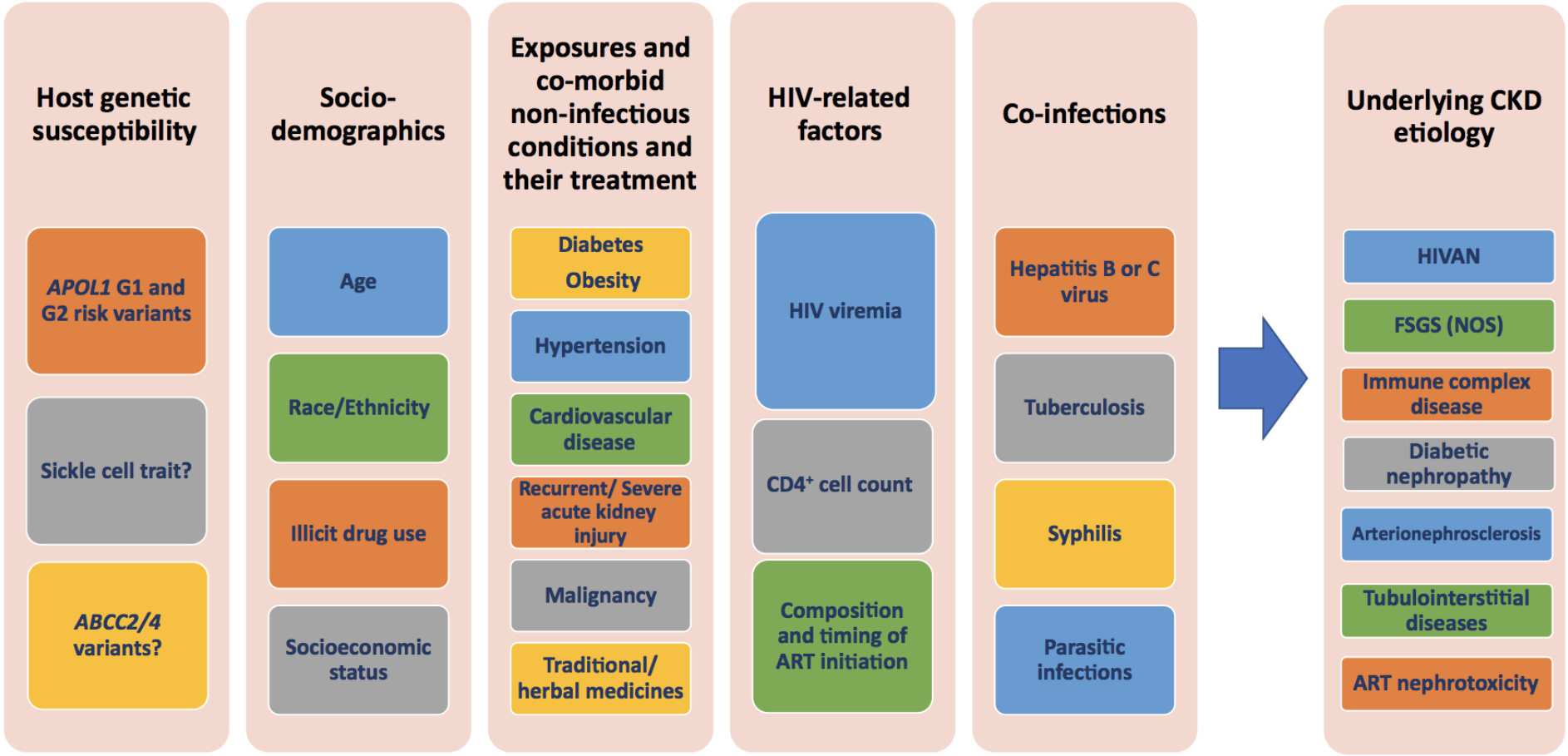
- Primary FSGS
- Secondary: Associated with hyperfiltration states: obesity, VLBW, sleep apnea, severe HTN



Rise in comorbid CKD offsets decline in HIVAN in US Blacks

- Lucas AIDS 2007 - 15 year cohort study
  - 1% per year incidence of ESRD in AA
  - 10x age matched HIV- AA
  - 30x risk in ESRD compared to HIV+ whites
- Among HIV+ blacks with non-HIVAN CKD, those with high risk APOL1 had 3x risk of ESRD compared to low risk APOL1 (Fine JASN 2012)
  - No change in ESRD incidence in Blacks since HAART initiation

Changing epidemiology of CKD in HIV



Swanepoel CR. Kidney International. 2018

Questions

- msise@partners.org