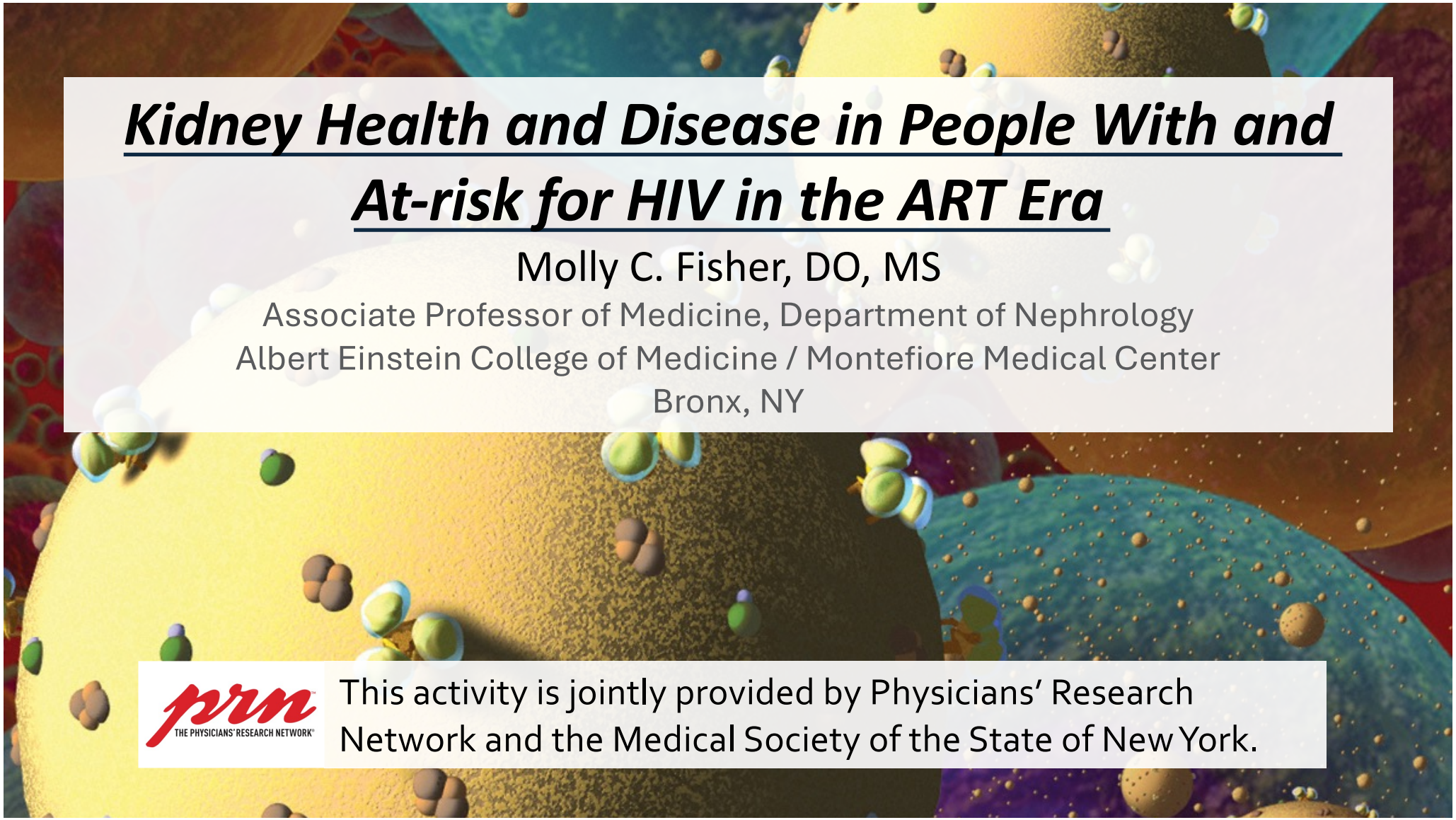

Kidney Health and Disease in People With and At-risk for HIV in the ART Era

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Disclosures

- Honorarium from the American Academy of HIV Medicine

- Royalties from UpToDate – authorship on topics pertaining to HIVAN, HIV and dialysis, HIV and kidney disease

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Learning objectives

- How to assess kidney function in people with HIV (PWH)
- Which antiretroviral therapy (ART) medications are nephrotoxic
- How to evaluate the spectrum of kidney diseases in the ART era
- How to manage chronic kidney disease in PWH

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Clinical Case

- *41-year-old male with HIV referred for newly elevated creatinine.*

- His HIV is well-controlled. CD4 count is 508 cells/mm^3 and plasma HIV RNA is undetectable. He has no other medical problems.
- Exam unremarkable, weight 72 kg, BMI 25 kg/m^2

Kidney Function	6 months ago	Today
Creatinine, mg/dL	1.2	1.6
eGFR, mL/min/1.73m^2	74	54
CrCl, mL/min	84	65

- **Does he have kidney disease?**

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Estimating Kidney Function in People with HIV

- ART dosing guidelines based on creatinine clearance from the Cockgroft-Gault equation

- Creatinine based estimating GFR equations – CKD-EPI most accurate

- Creatinine
  - Disadvantages in PWH
    - Affected by muscle mass, protein supplements
    - Certain ART that inhibit tubular secretion of creatinine

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Clinical Case: More History

- *41-year-old male with HIV referred for newly elevated creatinine.*

- Home Medications
  - ART regimen changed 1 month ago
    Efavirenz-emtricitabine-tenofovir disoproxil fumarate
    → dolutegravir-lamivudine
  - Protein supplements

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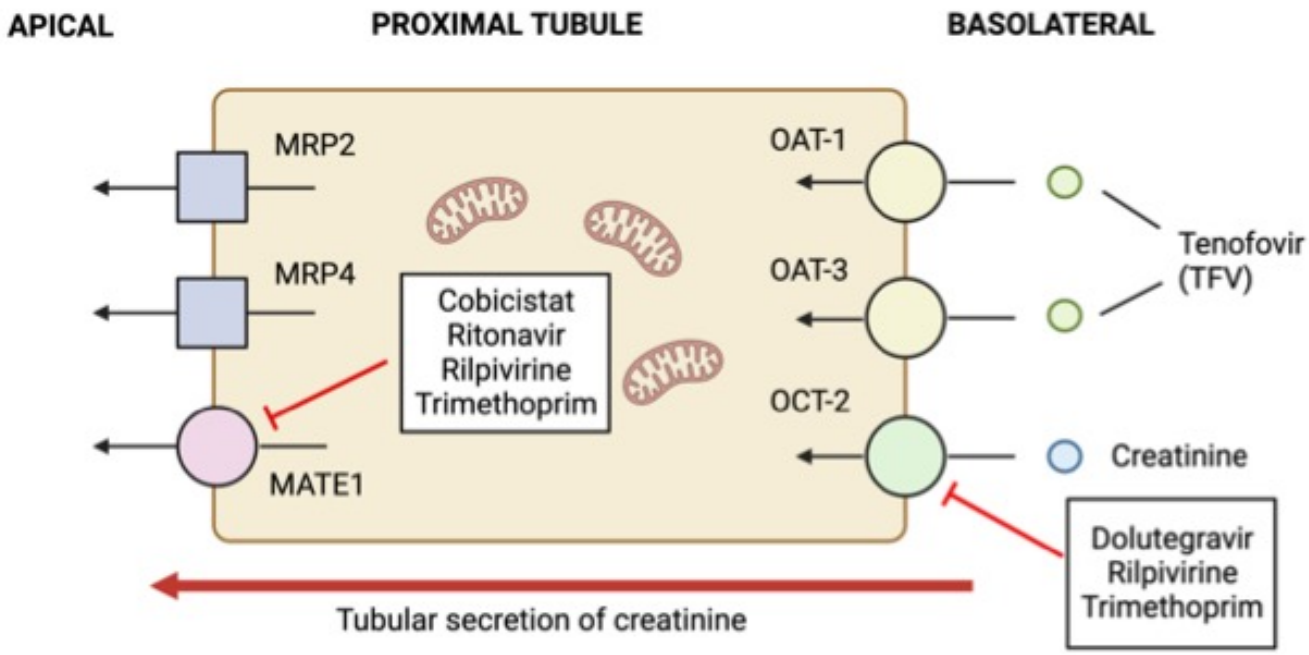
HIV Medications that increase creatinine



Inhibit excretion of creatinine

- Cobicistat
- Ritonavir
- Trimethoprim
- Rilpivirine
- Dolutegravir

Adapted from Atta et al CJASN 2019

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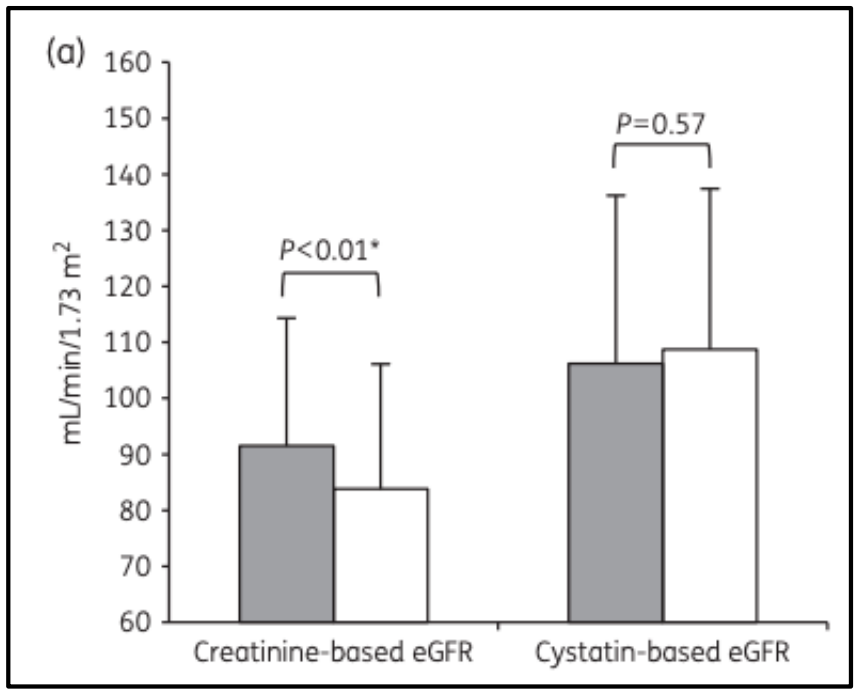
Effect of Dolutegravir (DGT) on eGFR equations

- 44 PWH with controlled HIV

  →Switched to DGT

- Pre and post assessment with creatinine and cystatin C eGFR
  - Creatinine eGFR: **-7.7 mL/min**
  - Cystatin C eGFR: no change



Palich R, Tubiana R, Abdi B, et al. Plasma cystatin C as a marker for estimated glomerular filtration rate assessment in HIV-1-infected patients treated with dolutegravir-based ART. *J Antimicrob Chemother*. 2018;73(7):1935-1939.

Estimating Kidney Function with Cystatin C

- Produced by all nucleated cells & cleared completely by glomerular filtration

- Advantages
  - Less affected by extremes of muscle mass or age
  - Levels are not affected by ART

- Disadvantage
  - Can be elevated due to systemic inflammation

- Currently not recommended alone to estimate GFR among PWH
  - Combined creatinine-cystatin C eGFR may be more accurate than either equation alone among PWH on stable ART

Expected change in kidney function after starting an integrase inhibitor

- Changes occur within the first 4 weeks of therapy and then stabilize
- Can occur with any integrase inhibitor
- *Expected change*
  - **Creatinine:** ↑ **0.1-0.2** mg/dL
  - **eGFR:** ↓ **5-20** mL/min
- Clues that the ↓ in eGFR is benign – absence of proteinuria, tubular toxicity or structural damage

Lindeman TA, et al. Evaluation of Serum Creatinine Changes With Integrase Inhibitor Use in Human Immunodeficiency Virus-1 Infected Adults. Open Forum Infect Dis. 2016 Mar 11;3(2):ofw053

Clinical Case: Comparing GFR Estimating Equations

Results

eGFR_cr	**54 mL/min**
eGFR_cr-cys	**77 mL/min**
eGFR_cys	**90 mL/min**

https://www.kidney.org/professionals/kdoqi/gfr_calculator

Clinical Case: Conclusion

- Workup
  - Urinalysis bland
  - Urine protein-creatinine <200 mg/g
  - Cystatin C eGFR 90 >>> Creatinine eGFR 54

- Conclusion
  - Elevated creatinine attributed to dolutegravir +/- creatine-containing protein supplement
  - No evidence of CKD

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Summary 1: Estimating Kidney Function in PWH

- Integrase inhibitors, pharmaco-enhancers can result in a mild increase in creatinine after initiation
  - IDSA Recommendation: Check kidney function prior to and 4 weeks after ART change

- Expect a 5-20 mL/min decrease in creatinine-based eGFR after starting dolutegravir or other integrase inhibitors

- Consider checking cystatin C-based eGFR before starting or switching ART

- The combined creatinine-cystatin C eGFR equation most accurate in PWH

Learning objectives

- How to assess kidney function in people with HIV (PWH)
- Which antiretroviral therapy (ART) medications are nephrotoxic
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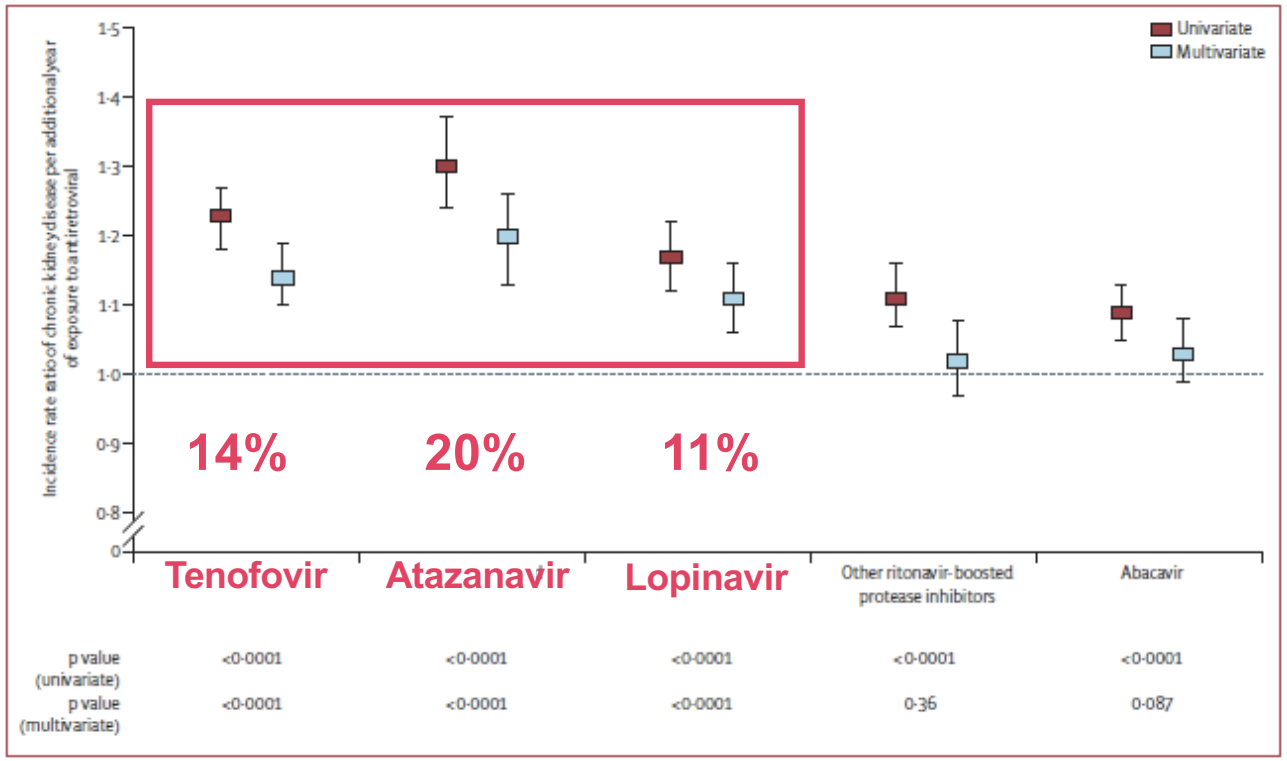
Some ART associated with development of CKD

↑ *incident CKD for every additional 1 year of exposure to:*



23,905 PWH – median eGFR 110, age 39

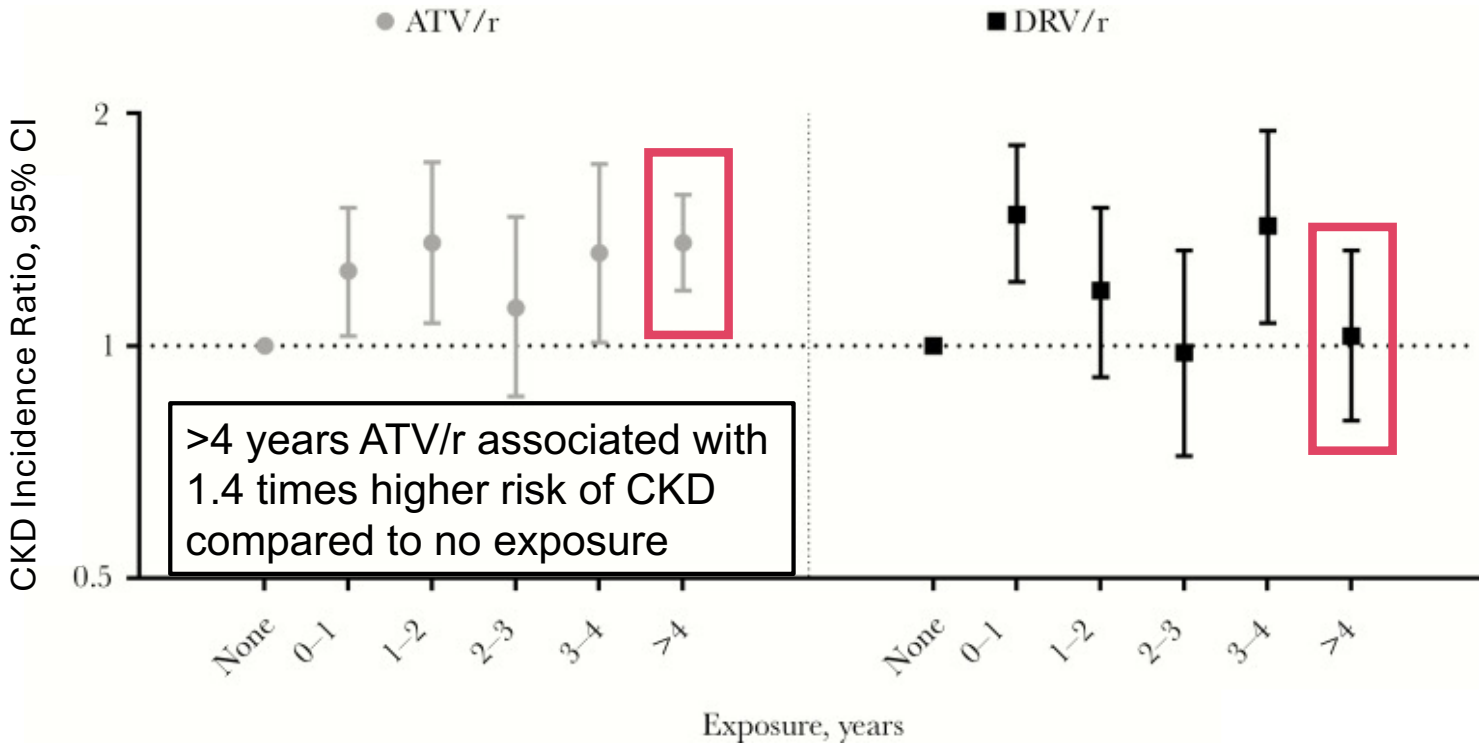
7.2 year follow up

→ 285 (1%) new CKD

Mocroft A, Lundgren JD, Ross M, et al; Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study. Lancet HIV. 2016 Jan;3(1):e23-32

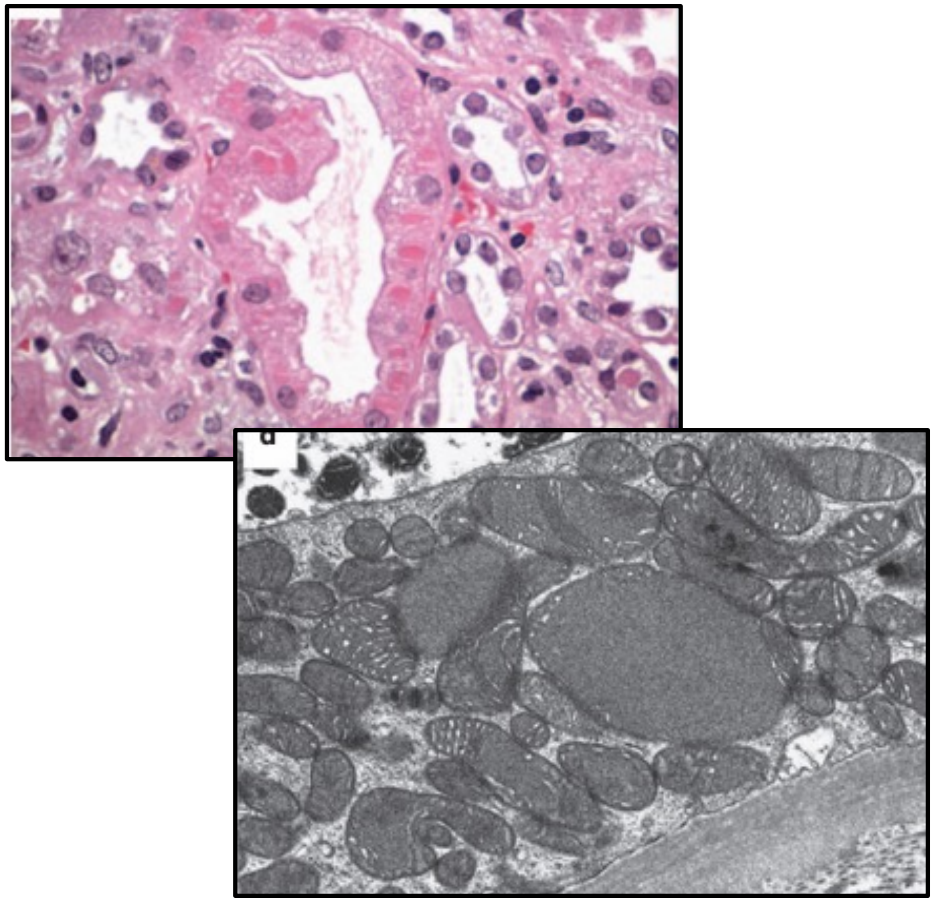
Cumulative Atazanavir (ATV) but not Darunavir (DRV) associated with incident CKD

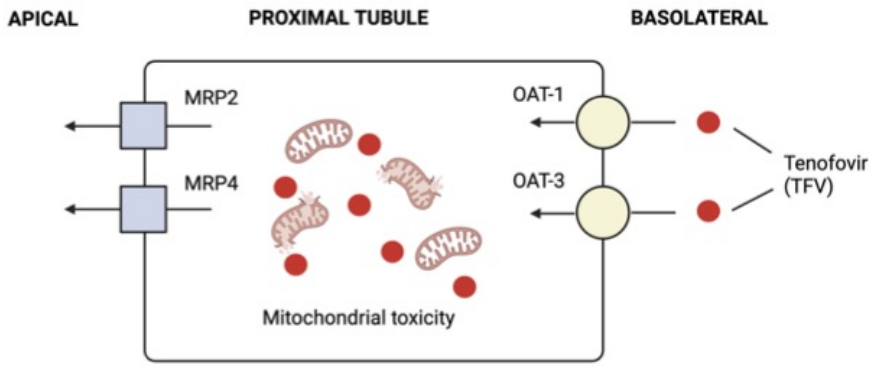
27,675 participants without CKD at baseline, median eGFR 101, majority men and White



Ryom L, Dilling Lundgren J, Reiss P, et al; Use of Contemporary Protease Inhibitors and Risk of Incident Chronic Kidney Disease in Persons With Human Immunodeficiency Virus: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. J Infect Dis. 2019 Oct 8;220(10):1629-1634.

Tenofovir (TDF) Nephrotoxicity



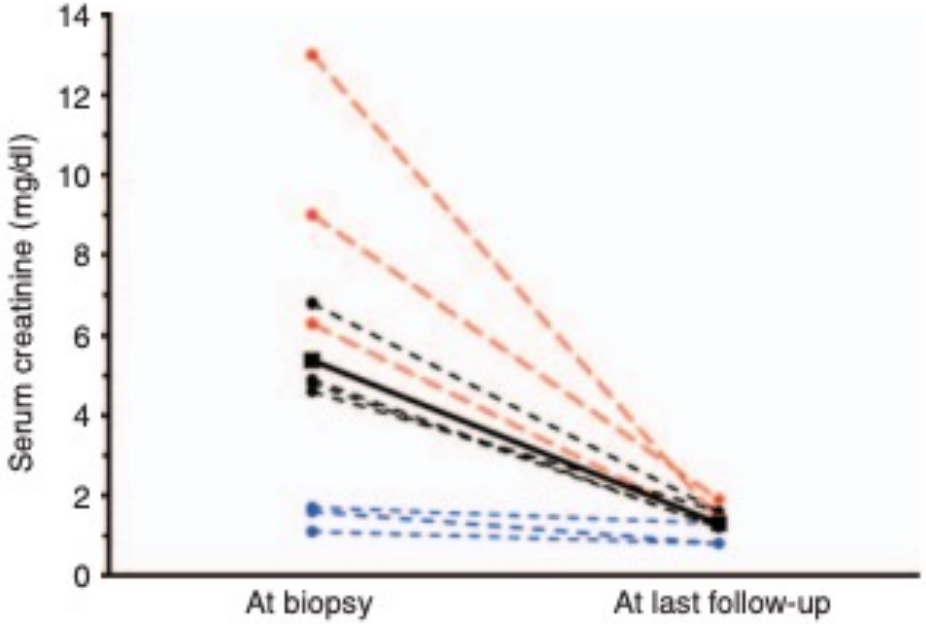


- Eliminated via secretion through organ anion transporters in the proximal tubule
- Accumulation causes mitochondrial toxicity

TDF and Proximal Tubulopathy

- Clinical characteristics
  - AKI, low molecular weight proteinuria, glycosuria, renal phosphate wasting
- Largely reversible BUT….GFR may not fully recover
- Risk factors
  - PI/r, cobicistat
  - Lower baseline eGFR
  - Female sex
  - Low body weight

13 patients TDF toxicity on biopsy
~50% complete recovery



Herlitz LC et al. Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities. *Kidney Int*. 2010;78(11):1171-1177

Should we worry about kidney function in people without HIV receiving TDF-based PrEP?

- >14,000 PrEP users → 2.4% had decrease in CrCl to <60
  - Biggest risk factors for kidney function decline
    → age, baseline CrCl

- CDC guidelines do not support PrEP use if CrCl <60

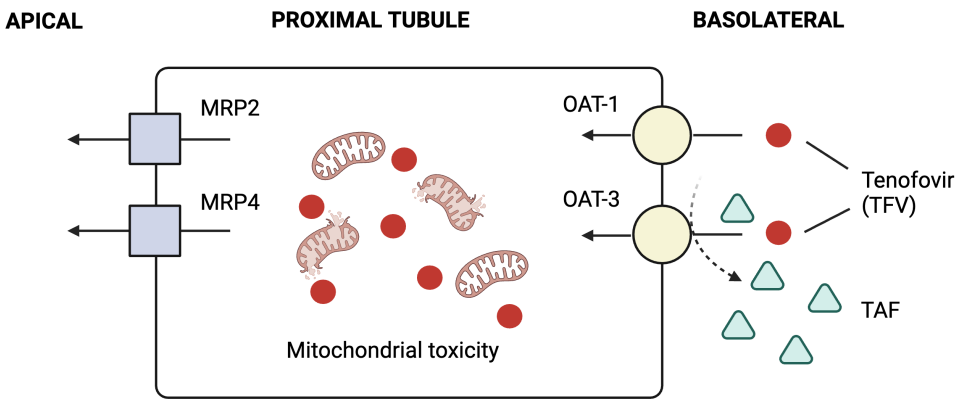
- Monitoring of kidney function
  - Twice a year if risk factors (diabetes, HTN, age >50, baseline CrCl <90)
  - Annually in everyone else
  - Not necessary if age <30 and healthy

Common regimen: TDF/FTC

Schaefer R et al. Kidney function in tenofovir disoproxil fumarate-based oral pre-exposure prophylaxis users: a systematic review and meta-analysis of published literature and a multi-country meta-analysis of individual participant data. *Lancet HIV*. 2022;9(4):e242-e253

What about Tenofovir Alafenamide?

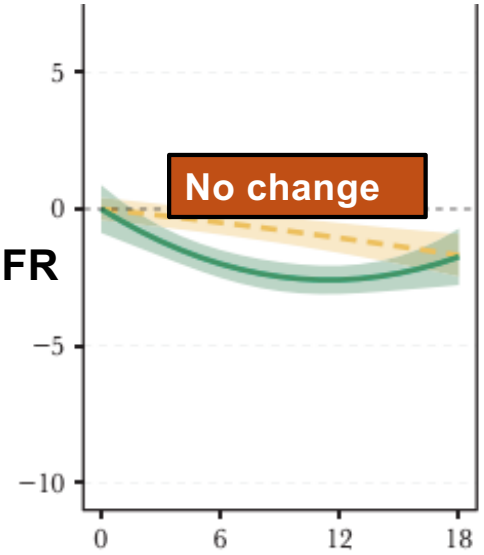
- Alternative tenofovir prodrug (FDA approved in 2015)
- Higher intracellular concentrations → 90% lower plasma concentrations
  - Lower potential for kidney and bone toxicity
- Fixed dose combinations approved for HIV
- TAF also approved for hepatitis B
- Don’t start if CrCl <30 mL/min



What happens after Switching from TDF to TAF?

>90 mL/min

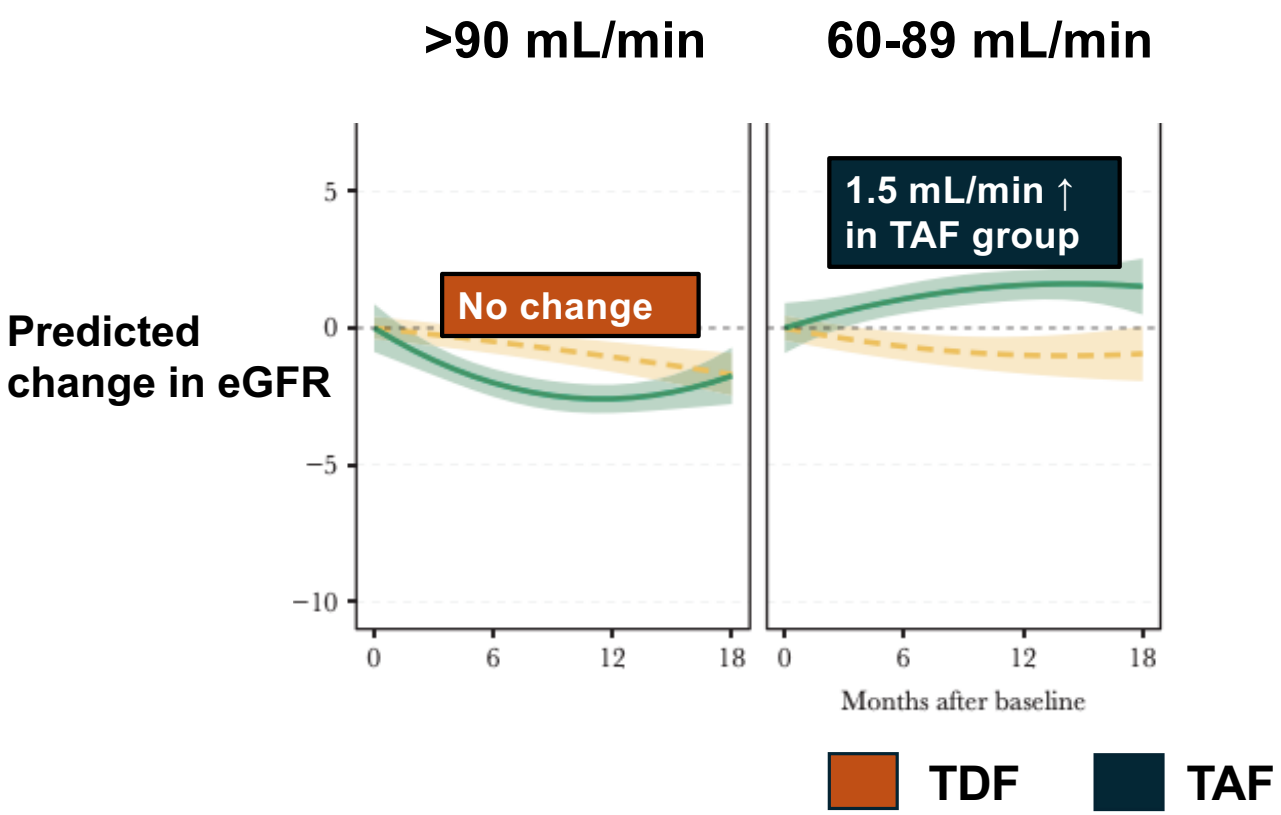
Predicted change in eGFR



TDF **TAF**

Surial B et al. Changes in Renal Function After Switching From TDF to TAF in HIV-Infected Individuals: A Prospective Cohort Study. *J Infect Dis*. 2020;222(4):637-645

What happens after Switching from TDF to TAF?



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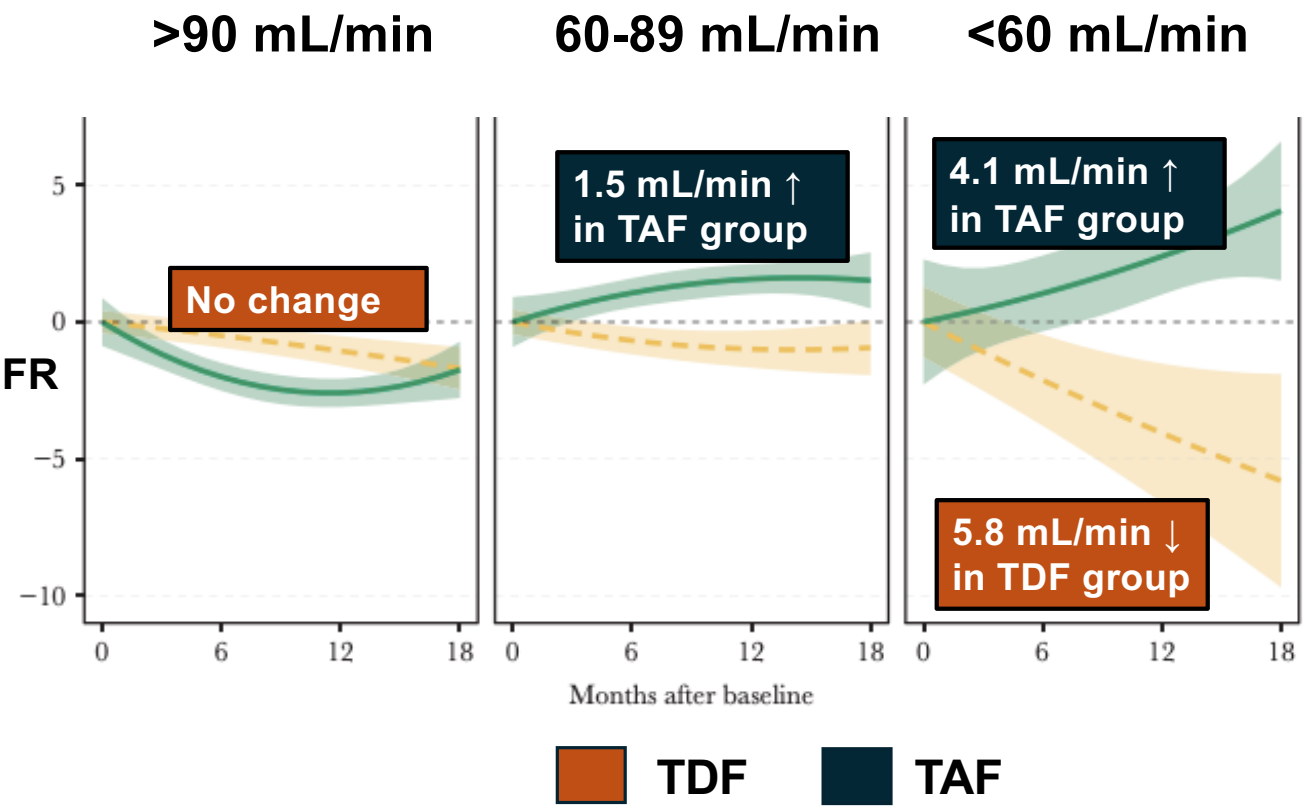


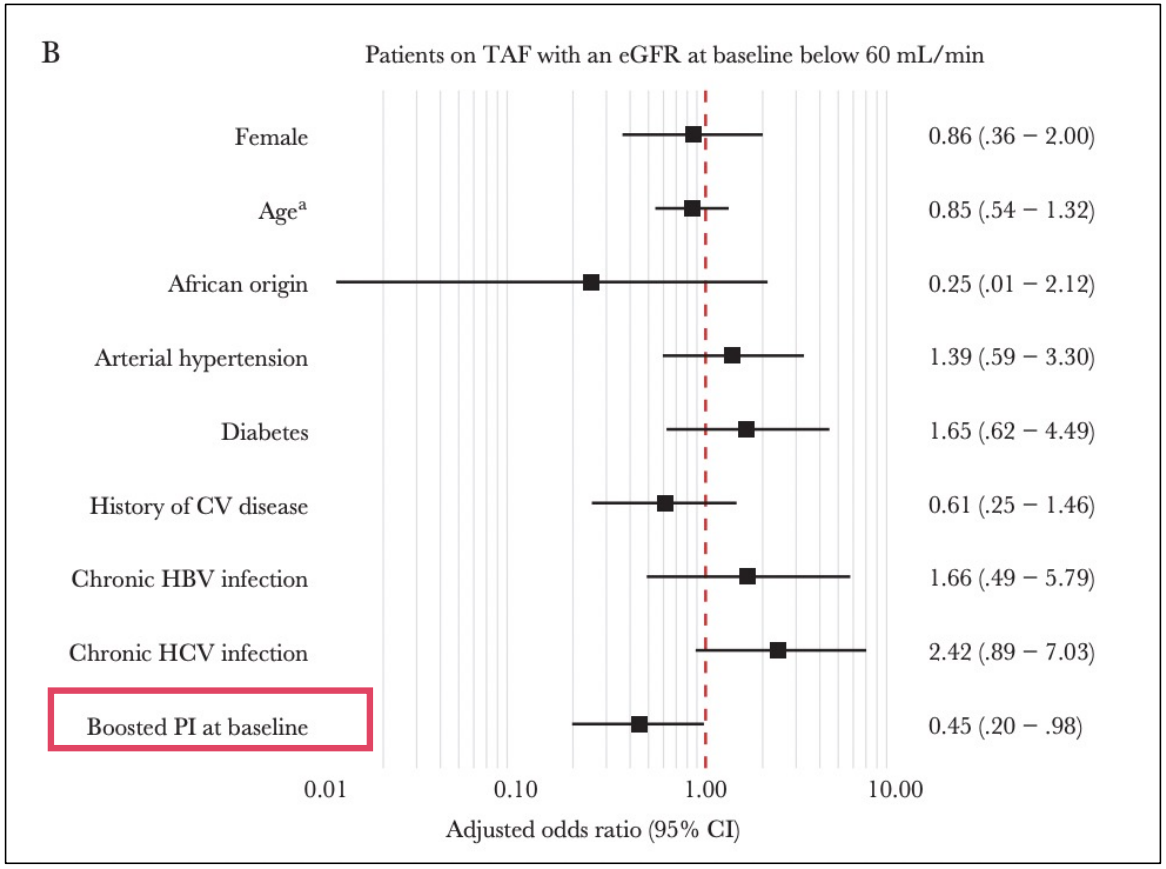
3,520 PWH - 26.6% women, median age 50 years

2404 (68.5%) switched to TAF

18 month follow up

Surial B et al. Changes in Renal Function After Switching From TDF to TAF in HIV-Infected Individuals: A Prospective Cohort Study. *J Infect Dis*. 2020;222(4):637-645

Predictors of GFR increase after switching to TAF

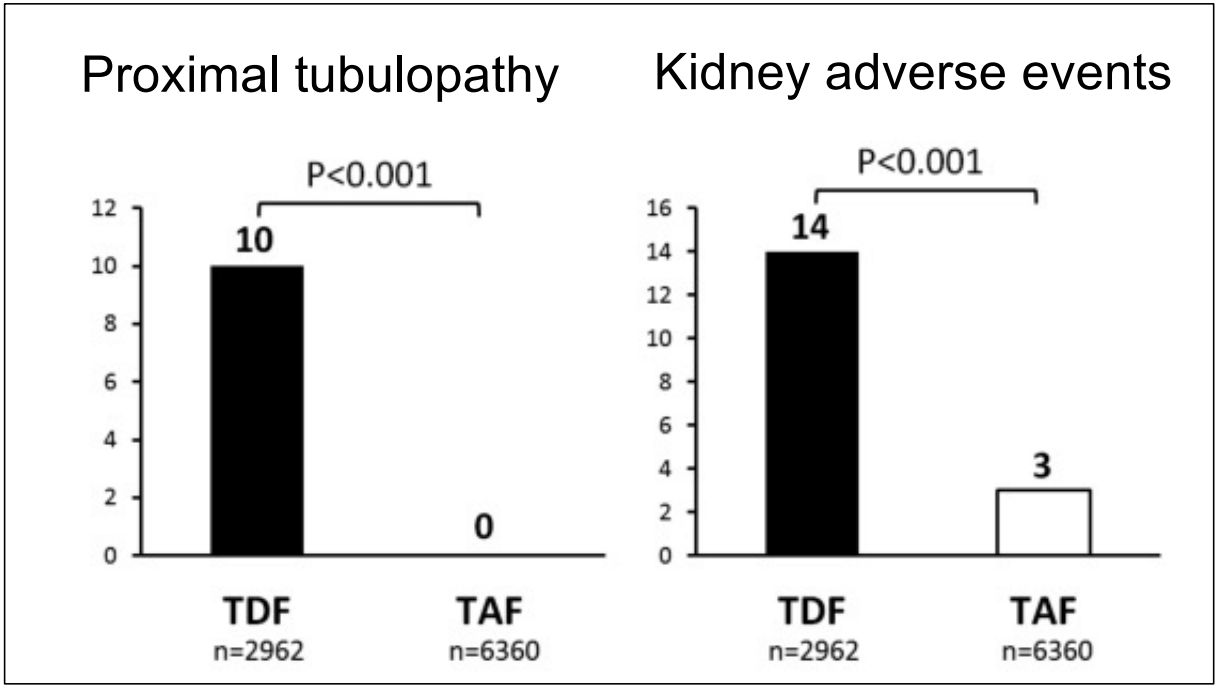


Likelihood of improving eGFR by ≥10% after 12 months in those with CKD:

- Similar among patients with different comorbidities
- ***65% less likely to have improvement in eGFR if on a boosted protease inhibitor***

Surial B et al. Changes in Renal Function After Switching From TDF to TAF in HIV-Infected Individuals: A Prospective Cohort Study. *J Infect Dis*. 2020;222(4):637-645

Kidney Safety of TAF versus TDF



- Limited data on hard outcomes
- Pooled data across 26 RCTs
- Mean CrCl 108 mL/min
- No cases of proximal tubulopathy in those on TAF
- Fewer kidney discontinuation events on TAF

Gupta SK, Post FA, Arribas JR, et al. Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials. *AIDS*. 2019;33(9):1455-1465

What about TAF in patients who experienced proximal tubulopathy on TDF?

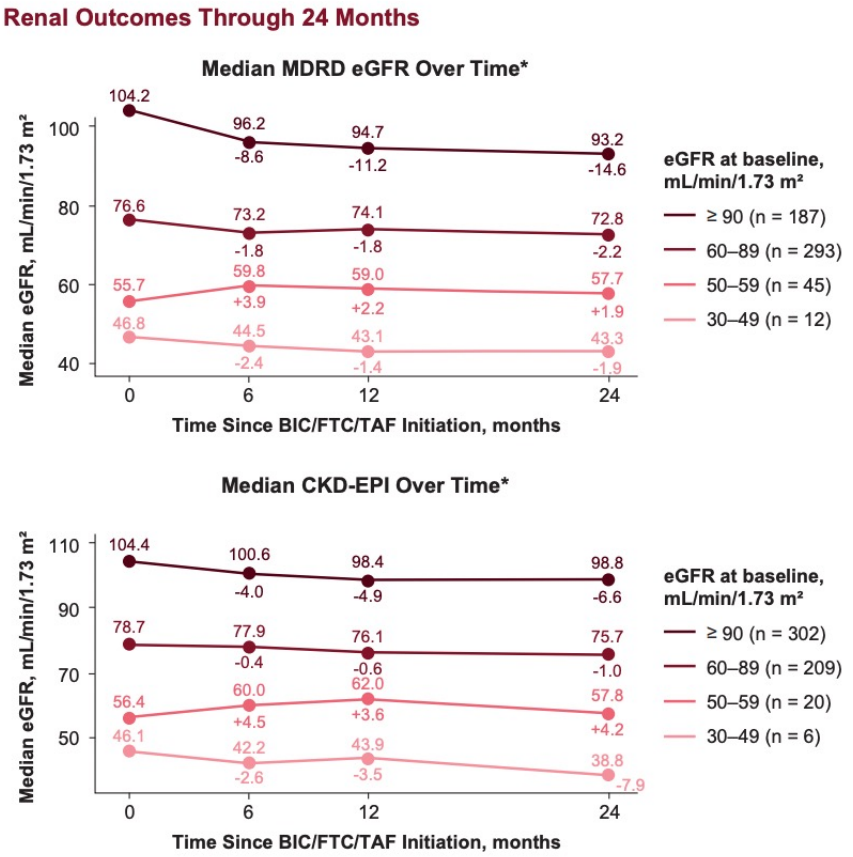
- *31 PWH with prior proximal tubulopathy on TDF given TAF*
  - Defined as at least 2 of the following: proteinuria, normoglycemic glycosuria, hypophosphatemia, rapid eGFR decline >5 mL/min/year, tubular injury on kidney biopsy, clinical resolution after TDF discontinuation
- 2 year follow up
  - ✓No change in cystatin C eGFR
  - ✓No glycosuria
  - ✓No recurrent proximal tubulopathy
  - ✓No change in other kidney biomarkers or bone mineral density
- *Suggests* TAF is safe in those with prior TDF nephrotoxicity

Campbell L, Barbini B, Burling K, et al. Safety of Tenofovir Alafenamide in People With HIV Who Experienced Proximal Renal Tubulopathy on Tenofovir Disoproxil Fumarate. *J Acquir Immune Defic Syndr*. 2021;88(2):214-219.

Real world safety of TAF in patients with CKD

- *Limited safety data in patients with CKD*

- **BicStar Study**
  - 843 treatment naïve and treatment experienced PWH received biktarvy
  - 90 (11%) had CKD
    - 18 with eGFR <50
    - 72 with eGFR 50-59
  - Overall eGFR stable over 24 months
  - 1 reported kidney adverse event (proteinuria) that did not require TAF discontinuation



Data from Gilead, presented at American Society of Nephrology Kidney Week 2023

Summary 2: ART Safety in CKD

- Older protease inhibitors associated with CKD (atazanavir, lopinavir) but no association with darunavir

- Highest risk of declining kidney function on TDF seen in those with baseline eGFR <60; this improves after stopping TDF but is often not fully reversible

- Trial data on TAF with very few adverse kidney events – however, has not been well studied in those with more advanced CKD
  - Not recommended to start in non-dialysis CKD patients if CrCl <30 mL/min

Learning objectives

- How to assess kidney function in people with HIV (PWH)
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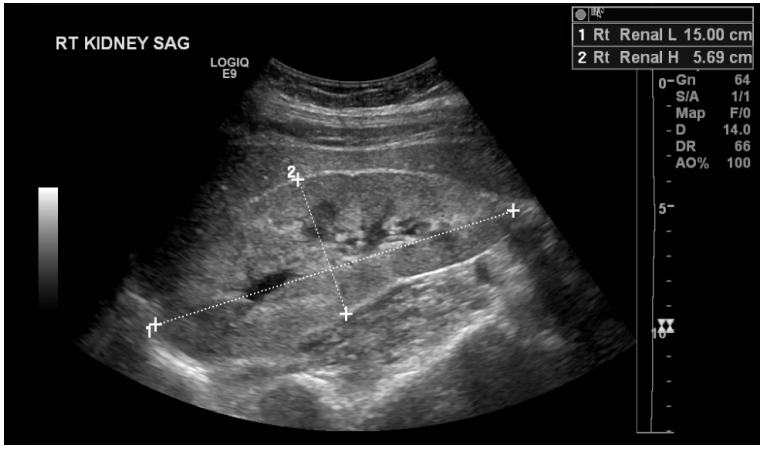
Clinical Case

- *33 y/o African American male was sent to the emergency room by his primary care doctor for for severe kidney failure.*

Laboratory Data	Value
CD4 count, cells/mm^3	50
HIV RNA, copies/mL	50,000
Serum albumin, g/dL	2.6
Creatinine, mg/dL	7
Urine protein-creatinine, mg/g	7,200

- Ultrasound – Enlarged, hyperechogenic kidneys, 15-16 cm in length



What is the most likely cause of his kidney failure?

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Classic clinical features of HIVAN

- Advanced HIV infection or newly diagnosed HIV
  - CD4 <200 cells/mm^3, unsuppressed viral load
- Progressive kidney failure → weeks-to-months without treatment
  - Slower in patients treated with ART
- Proteinuria → typically nephrotic range (>3g)
  - Urinalysis nonspecific (proteinuria, no hematuria, no cellular casts)

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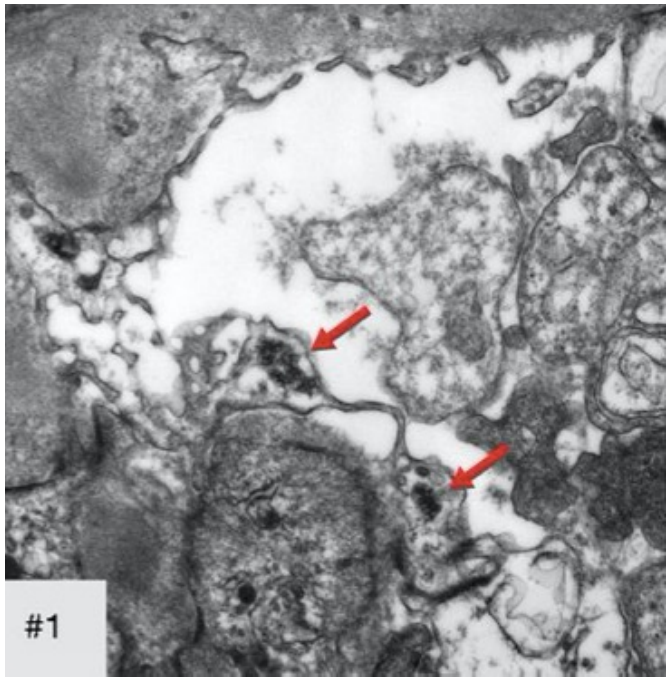
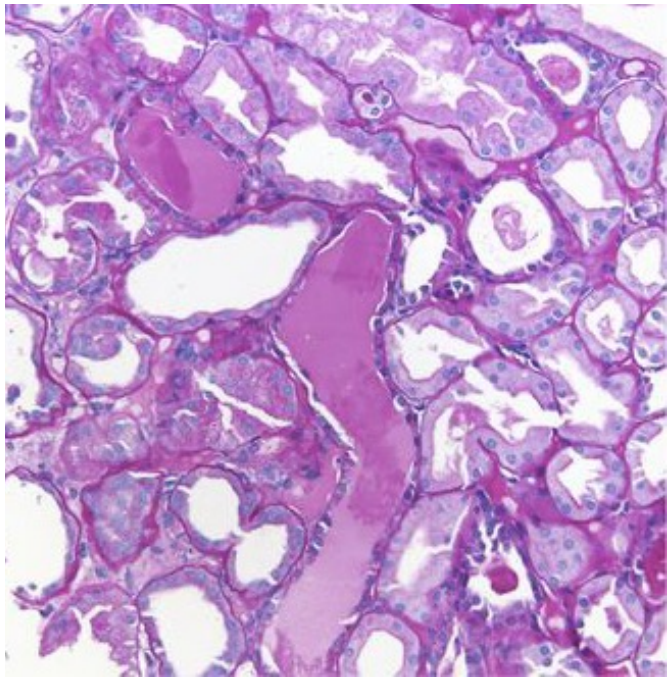
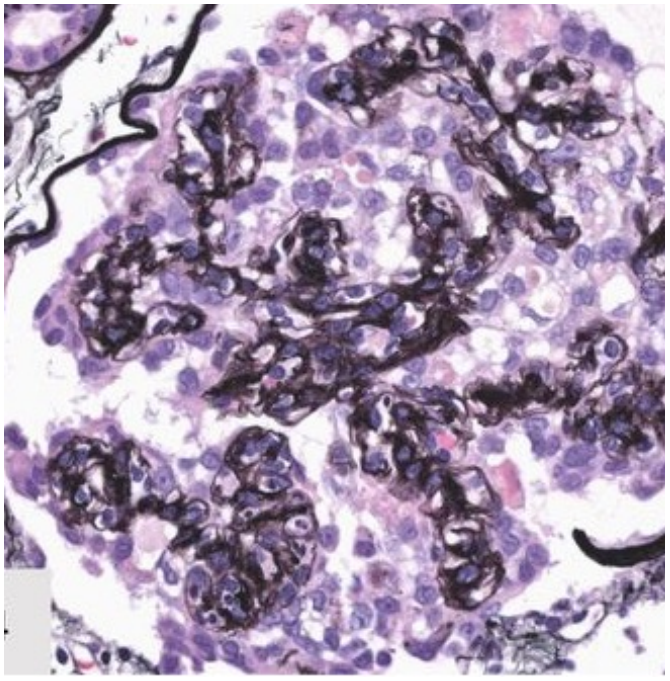






Histological Features of HIVAN

- Acute tubular injury, microcystic tubules
- Glomerular tuft collapse
- Parietal epithelial cell hypertrophy and hyperplasia
- Extensive foot process effacement
- Tubuloreticular inclusions

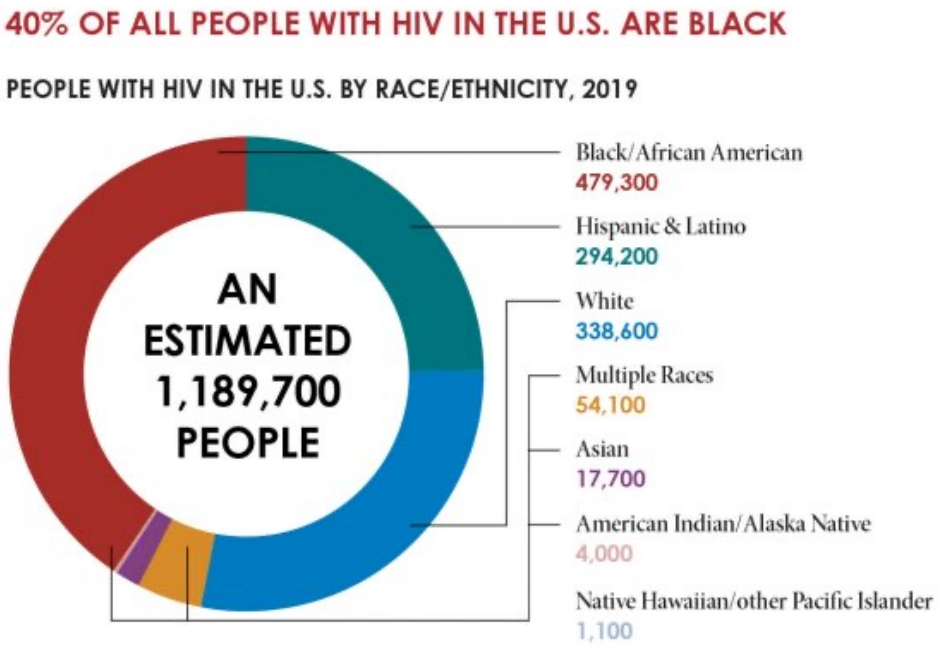
Kidney disease disproportionately affects PWH of African Ancestry

Patient No.	Age/ Race/Sex	Risk Factor	Renal Manifestation	Renal Histology *	Initial C_{cr} †	Time to Severe Uremia	Current Status ‡
					ml/min	*wk*	
1	28/B/F	Heroin	Nephrotic syn.	FSGS	90		Dead (cr, 2.0)
2	38/B/M	Heroin, homosexual	Nephrotic syn.	FSGS (A)	(1.4)	8–10	Dead (RF)
3	27/B/M	Heroin	Nephrotic syn.	FSGS	75	16	Dead (RF)
4	33/B/M	Heroin	Nephrotic syn.	FSGS (A)	90	12	Dead (RF)
5	39/B/M	Heroin	Nephrotic syn.	FSGS	65	8	Dead (RF)
6	31/B/F	None	Azotemia, proteinuria	FSGS	70	8	Dead (RF)
7	32/B/M	Haitian	Nephrotic syn.	FSGS	80	14	Dead (RF)
8	26/B/M	Homosexual	Nephrotic syn.	FSGS	(1.3)	16	Dead (RF)
9	46/B/M	Haitian	Azotemia, proteinuria	Mesangial increase	50	—	Dead (cr, 3.5)
10	36/B/M	Homosexual	Nephrotic syn.	FSGS (A)	(1.2)	8–10	Dead (RF)
11	22/B/F	Haitian	Nephrotic syn.	FSGS	70	8	On dialysis

Rao TK, Filippone EJ, Nicastri AD, et al. Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. N Engl J Med. 1984 Mar 15;310(11):669-73.

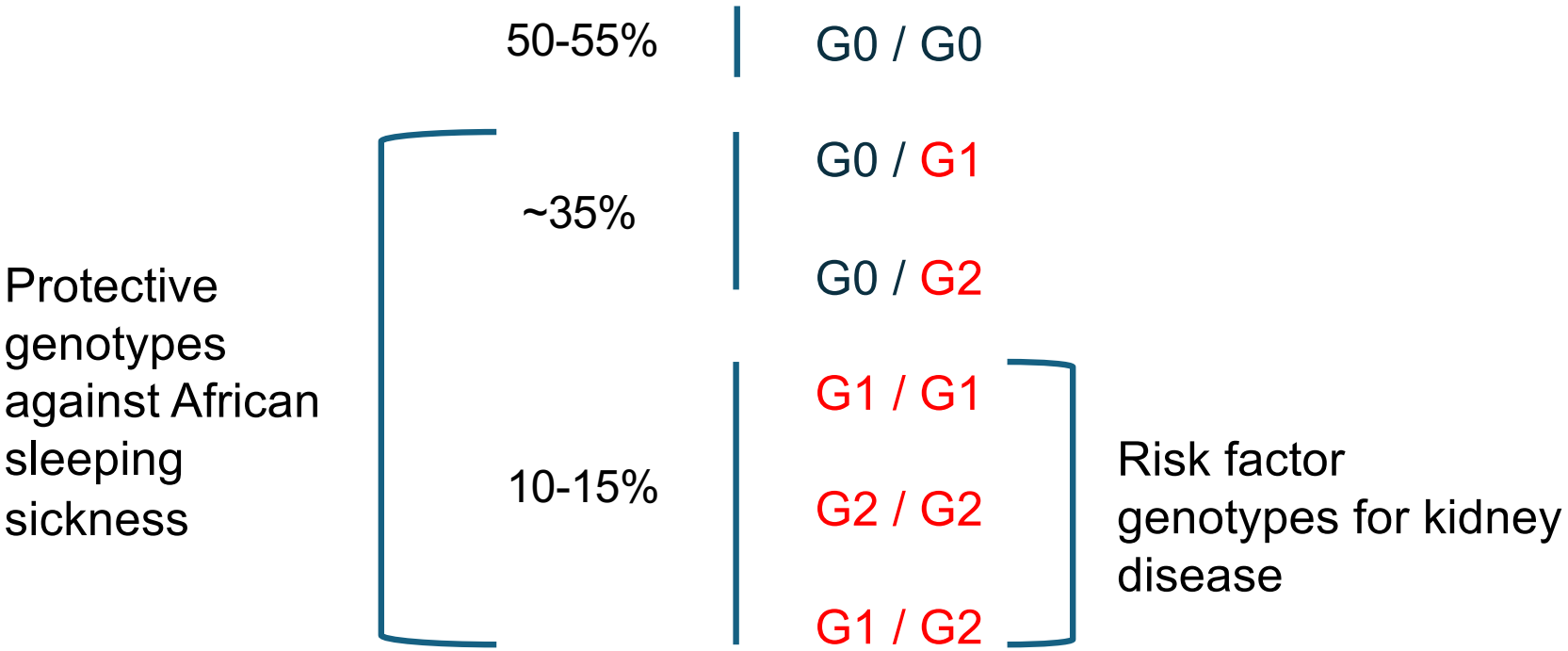
HIV and kidney disease disproportionately affect persons of African ancestry

- Worldwide: ~38 million PWH
  - 65% live in Sub-Saharan African
- United States: 1.2 million PWH
  - 40% are Black/ African American
  - 25% are Hispanic/ Latinx
- *90% of ESRD due to HIVAN seen in African Americans in the US*

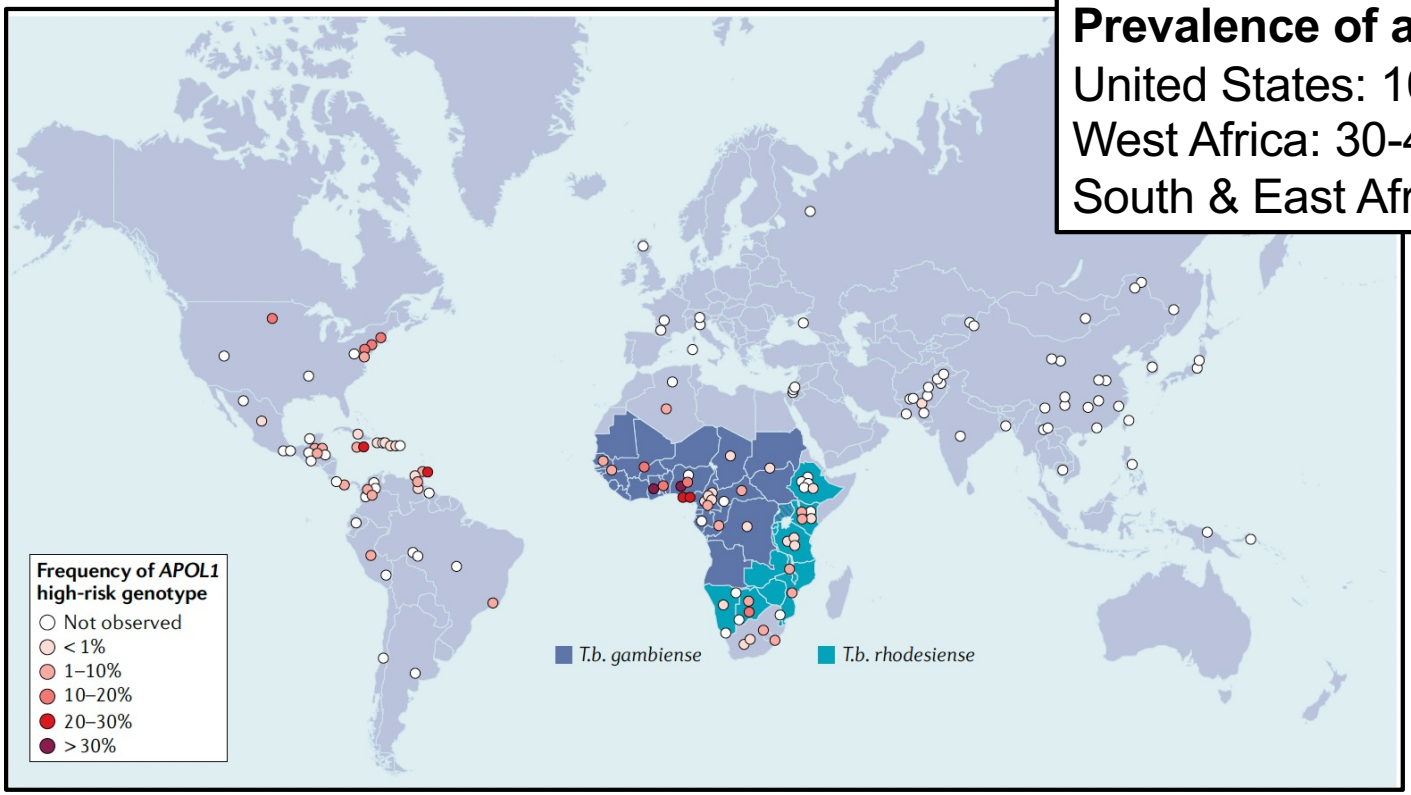


CDC Estimates, 2024

APOL1 genotype frequencies in African Americans



Frequency of APOL1 risk variants by region

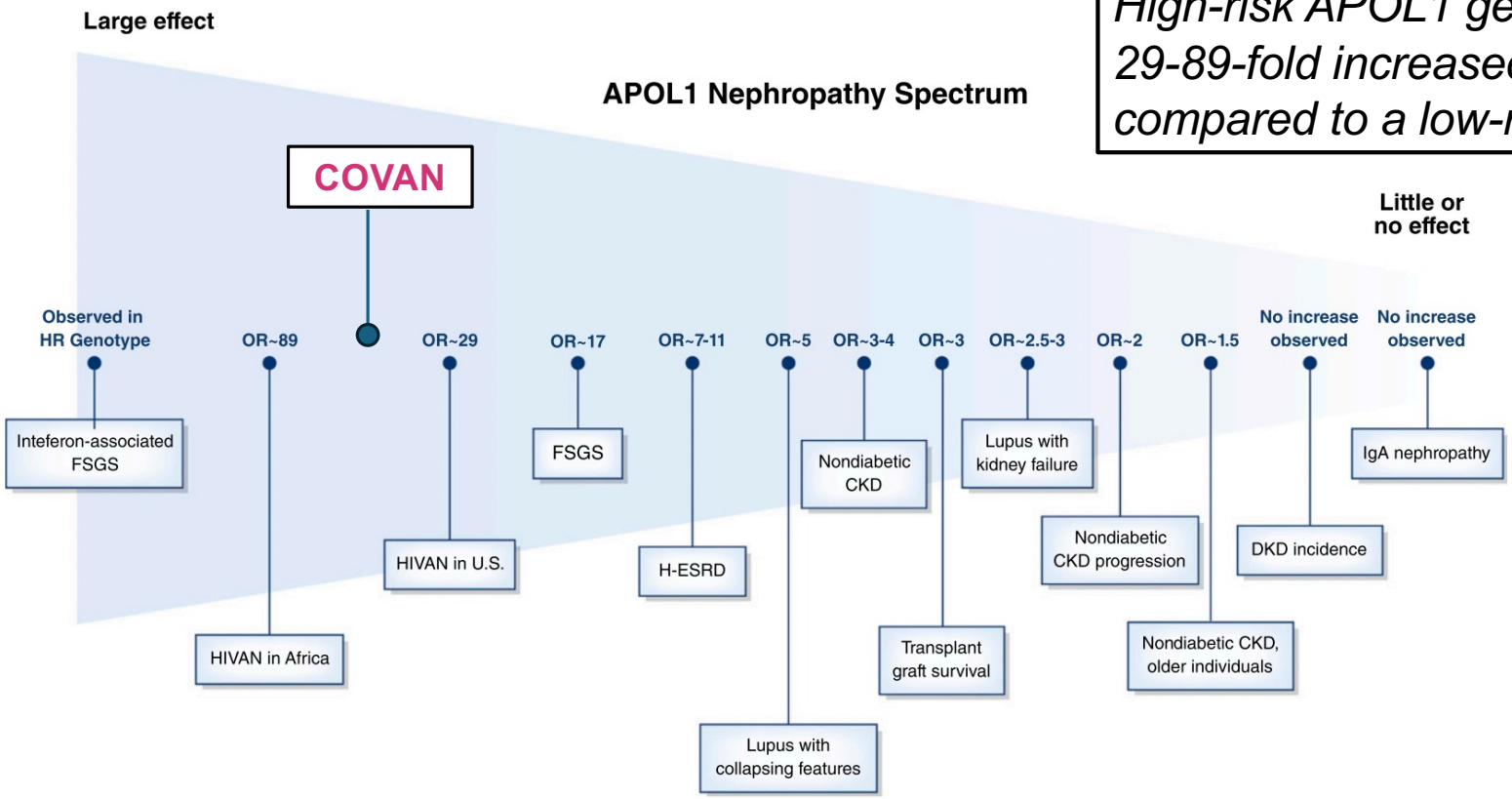


Prevalence of a high-risk genotype
United States: 10-15%
West Africa: 30-40%
South & East Africa: 5-12%

Daneshpajouhnejad P, et al. The evolving story of apolipoprotein L1 nephropathy: the end of the beginning. *Nat Rev Nephrol*. 2022;18(5):307-320.

HIVAN is the ultimate APOL1 nephropathy

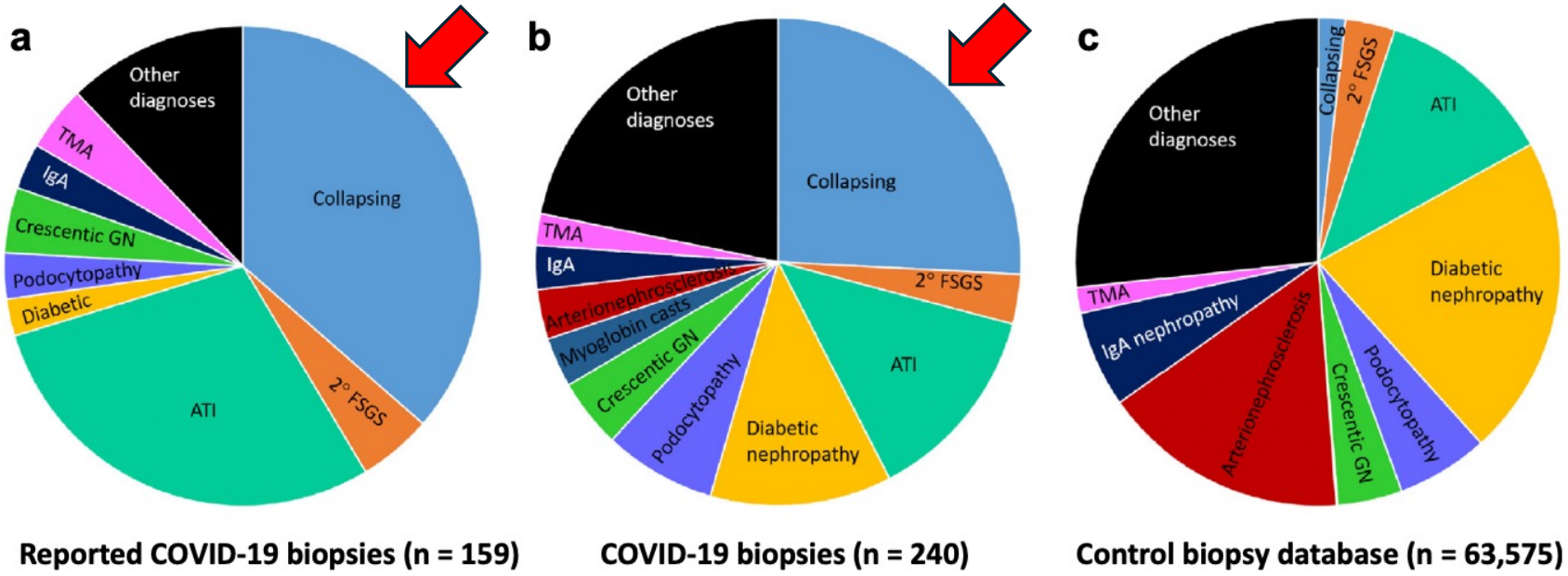
High-risk APOL1 genotype confers 29-89-fold increased odds of HIVAN compared to a low-risk genotype



Friedman DJ, Pollak MR. APOL1 Nephropathy: From Genetics to Clinical Applications. Clin J Am Soc Nephrol. 2021 Feb 8;16(2):294-303..

COVID-19 Associated Collapsing Glomerulopathy (COVAN) is the new HIVAN

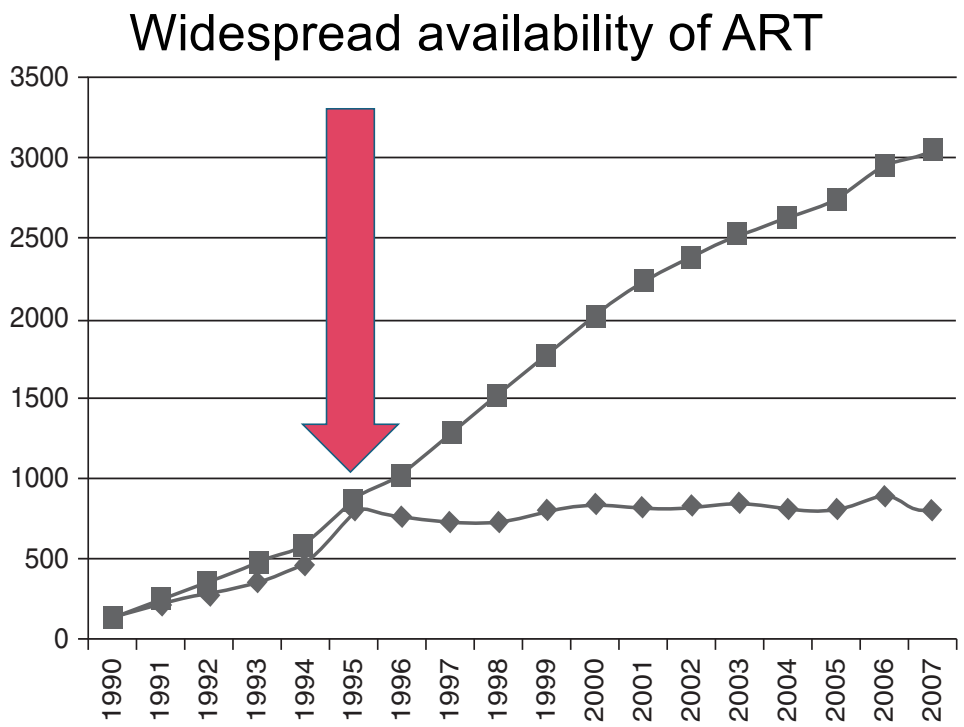
International review of 240 kidney biopsies from patients with COVID-19 associated AKI → COVAN most common finding → ***90% with 2 high risk APOL1 alleles***



Reported COVID-19 biopsies (n = 159) **COVID-19 biopsies (n = 240)** **Control biopsy database (n = 63,575)**

May RM, Cassol C, Hannoudi A, et al. A multi-center retrospective cohort study defines the spectrum of kidney pathology in Coronavirus 2019 Disease (COVID-19). Kidney Int. 2021 Dec;100(6):1303-1315.

ART halted the rising incidence of end-stage kidney disease due to HIVAN



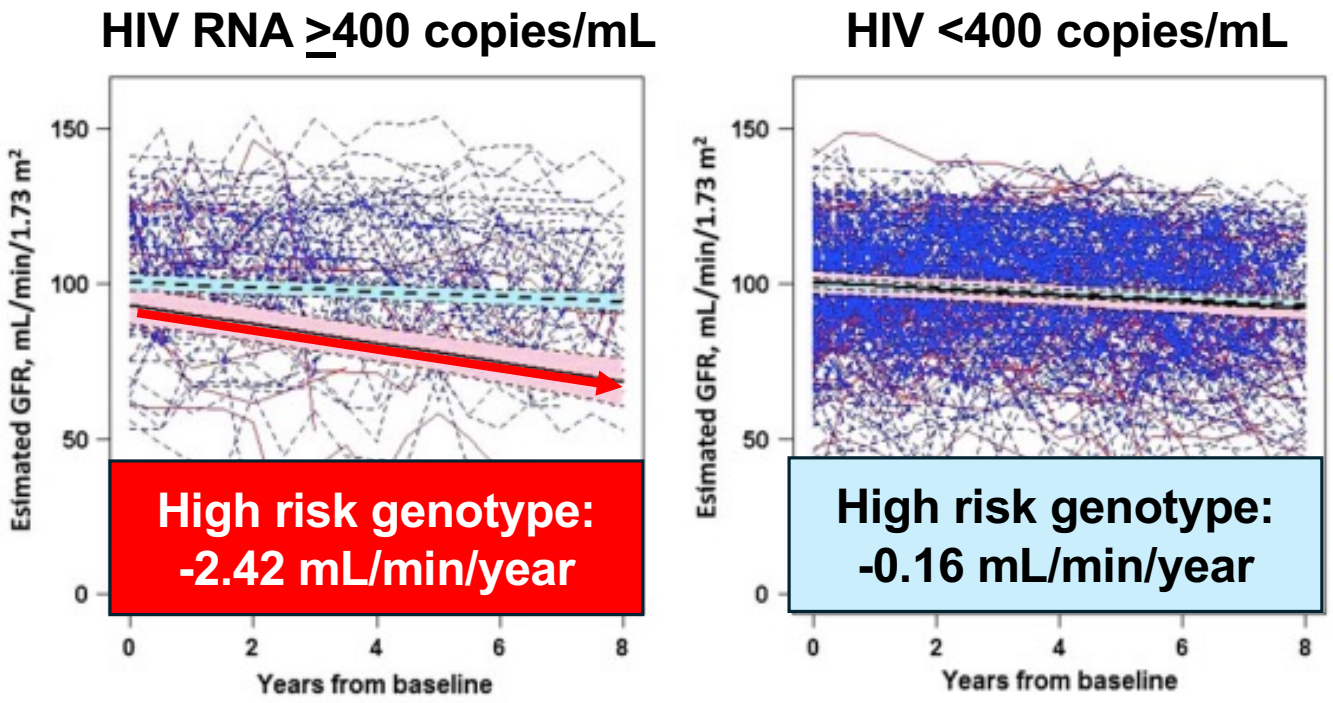
HIVAN is a *treatable* APOL1-related nephropathy

Incidence of ESRD from HIVAN (cases/yr)

Prevalence of ESRD from HIVAN (cases/yr)

Razzak CS, et al. Trends in the outcomes of end-stage renal disease secondary to human immunodeficiency virus-associated nephropathy. *Nephrol Dial Transplant*. 2015;30(10):1734-1740

Viral suppression modifies association between APOL1 and kidney function decline



P for interaction <0.001

Estrella MM, et al. The association between APOL1 risk alleles and longitudinal kidney function differs by HIV viral suppression status. Clin Infect Dis. 2015 Feb 15;60(4):646-52.

What does HIVAN look like in 2024?

- Classic HIVAN still seen in ART-naïve or PWH nonadherent to ART
  - 14% of kidney biopsies at Columbia from 2010-2019 (36% on ART)

- Rise in the prevalence of non-collapsing FSGS in the ART era
  - Seen in those receiving ART
  - CD4 count >200 cells/mm^3
  - Undetectable HIV RNA

- Non-collapsing FSGS hypothesized to represent partially treated HIVAN

A patient with controlled HIV and proteinuria

- *55 y/o male with HIV and hypertension referred for proteinuria*
- *HIV diagnosed >20 years ago, controlled*

Laboratory Data	Value
CD4 count, cells/mm^3	351
HIV RNA, copies/mL	<20
Serum albumin, g/dL	4.1
Creatinine, mg/dL	1.2
eGFR, mL/min/1.73m^2	71
Urine protein-creatinine, mg/g	3200

Home Medications:
Bictegravir-emtricitabine-tenofovir alafenamide
Amlodipine

What is the most likely cause of his kidney failure?

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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

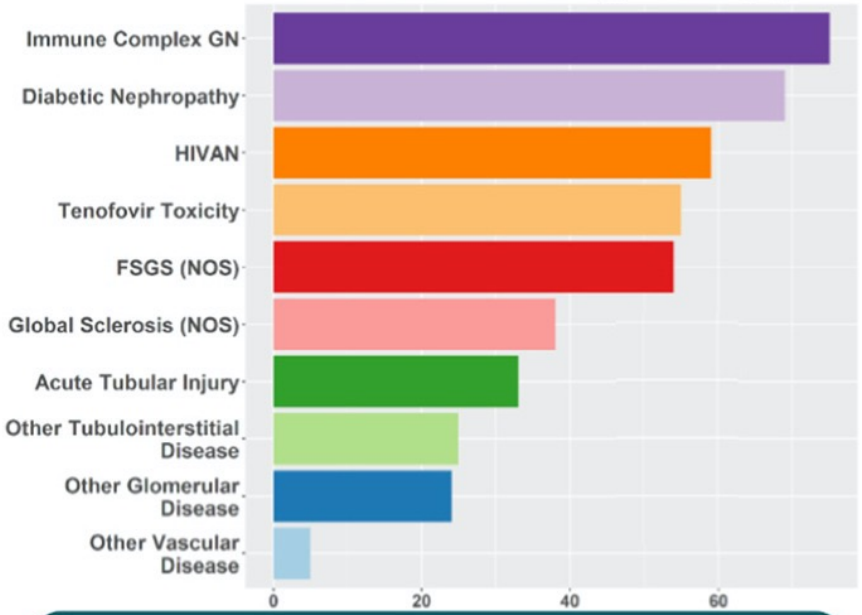
Study cohort

437 (1.6%) from HIV-infected pts
Mean age: 53 yrs
Sex: 66% male
Race: 58% black, 25% white,
17% Hispanic, <1% Asian
On antiretroviral therapy (ART): 80%

Comorbidities:
- Hypertension: 57%
- Diabetes: 31%
- HCV co-infection: 27%

*Dual diagnoses were present in 17% of cases

Breakdown of diagnoses (n)*



CONCLUSION:

ART has changed the landscape of HIV-associated kidney disease toward diverse immune complex GN, diabetic nephropathy, and non-collapsing glomerulosclerosis, but has not eradicated HIVAN.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Kudose et al, 2019

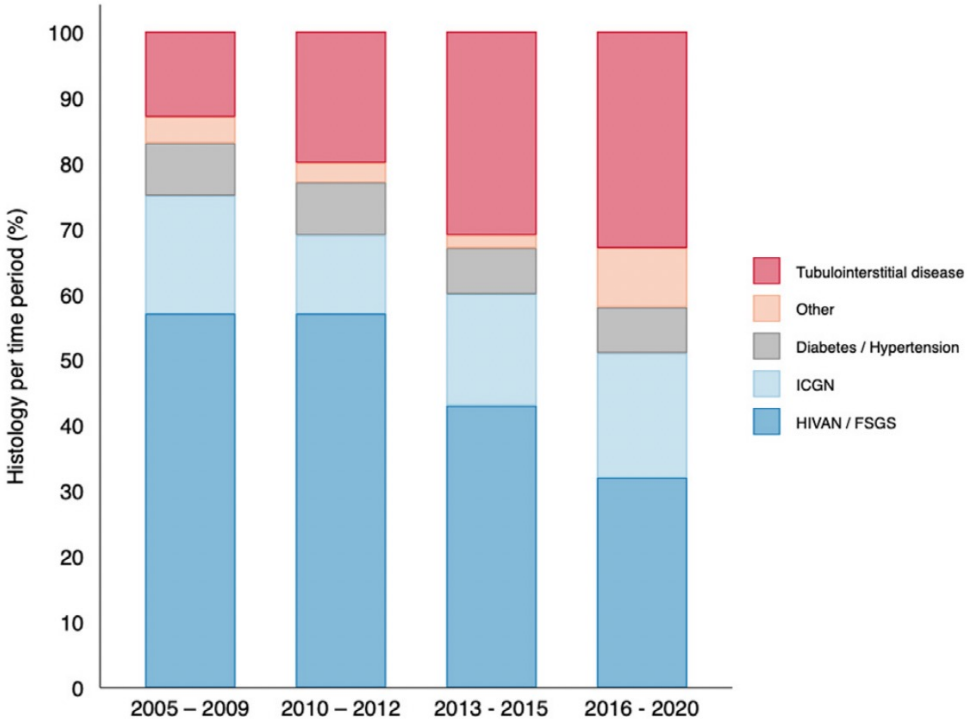
Clinical Features of Kidney Diseases in PWH

	N	Age	Black	ART	HTN	DM	CVD	Cr, mg/dL median (IQR)	UPCR, g/g median (IQR)	Nephrotic range proteinuria	Nephrotic syndrome
HIVAN	59	43	**94%**	**36%**	47%	12%	2%	5.0 (3.6, 7.7)	6 (3.6, 10.4)	74%	62%
Immune complex GN	75	51	47%	71%	63%	15%	9%	1.9 (1.2, 3.2)	4 (2, 7)	58%	42%
FSGS	54	53	68%	77%	65%	13%	13%	2.5 (1.5, 3.8)	3.3 (2, 5)	45%	18%
Global sclerosis	9	57	52%	88%	74%	24%	11%	2.1 (1.7, 3.9)	2.8 (1.2, 4.6)	34%	14%
Diabetic nephropathy	16	56	59%	88%	**78%**	100%	**22%**	2.4 (1.7, 4.2)	5.5 (3.5, 9.2)	71%	57%

In those with controlled HIV, difficult to determine cause of heavy proteinuria clinically

Kudose S et al. The spectrum of kidney biopsy findings in HIV-infected patients in the modern era. *Kidney Int*. 2020;97(5):1006-1016.

TDF use predictor of tubulointerstitial disease on kidney biopsy in South Africans



ART rollout | TDF | fixed dose TDF| ART at HIV diagnosis

671 participants
49% female, median age 36

Marked ↑ tubulointerstitial disease (TID)

- 48% due to TB
- Exposure to TDF → ~3 fold higher odds of TID

Independent predictors of HIVAN/FSGS

- CD4 <200
- Black race
- Not on ART

Wearne N, Manning K, Price B, et al. The Evolving Spectrum of Kidney Histology in HIV-Positive Patients in South Africa. Kidney Int Rep. 2023 Feb 23;8(5):1087-1096.

Immune complex glomerulopathy (ICGN) in PWH

- KDIGO classification replaced the term “HIVICK” with ”immune complex glomerulonephritis in the setting of HIV” in 2018

- Heterogeneous spectrum → limits ability to study
  - Membranous nephropathy
  - IgA nephropathy
  - Lupus like glomerulonephritis
  - Fibrillary glomerulonephritis

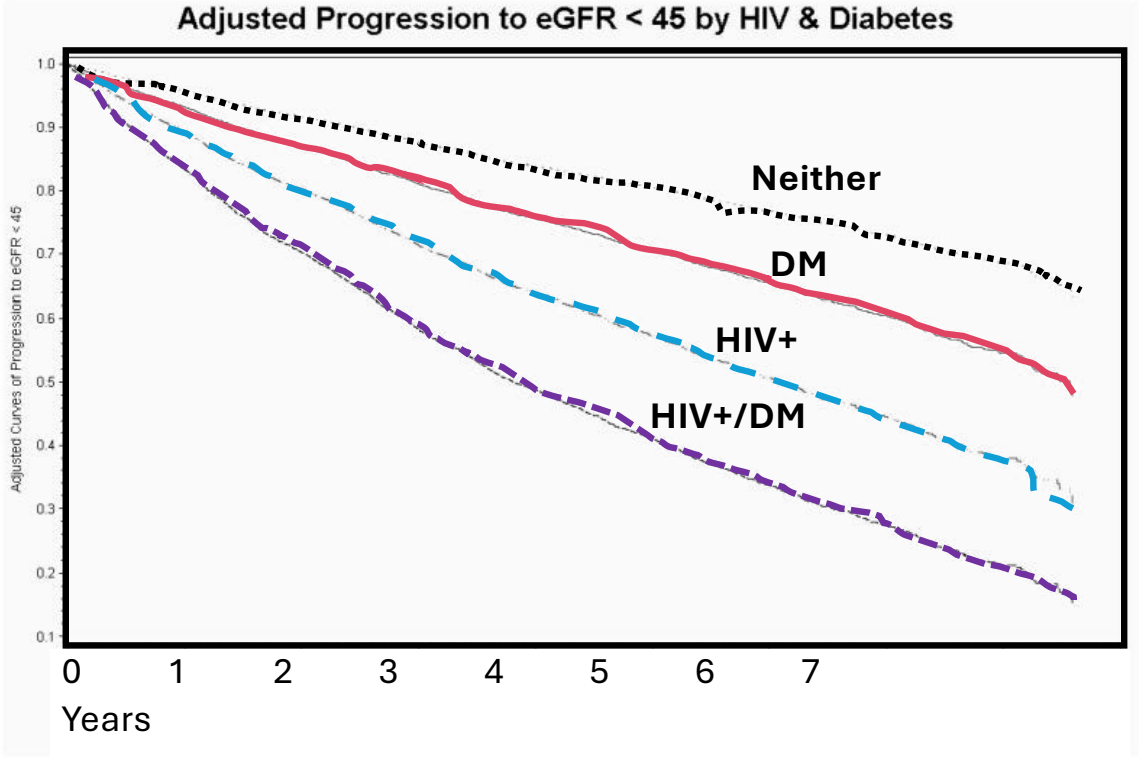
- Causal relationship to HIV unclear
  - Hypothesized to be due to host immune response to HIV – immune complexes eluted from PWH with ICGN found to be directed against HIV antigens
  - Lack of animal models

Comorbidity related CKD in PWH

- >50% of PWH in the US are over the age of 50
- Traditional CKD risk factors common
- *May have additive/ synergistic effect on CKD progression*

Estimated Prevalence of CKD Risk Factor Comorbidities		
	General population	**People with HIV**
Diabetes	8.5%	**14%**
Hypertension	30%	**35%-50%**
Hepatitis C	1%	**30%**
Tobacco use	15%	**34-47%**

HIV + diabetes Additive Effect on CKD Progression



31,072 Veterans with baseline eGFR >45 followed for median 5 years

HIV + diabetes
4.5-fold higher risk of eGFR decline to <45 mL/min

Medapalli RK, Parikh CR, Gordon K, et al. Comorbid diabetes and the risk of progressive chronic kidney disease in HIV-infected adults: data from the Veterans Aging Cohort Study. J Acquir Immune Defic Syndr. 2012 Aug 1;60(4):393-9

Additive Effect of HIV + Hepatitis C on CKD Risk

Among a cohort of PWH: 52,602 HCV negative; 9,508 HCV with viremia; 913 HCV +Ab only

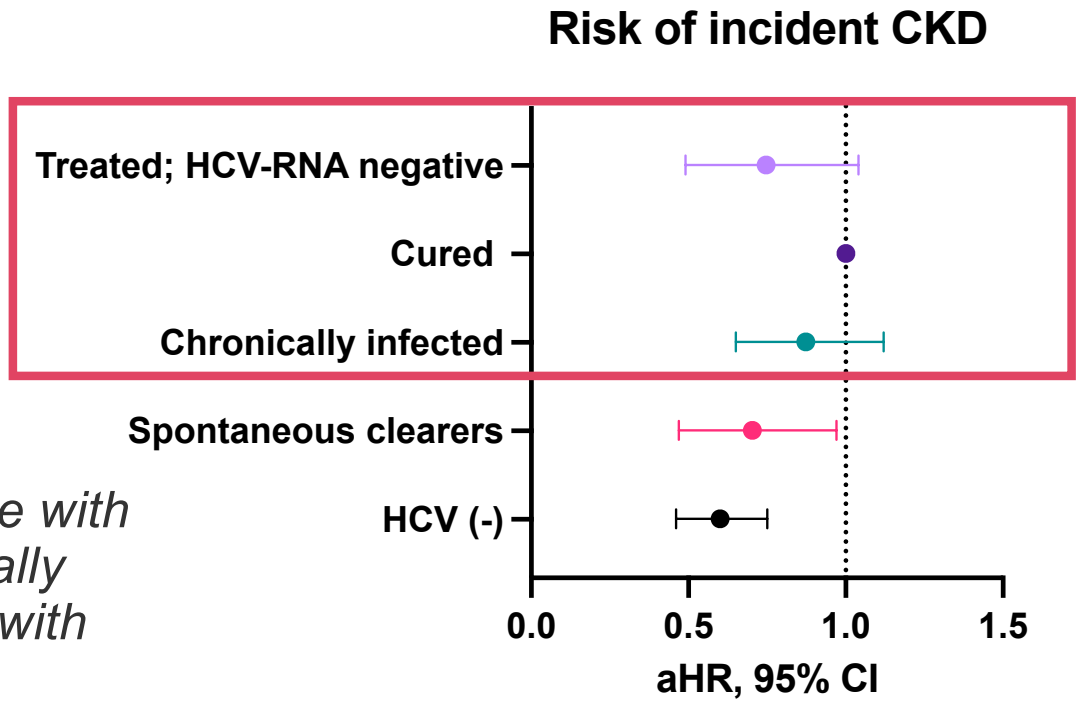
Outcome	Event number	Adjusted
CKD Stage 3		
HCV (-)	5,090	-
HCV (+) viremia	1,662	**1.36** (1.26, 1.46)
HCV (+) no viremia	122	1.19 (0.98, 1.45)
Progressive CKD		
HCV (-)	699	-
HCV (+) viremia	376	**1.95** (1.64, 2.31)
HCV (+) no viremia	23	**1.69** (1.07, 2.65)
CKD Stage 5		
HCV (-)	2,885	-
HCV (+) viremia	984	**1.31** (1.19, 1.44)
HCV (+) no viremia	76	**1.31** (1.02, 1.68)

Adjusted for age, sex, race, IVDU, hepatitis B surface antigen, baseline eGFR, nephrotoxic ART, HTN, diabetes, CD4, HIV RNA

Lucas GM, Jing Y, Sulkowski M, et al. Hepatitis C viremia and the risk of chronic kidney disease in HIV-infected individuals. J Infect Dis. 2013 Oct 15;208(8):1240-9.

Incident CKD after hepatitis C cure in PWH

- ~15,000 PWH
- Median age 43
- 85% White
- 75% HIV viral suppression
- 50% smokers
- Median follow-up of 7 years
  - *Risk of CKD similar in those with HCV cure to those chronically infected and those treated with viremia*



Mocroft A, Ryom L, Oprea C, et al; EuroSIDA study group. Influence of hepatitis C virus co-infection and hepatitis C virus treatment on risk of chronic kidney disease in HIV-positive persons. AIDS. 2020 Aug 1;34(10):1485-1495.

Summary 3: The patient with HIV who presents with heavy proteinuria

- Young, African ancestry, absence of comorbidities, low CD4, unsuppressed HIV viral load → most likely HIVAN

- Everyone else → cannot differentiate etiology clinically

- Any virally suppressed PWH with heavy proteinuria +/- declining kidney function → refer to nephrology for consideration of kidney biopsy

- Comorbidity-related CKD risk factors have an additive effect on CKD progression

Learning objectives

- How to assess kidney function in people with HIV (PWH)
- Which antiretroviral therapy (ART) medications are nephrotoxic
- How to evaluate the spectrum of kidney diseases in the ART era
- How to manage chronic kidney disease in PWH

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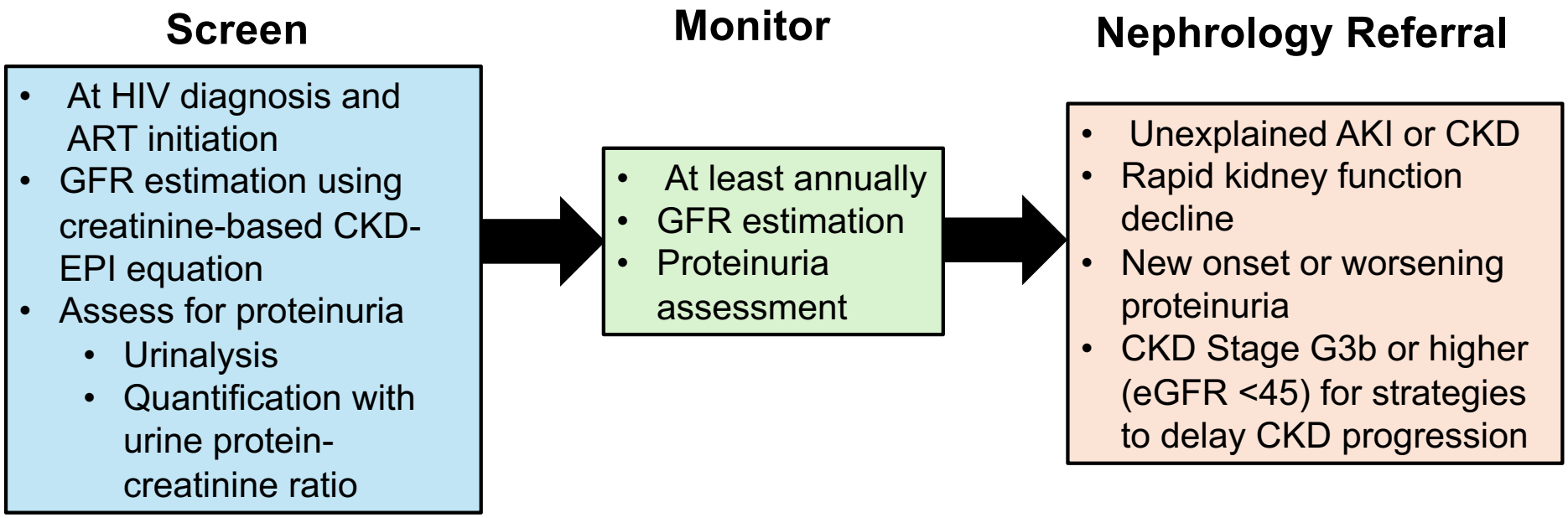
Recommended CKD screening and monitoring



Swanepoel CR et al. Kidney disease in the setting of HIV infection: Conclusions from a kidney disease: Improving global outcomes (KDIGO) controversies conference. *Kidney Int.* 2018;93(3):545-559.

Monitoring Kidney Function

Low CKD risk	GFR estimation and proteinuria assessment Yearly during follow up if stable and virologically suppressed Before and 1 month after ART modification
High CKD risk	GFR estimation and proteinuria assessment Twice yearly if stable and virologically suppressed Before and 1 month after ART modification
On TDF + ritonavir or cobicistat	Same as high-risk + Serum phosphorus Urinalysis Fractional excretion of phosphorus + urine low-molecular weight protein in those with suspected proximal tubulopathy

Swanepoel CR et al. Kidney disease in the setting of HIV infection: Conclusions from a kidney disease: Improving global outcomes (KDIGO) controversies conference. *Kidney Int.* 2018;93(3):545-559.

Management of CKD in People with HIV

- Clinical guidelines for CKD prevention and treatment in PWH are extrapolated from studies in the general population

- Co-management between HIV specialist and nephrologist

- Focused on interventions to delay CKD progression in those at high risk - GFR <45 mL/min per 1.73 m^2 and/or $\geq$ 300 mg/g albuminuria

- Kidney transplant referral in PWH with controlled HIV and eGFR <25

Co-Management of CKD with Nephrology

- Establish a diagnosis
  - Quantification of proteinuria with urinalysis or urine albumin-creatinine ratio
  - Kidney biopsy if could alter treatment

- Recognize and treat complications of CKD
  - Electrolyte disturbances – hyperkalemia, metabolic acidosis
  - Anemia
  - Mineral bone disease

- Delay CKD progression

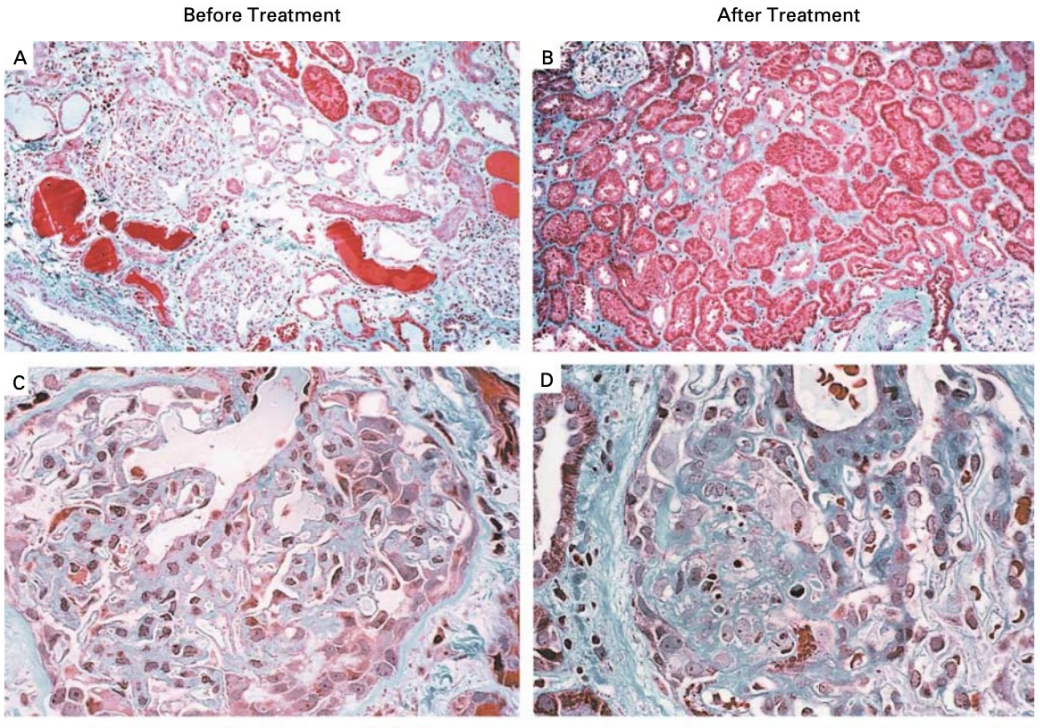
Strategies to delay CKD Progression in PWH

- Treatment with ART
  - Avoid nephrotoxic ART (TDF, atazanavir)

- Supportive care – same as general population with CKD
  - Control BP
    - ACC/AHA: BP <130/80 mm Hg
    - KDIGO: Standardized office SBP <120 mm Hg
  - Treat albuminuria (>300 mg)
    - ACE inhibitor or ARB
    - SGLT2 inhibitors

- Targeted treatment
  - Immunosuppression if glomerulonephritis in a patient on stable ART

HIVAN is reversible with ART treatment

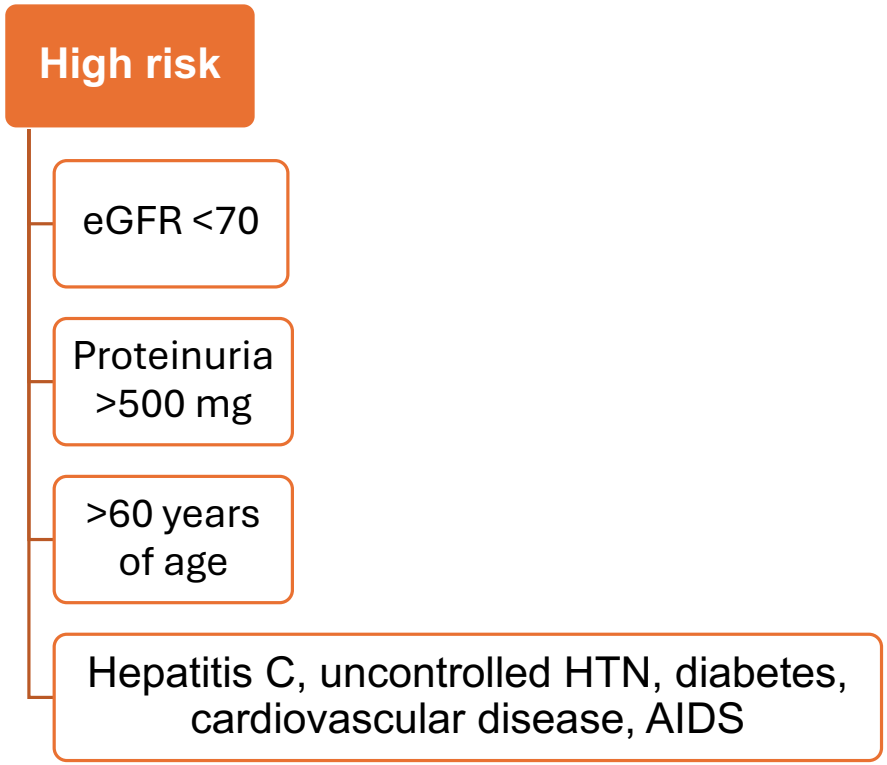


- Reversal of histological lesions after ART initiation
- Even those with HIVAN requiring dialysis can come off after ART initiation

Winston JA, Bruggeman LA, Ross MD, et al. Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. N Engl J Med. 2001 Jun 28;344(26):1979-84.

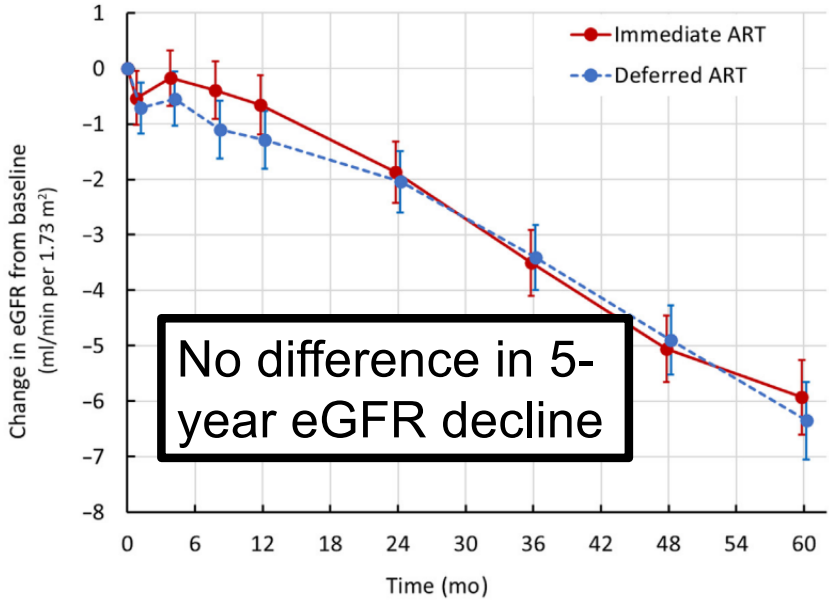
ART in those at risk and with preexisting CKD

- Don't start TDF, Atazanavir, or Lopinavir if eGFR <70
- If eGFR falls to <60 while on these medications → change to alternative regimen



Swanepoel CR, et al; Conference Participants. Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2018 Mar;93(3):545-559

Early initiation of ART does not negatively impact kidney function decline long-term



Visit month	0	12	24	36	48	60
Immediate	2115	2019	1971	1913	1875	1413
Deferred	2169	2017	1964	1923	1870	1407

Immediate vs delayed ART in ~4600 ART-naïve adults with CD4 >500

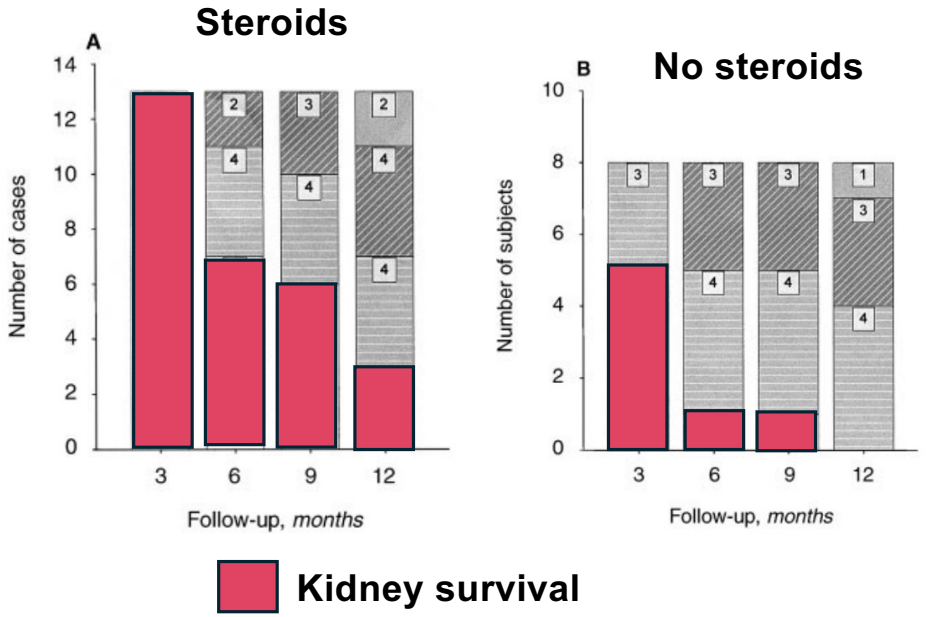
At baseline: age 36, 73% men, 30% Black, CD4 651, eGFR 111

Initial ART included TDF in 85%
Cumulative TDF duration 59 vs 29 months

INSIGHT START Study Group. Long-term impact of immediate versus deferred antiretroviral therapy on kidney health in people with HIV. Kidney Int. 2024 May 1:S0085-2538(24)00313-2.

What about Steroids in HIVAN?

- *Limited to case series in pre-ART era*
  - 21 patients
    - 13 treated with 60 mg prednisone x 1 month followed by taper
    - 8 not given steroids
  - Mean creatinine ~6 mg/dL
  - Mean proteinuria 3-6 g
  - All CD4 <200
  - Only 1 on an ACE inhibitor
  - 30-50% on ART



Eustace JA, Nuermberger E, Choi M, et al. Cohort study of the treatment of severe HIV-associated nephropathy with corticosteroids. Kidney Int. 2000 Sep;58(3):1253-60.

No clear benefit of steroids in COVAN

- 43 patients with COVAN and longitudinal follow up data

- *At time of diagnosis*
  - **90%** AKI
  - **96%** hypoalbuminemia
  - **81%** nephrotic range proteinuria
  - **86%** high risk APOL1 genotype

- Mean follow up 244 days
  - 37% AKI requiring dialysis → 50% remained dialysis dependent
  - 12 patients given corticosteroids – no difference in kidney survival

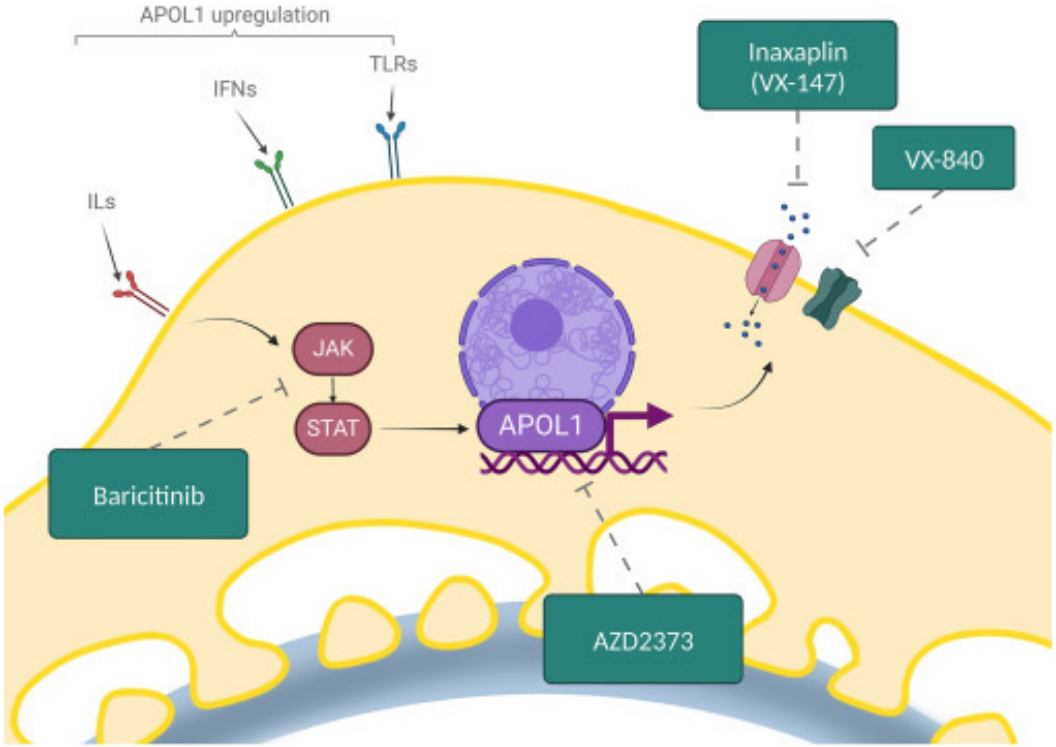
Giannini G, Carlos Q Velez J, et al. Renal Prognosis of COVID-19 Associated Nephropathy. Kidney Int Rep. 2022 Dec;7(12):2722-2725.

Immunosuppression for immune complex glomerulonephritis (ICGN) in the setting of HIV

- Role not established
  - Data limited to case reports
  - Lack of data on long-term outcomes with use of specific immunosuppression

- *Consider immunosuppression based on proliferative lesions on biopsy and degree of proteinuria in patients with controlled HIV*

Novel therapies – targeting APOL1



70% of PWH with HIVAN have a high risk APOL1 genotype

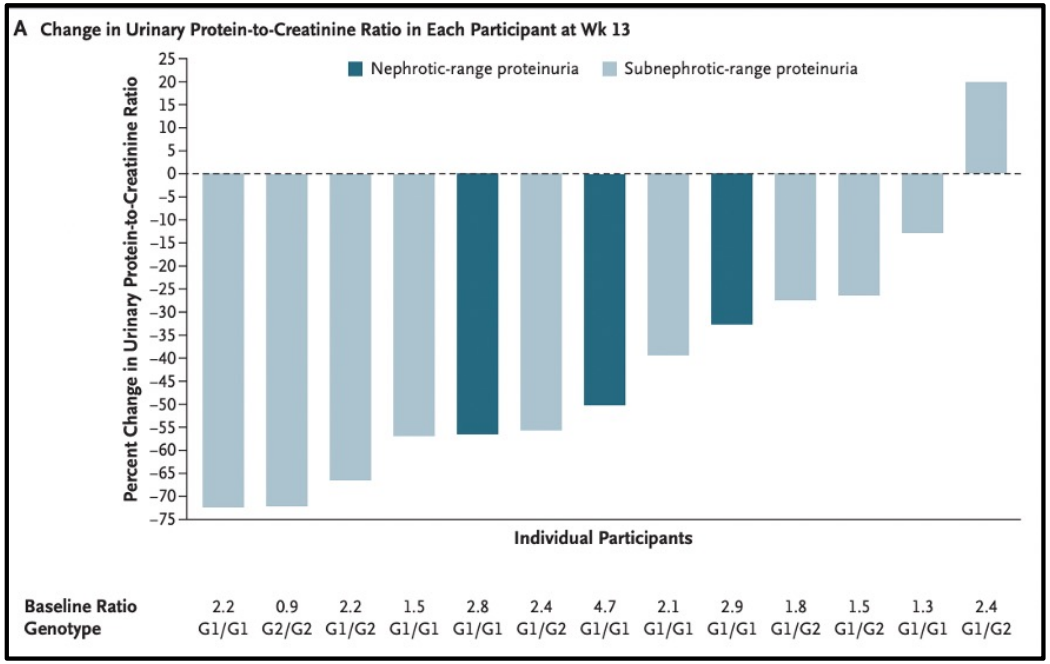
Small molecular inhibitors of APOL1 – block APOL1 channel (phase 2/3 trial)

***APOL1* ASOs** – oligonucleotide analogs that modify expression of specific RNAs and can alter protein synthesis (phase 1 trial)

JAK inhibitor (phase 2 trials)

Inaxaplin (APOL1 inhibitor)

- 13 patients with FSGS + high-risk APOL1 genotype treated with inaxaplin x 13 weeks
  - UPCR: ≥ 700-10,000 mg/g
  - eGFR ≥ 27 mL/min/1.73 m^2
- Significant reduction in proteinuria
  - Change in UPCR: **−47.6%** (95% CI, −60.0 to −31.3)



Egbuna O, et al. VX19-147-101 Study Group. Inaxaplin for Proteinuric Kidney Disease in Persons with Two *APOL1* Variants. N Engl J Med. 2023 Mar 16;388(11):969-979.

Novel APOL1 therapeutics in clinical trials

- Adaptive Study of VX-147 in adults and adolescents with APOL1 mediated kidney disease
  - Phase 2/3, double blind, randomized, placebo-controlled study in patients with non-diabetic proteinuric CKD with high risk APOL1 genotype

- JAK/STAT inhibitor to Reduce APOL1 mediated kidney disease (JUSTICE)
  - Phase 2, double-blind, randomized, placebo-controlled study of Baricitinib in patients with FSGS or HTN-CKD

- ***Patients with HIV to date have been excluded from these trials***

Significant Progress in Kidney Transplant in PWH

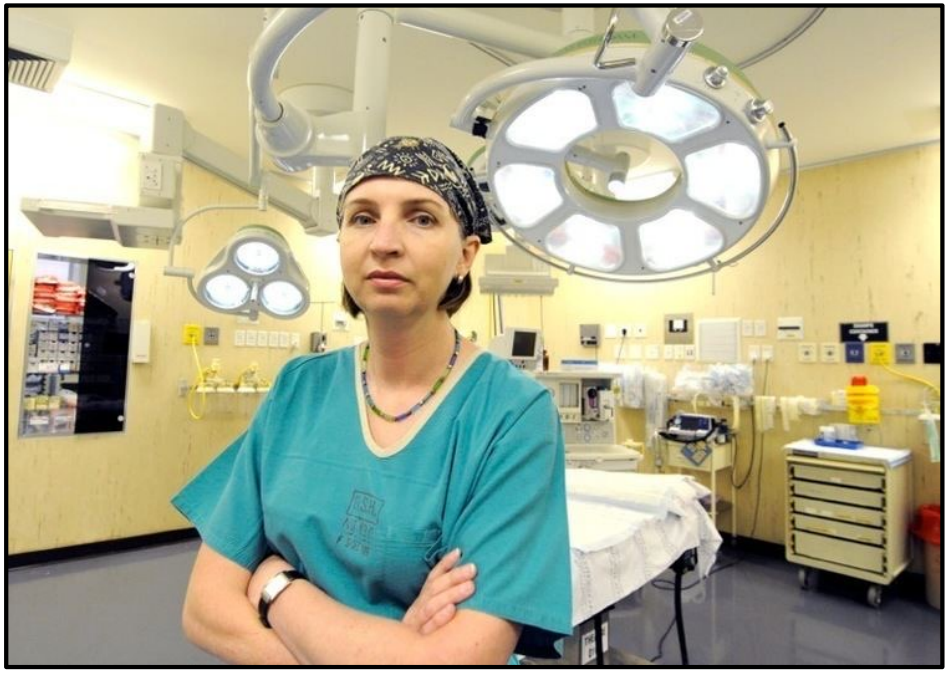
- Overall good short and long-term outcomes
  - 1- and 3-year recipient and allograft survival similar to general population

- Higher rates of acute rejection

- Drug-drug interactions with immunosuppression and antiretrovirals
  - Consult with infectious disease
  - Avoid protease inhibitors and pharmaco-enhancers (ritonavir, cobicistat)
    → switch to integrase inhibitor pre-transplant recommended

Zarinsefat A, et al. JAMA Surg. 2022
Blumberg EA et al; American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019

HIV+ Donor to HIV+ Recipient Kidney Transplantation



2008: First HIV+ Donor Kidney Transplant into HIV+ Patient in South Africa

2013: HIV Organ Policy Equity Act passed in the US

2015: OPTN policy and system change to implement the HOPE act

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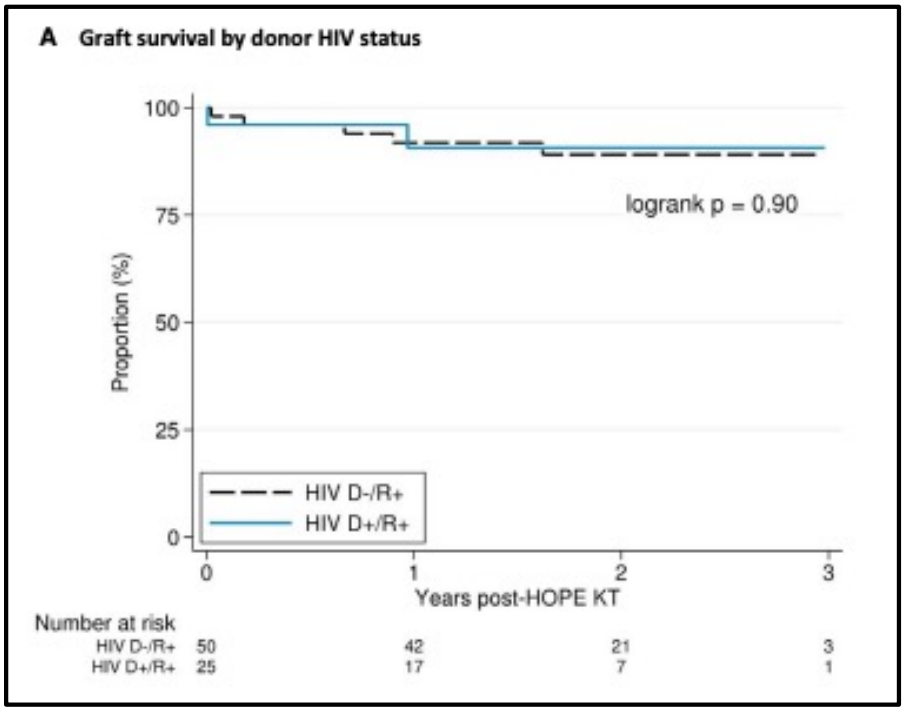
HIV+ deceased donor to HIV+ recipient kidney transplantation

- 75 HIV+ kidney transplants
  - 25 donor (+) and 50 donor (-)

- Excellent short-term outcomes
  - No deaths
  - No difference 1-year graft survival
  - No difference 1-year eGFR
  - No difference in HIV breakthrough, infectious hospitalizations or opportunistic infections



Durand CM, et al. A prospective multicenter pilot study of HIV-positive deceased donor to HIV-positive recipient kidney transplantation: HOPE in action. *Am J Transplant*. 2021;21(5):1754-1764.

2019: First Living HIV+ Donor provides Kidney Transplant to an HIV+ Recipient

Potential to expand kidney donor organ pool with live donation

Durand CM, et al; HOPE in Action Investigators. Living kidney donors with HIV: experience and outcomes from a case series by the HOPE in Action Consortium. Lancet Reg Health Am. 2023 Jul 24;24:100553.

Does HIVAN come back after kidney transplant?

- South Africa → 24% of kidney transplants with some histological features of HIVAN (N=51)
  - In most, this did not affect graft functioning
- Given the strong association between *APOL1* risk variants and HIVAN, recipients of African descent and those who receive an allograft from a donor of African descent should be monitored for recurrent HIVAN
- Contribution of donor and recipient *APOL1* risk variants being evaluated in the APOLLO study

Summary 4: Management of CKD in HIV

- Early referral to nephrologist for evaluation of CKD and strategies to delay CKD progression
- Avoid nephrotoxic ART in those at high risk or with preexisting CKD
- New APOL1 therapies for APOL1-mediated kidney disease in clinical trials
- Kidney transplant outcomes similar to the general population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