Kidney diseases in the setting of HIV infection

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Disclosure

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  - Gilead
  - ViiV
  - MSD
  - Pfizer
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Outline

- The determinants of organ damage in HIV infection
- HIV-related kidney diseases
- Renal effects of ART
- CKD related to non-infectious co-morbidities

KIDNEY DISEASES IN THE SETTING OF HIV INFECTION

THE DETERMINANTS OF ORGAN DAMAGE IN HIV INFECTION

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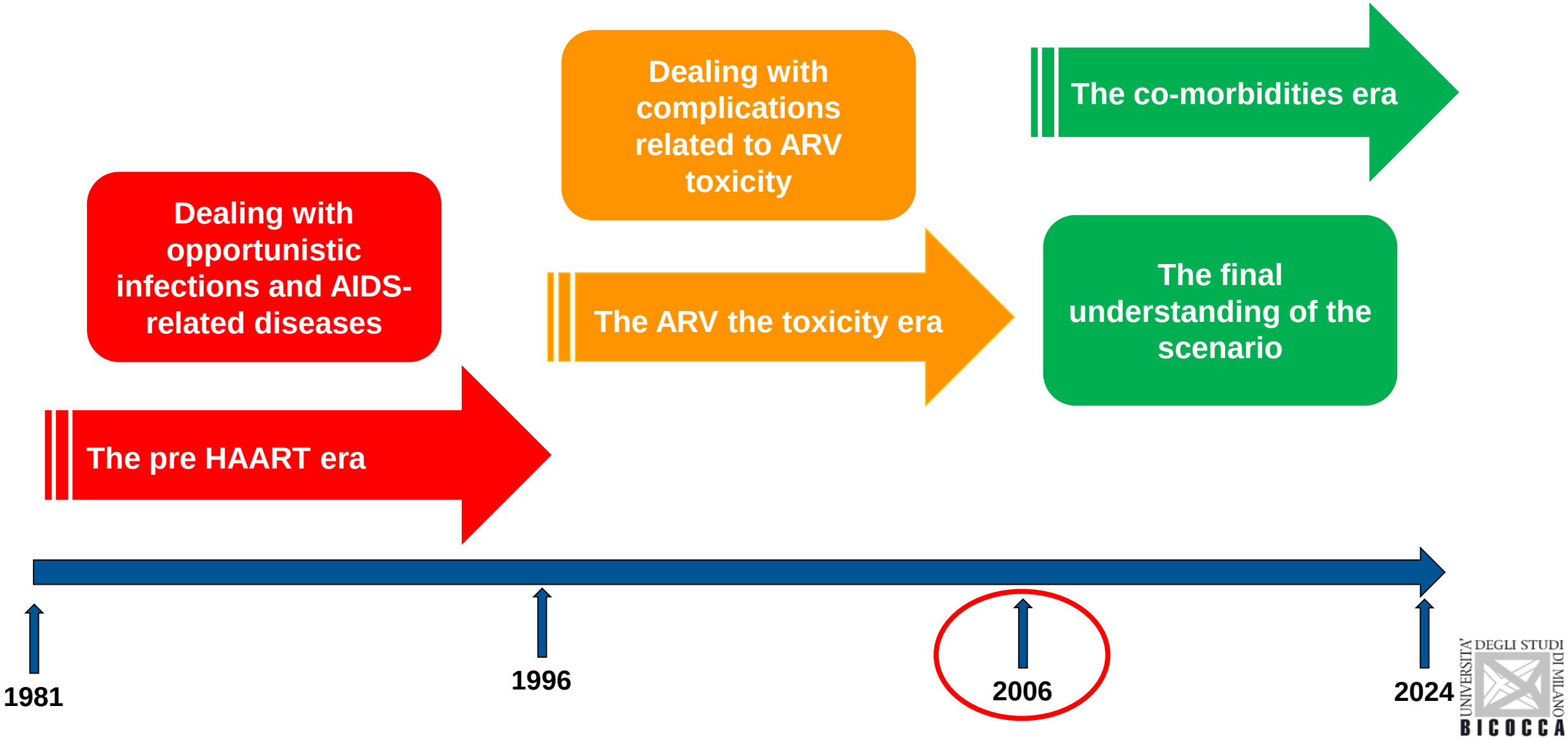
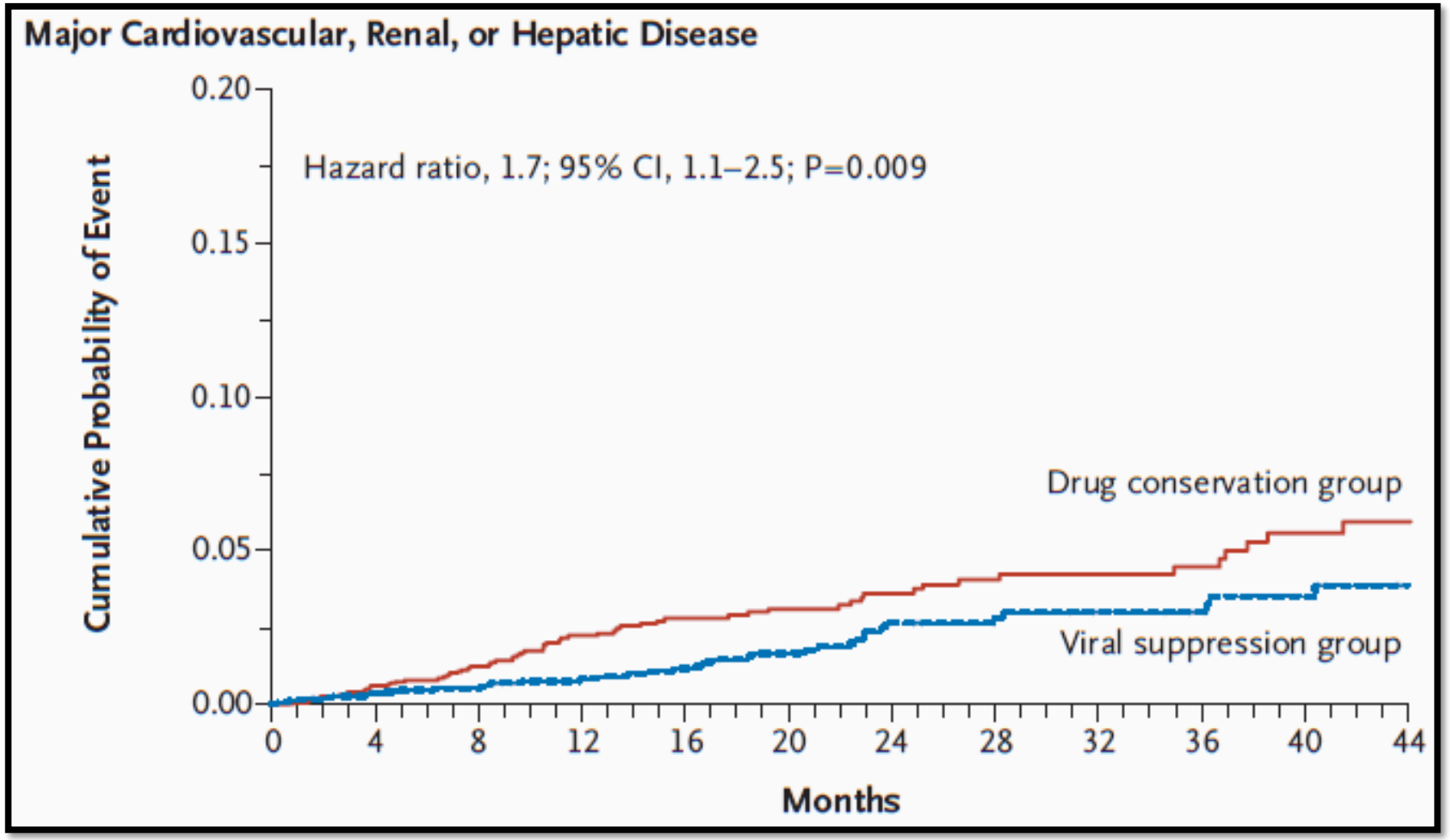
The evolution of the eras of clinical management of HIV infection



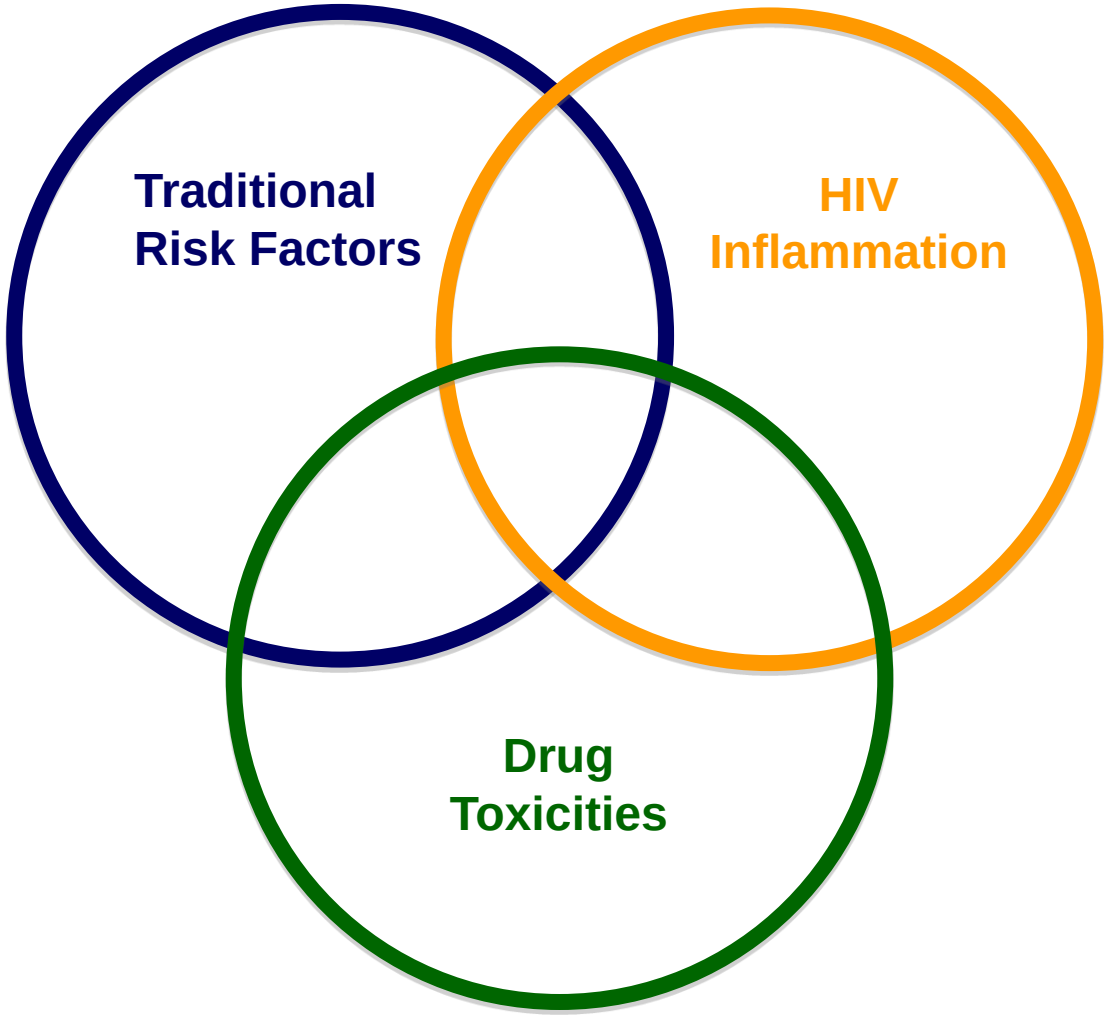
The SMART Study

The heterogenesis of ends

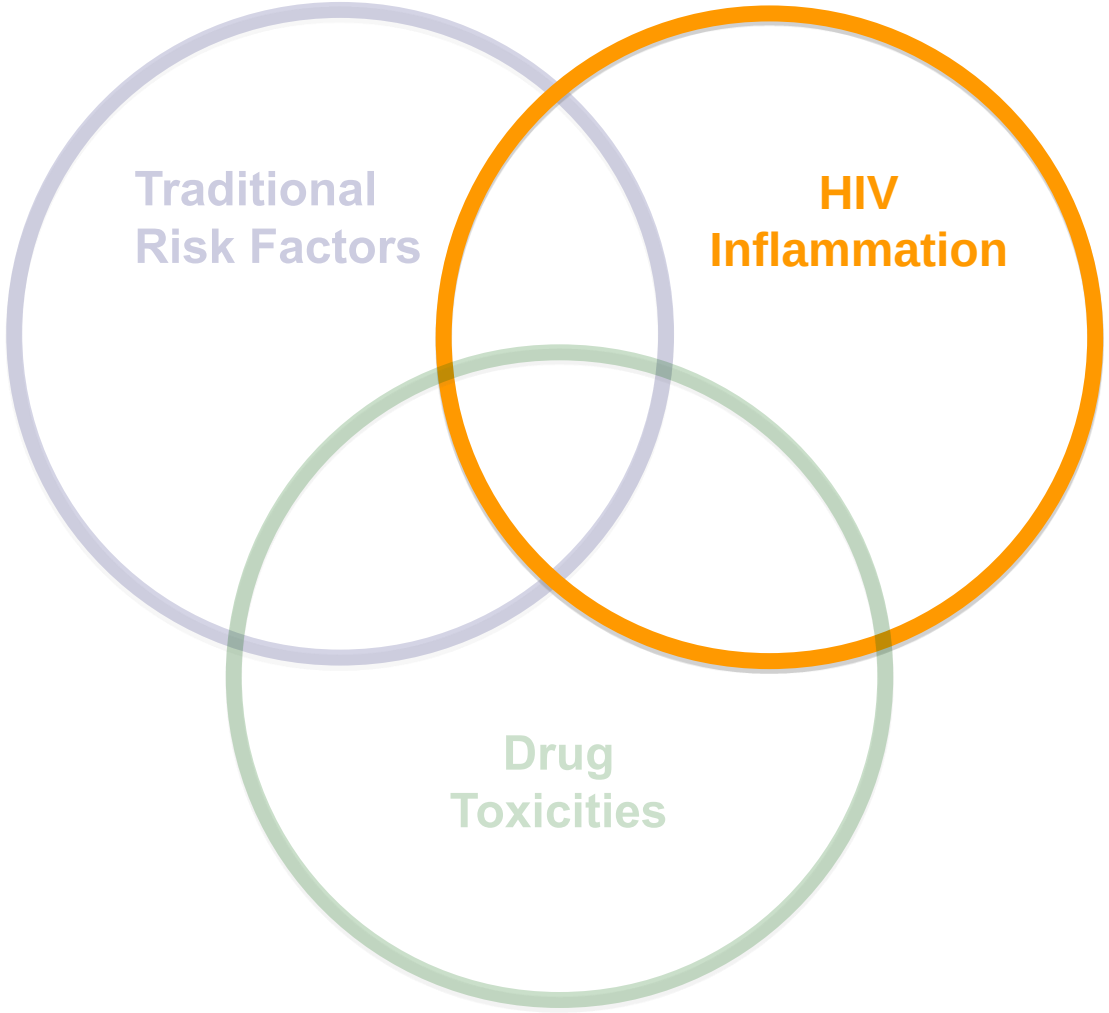


SMART Study Group, *N Engl J Med 2006*

What Contributes to the Risk of NCDs in HIV?



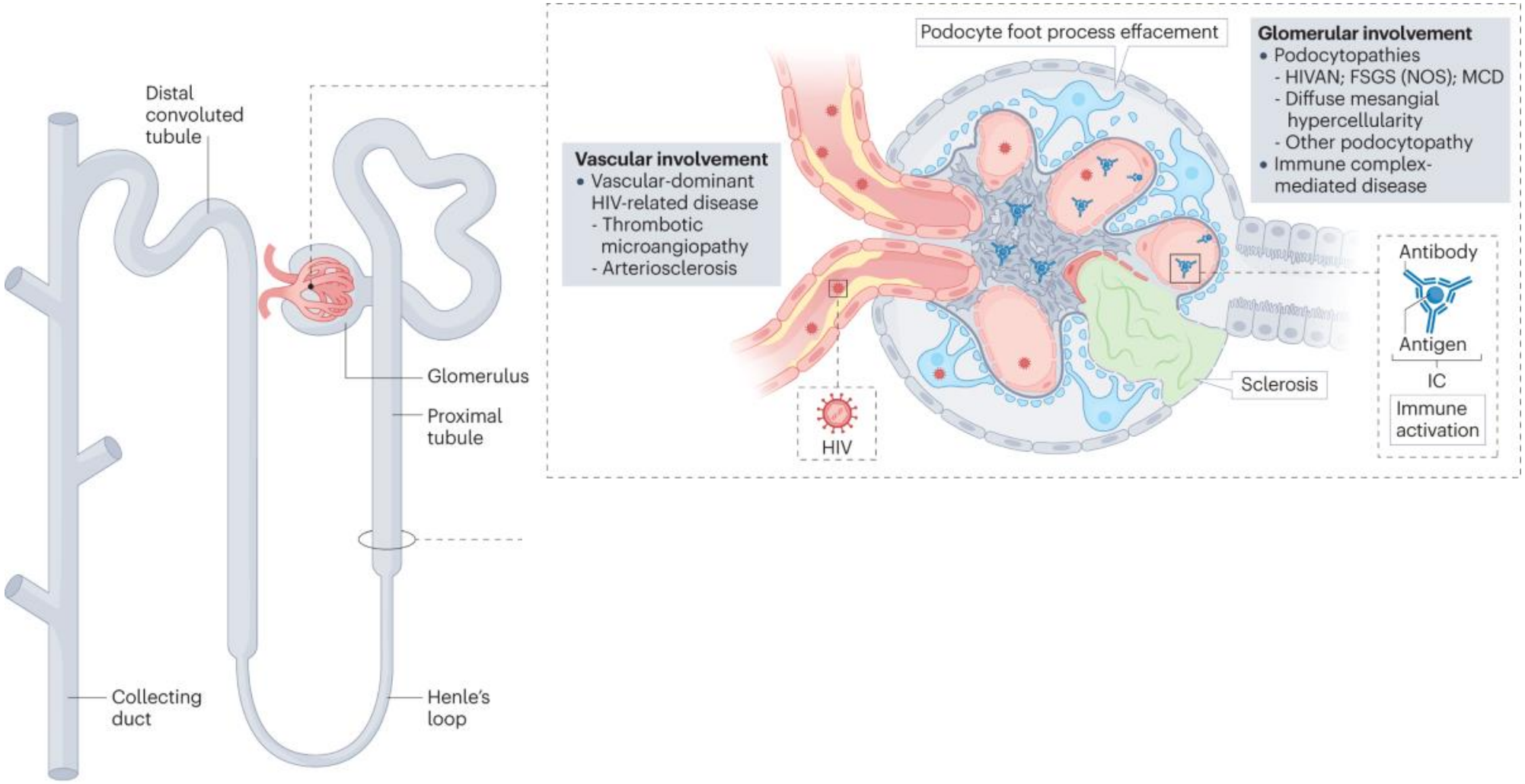
What Contributes to the Risk of NCDs in HIV?



KIDNEY DISEASES IN THE SETTING OF HIV INFECTION

HIV-RELATED KIDNEY DISEASE

HIV-related kidney diseases



Diana NE et al, *Nat Rev Nephrol 2024*

HIV-related kidney diseases

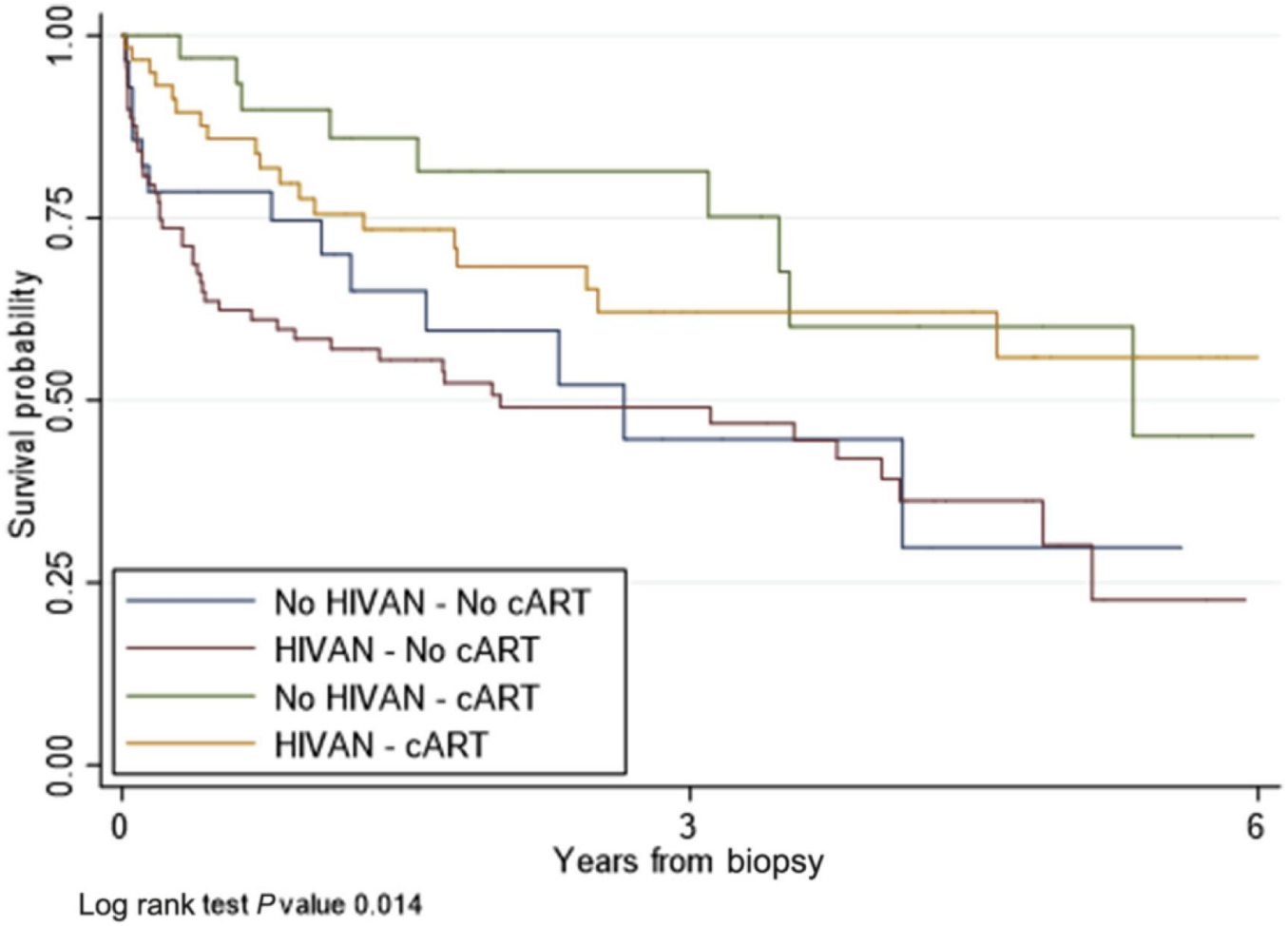
- **HIV-associated nephropathy (HIVAN):** The most common, or "classical", type of HIVAN is a collapsing focal segmental glomerulosclerosis (FSGS), it is usually seen as a late complication of chronic HIV-infection in patients with advanced immunocompromise. Commonly seen in African-American patients with HIV compared to other ethnic groups.

- **HIV immune complex kidney disease (HIVICK):** These conditions include a lupus-like nephritis with negative autoimmune serologies and no other clinical signs of lupus. As well, IgA nephropathy, membranous and membranoproliferative disease have all been described.

- **Vascular conditions (TMA):** Thrombotic microangiopathy is a result of endothelial dysregulation. The condition manifests clinically with thrombocytopaenia, a microangiopathic anaemia and multisystem organ dys- function, including AKI. It is usually seen in those with high-level viral replication, not on ART.

Heron JE et al, *AIDS Res Ther 2020*

Mortality according to HIV-associated nephropathy (HIVAN) and combined antiretroviral therapy (ART) at biopsy



- Study conducted prospectively in South Africa from 2002 to 2018.
- 419 patients included in the study. Mean age was 36.5 years (SD, 9.4); 219 (52.3%) were women; and all were black.
- Seventy-nine patients (18.9%) were on dialysis at the time of biopsy
- the mean estimated glomerular filtration rate among the remainder was 41.4 ml/min per 1.73 m2 (SD, 39.2

Bookholane H et al, *Kidney Int Rep 2020*

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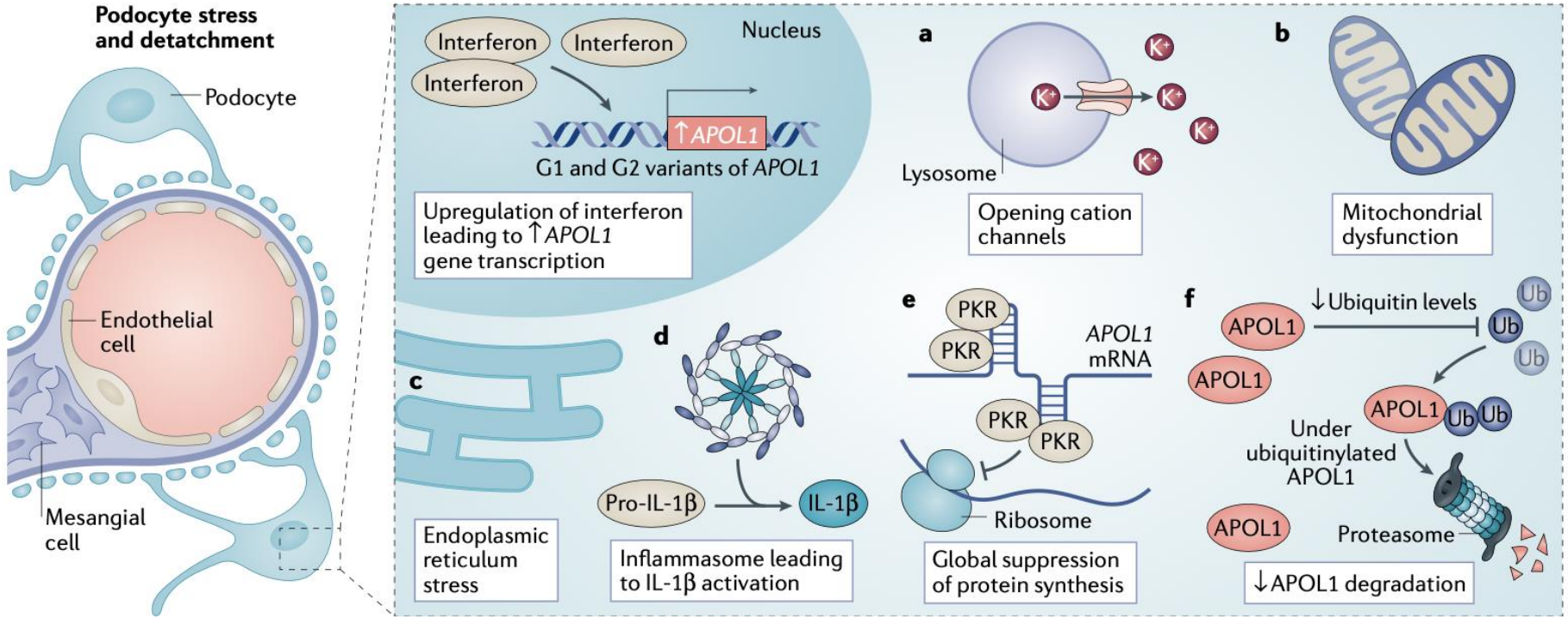
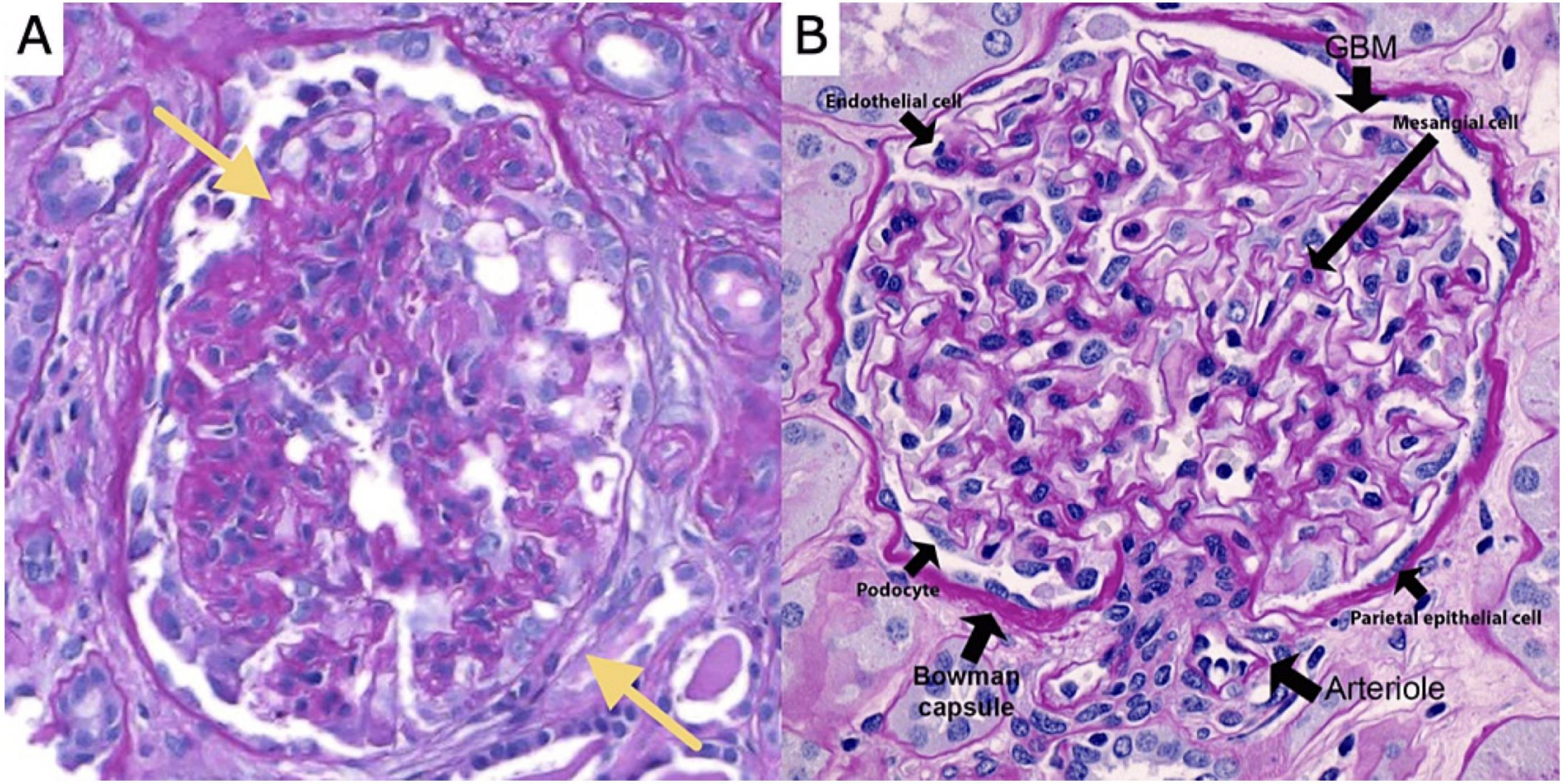
The evolving story of apolipoprotein L1 nephropathy

- *APOL1* renal risk alleles provide protection from african human trypanosomiasis but are a risk factor for progressive kidney disease in those carrying two risk alleles.
- *APOL1* risk allele frequency is ~35% in the african american population in the united States, with ~13% of individuals having two risk alleles; the highest allele frequencies are found in West african populations and their descendants.



Daneshpajouhnejad P et al, *Nat Rev Nephrol 2022*

COVID-19-Associated Nephropathy: A Devastating Complication



Kim A et al, *Cureus 2023*

KIDNEY DISEASES IN THE SETTING OF HIV INFECTION

RENAL EFFECTS OF HAART

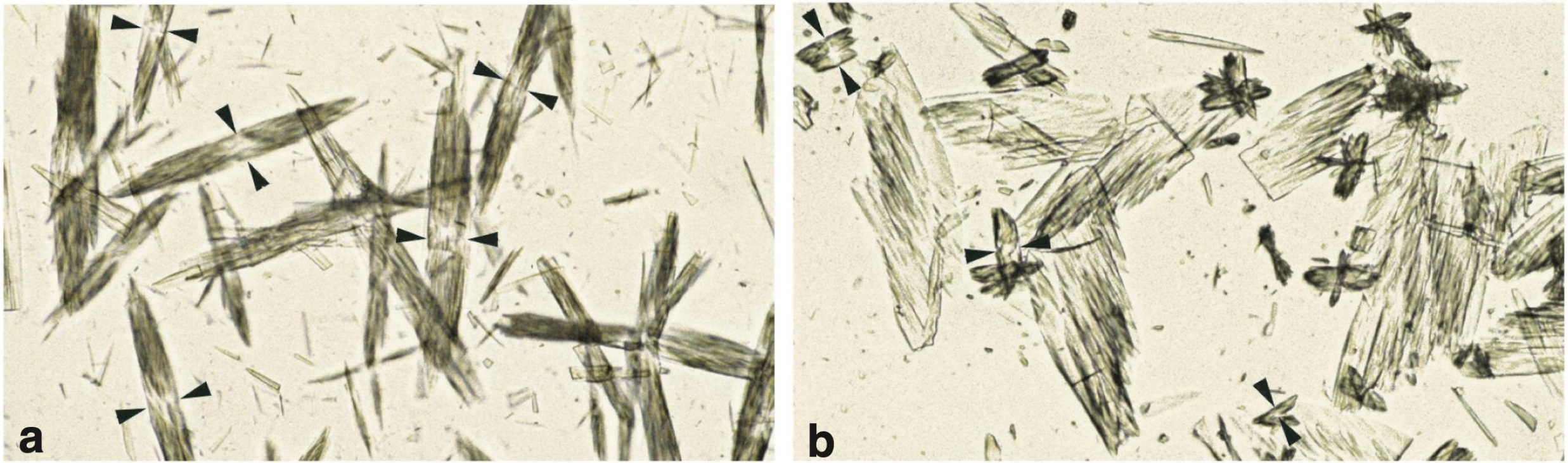
Drugs involved in renal toxicity

- **AKI:** abacavir, atazanavir, didanosine, indinavir, ritonavir, saquinavir, tenofovir DF
- **CKD**: abacavir, atazanavir, indinavir, lopinavir, tenofovir DF
- **Acute interstitial nephritis**: abacavir, atazanavir, indinavir
- **Fanconi syndrome**: tenofovir DF, didanosine, abacavir
- **Renal tubular acidosis**: lamivudine, stavudine,
- **Crystalluria, lithiasis**: indinavir, atazanavir and (rare): nelfinavir, amprenavir
- **Nephrogenic diabetes insipidus**: didanosine, tenofovir DF

Campos P et al, *Clin Kidney J 2016*

Indinavir crystalluria

Indinavir has a low solubility at neutral pH that can lead to precipitation within the urinary tract. There have been many reports of the occurrence of kidney stones, renal failure, interstitial nephritis, dysuria, and asymptomatic crystalluria attributed to precipitation of indinavir in the urinary tract



Gagnon RF et al, *Kidney Int 2006*

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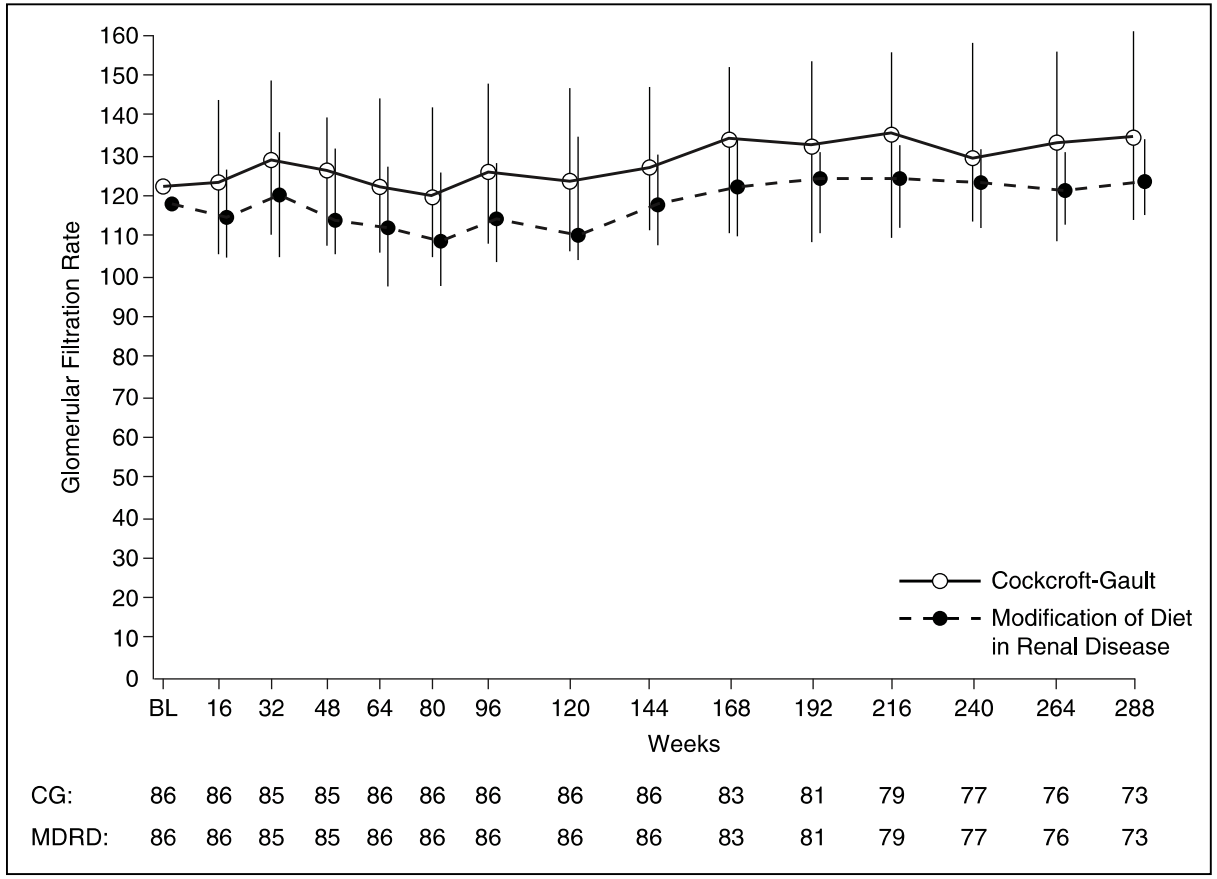
Campos P et al, *Clin Kidney J 2016*

The safety of tenofovir in combination with lamivudine and efavirenz through 6 years

Study 903 was designed to compare the efficacy and safety of a treatment regimen of Viread, lamivudine (3TC) and efavirenz to a regimen of stavudine (d4T), lamivudine and efavirenz in 600 antiretroviral-naive HIV-1 infected patients.



Cassetti I et al, *HIV Clin Trials 2007*

EuroSIDA Study:
Risk for Chronic Kidney Disease

- **Analysis of patients with ≥3 creatinine measurements + body weight**
  - 6,842 patients with 21,482 person-years of follow-up
- **Definition of CKD (eGFR by Cockcroft-Gault)**
  - If baseline eGFR ≥60 mL/min/1.73 m2, fall to <60
  - If baseline eGFR <60 mL/min/1.73 m2, fall by 25%
- **225 (3.3%) progressed to CKD**

	Univariable			**Multivariable**		
	IRR/year	95% CI	P-value	**IRR/year**	**95% CI**	**P-value**
Tenofovir	1.32	1.21-1.41	<0.0001	**1.16**	1.06-1.25	<0.0001
Indinavir	1.18	1.13-1.24	<0.0001	**1.12**	1.06-1.18	<0.0001
Atazanavir	1.48	1.35-1.62	<0.0001	**1.21**	1.09-1.34	0.0003
Lopinavir/r	1.15	1.07-1.23	<0.0001	**1.08**	1.01-1.16	0.030

Mocroft A et al, *AIDS 2010*

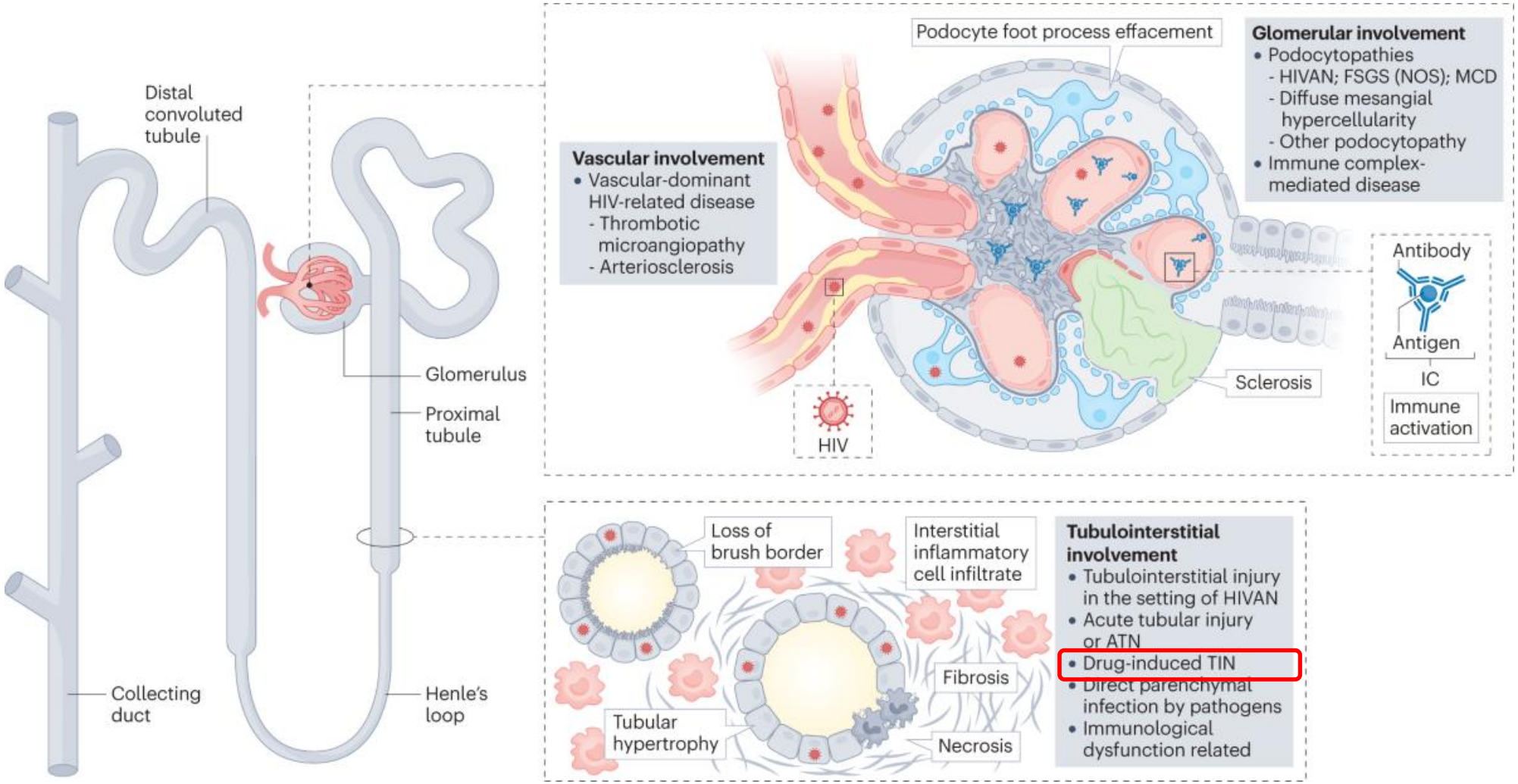
AJKD AMERICAN JOURNAL OF KIDNEY DISEASES
NATIONAL KIDNEY FOUNDATION®

Fanconi Syndrome and Renal Failure Induced by Tenofovir: A First Case Report

David Verhelst, MD, Matthieu Monge, MD, Jean-Luc Meynard, MD, Bruno Fouqueray, MD, PhD, Béatrice Mougenot, MD, Pierre-Marie Girard, MD, PhD, Pierre Ronco, MD, PhD, and Jerome Rossert, MD, PhD

• **Although nephrotoxicity of cidofovir and adefovir is well established, no renal side effects have been observed yet with tenofovir, which is the third member of this family. The authors report the case of a patient who had Fanconi syndrome, nephrogenic diabetes insipidus, and acute renal failure during treatment with tenofovir, a nucleotide reverse transcriptase inhibitor that recently has been approved by the Food and Drug Administration for treatment of patients infected with human immunodeficiency virus. *Am J Kidney Dis* 40:1331-1333.**

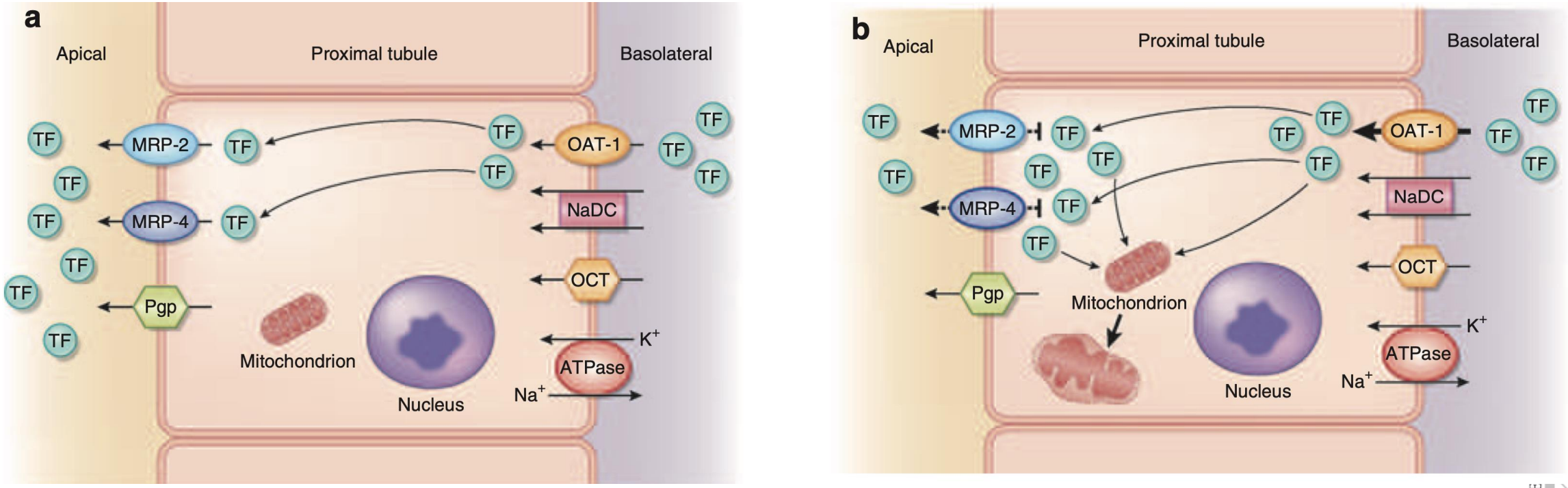
HIV-related kidney diseases



Diana NE et al, *Nat Rev Nephrol 2024*

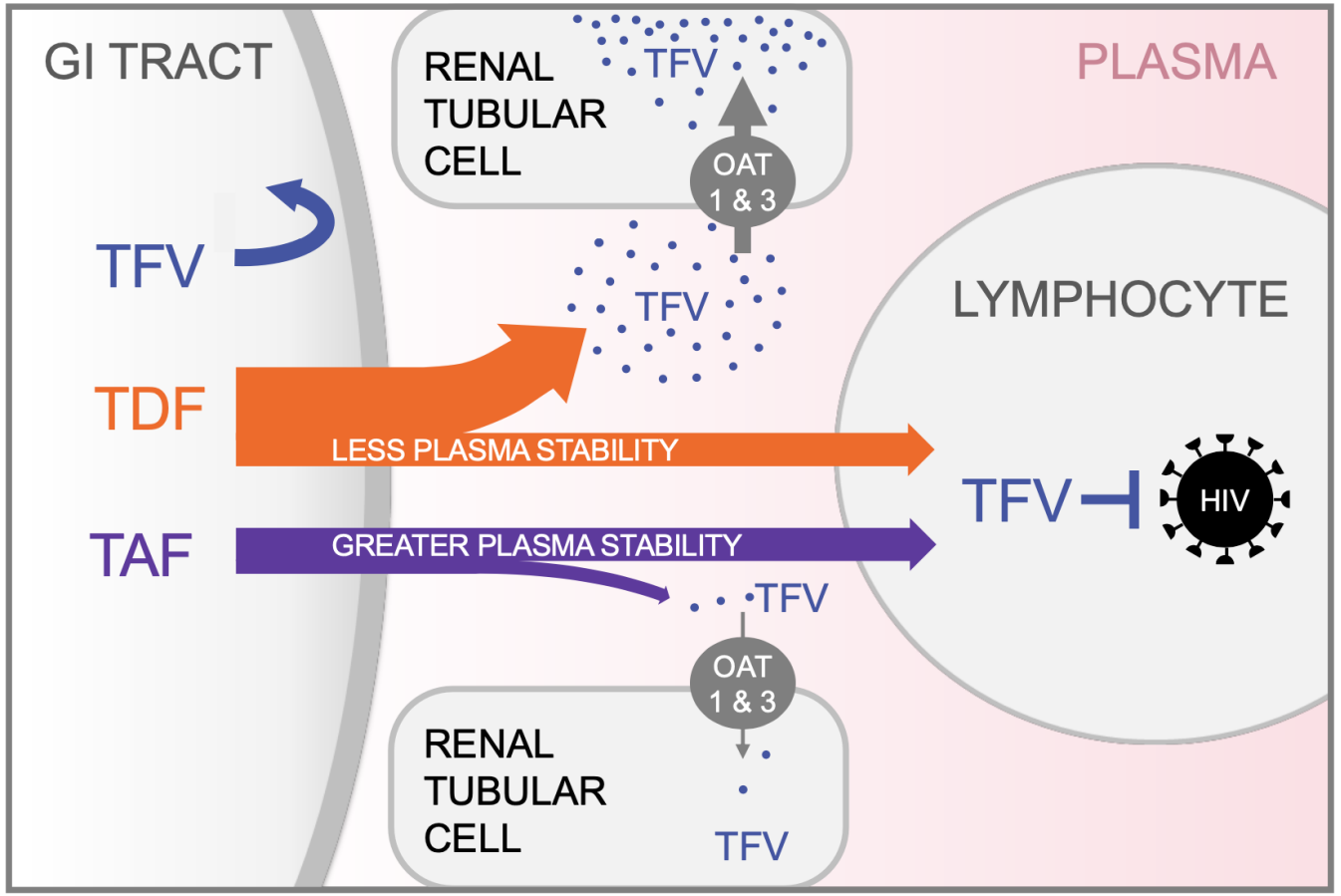
Tenofovir-induced kidney disease

- Tenofovir is transported via organic anion transporter-1 (OAT-1) from the basolateral circulation into proximal tubular cells, where it is translocated into the urine through apical efflux transporters such as multidrug resistance protein-2 (MRP-2) and MRP-4.
- Endogenous anions and other drugs may compete with tenofovir for these efflux transport pathways.



Perrazzella M, *Kidney Int 2010*

TDF versus TAF



TAF results in >90% lower TFV plasma levels[2,3,4]

OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir

Recommended approach to kidney injury screening in HIV-infected patients

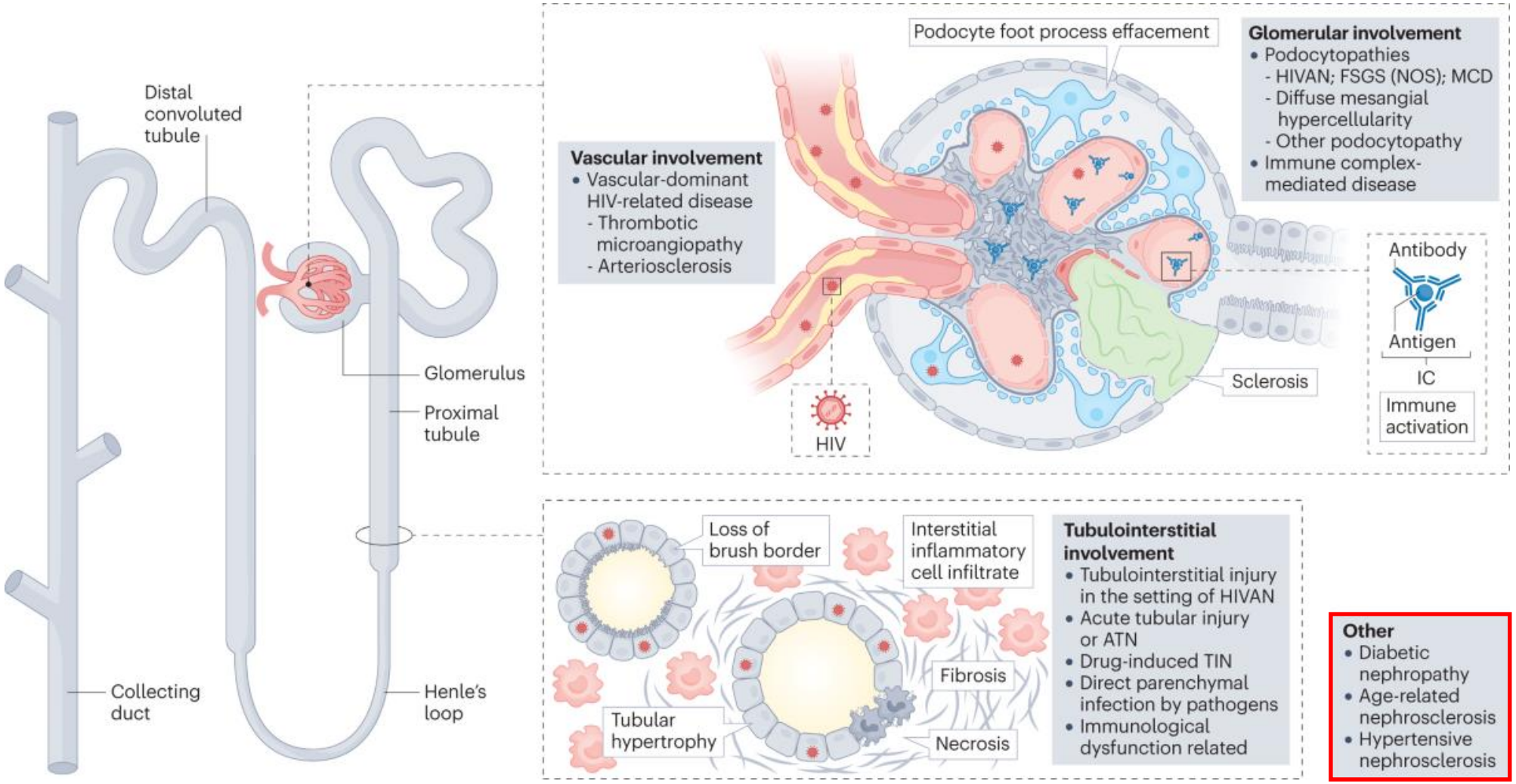
Approach to kidney screening	Abnormality	Actions[a] twice yearly in stable patients
Blood pressure measurement	>140/90 mmHg	Revise therapy
Glomerular filtration rate	<60 mL/min/1.73 m^2 or rapid	
Serum creatinine based eGFR (CKD-EPI equation)	decrease	Search cause, including nephrotoxicity
Serum cystatin C based eGFR (CKD-EPI equation)		Nephrology referral
		Change to quarterly evaluation
Glomerular injury		
uACR	>30 mg/g	
uPCR	>150 mg/g	Search for kidney disease (consider biopsy)
uAPR	>0.4	Search for glomerular disease
	>0.4	Consider tubulopathy, search for specific protein lost in urine
Urinary sediment (check also for crystals!)	Crystalluria	Search for cART toxicity
	Hematuria	Search for glomerular disease
Proximal tubulopathy		
Urine dipstick	Abnormal	If proteins: quantify uACR/uPCR
		If blood: sediment
		If leukocytes: sediment, culture
Glycosuria	Present	Check for Diabetes Mellitus or cART toxicity
FePi	>10%	Search for cART toxicity
FeUrate	>20%	Search for cART toxicity

Campos P et al, *Clin Kidney J 2016*

KIDNEY DISEASES IN THE SETTING OF HIV INFECTION

CKD RELATED TO NON-INFECTIOUS CO-MORBIDITIES

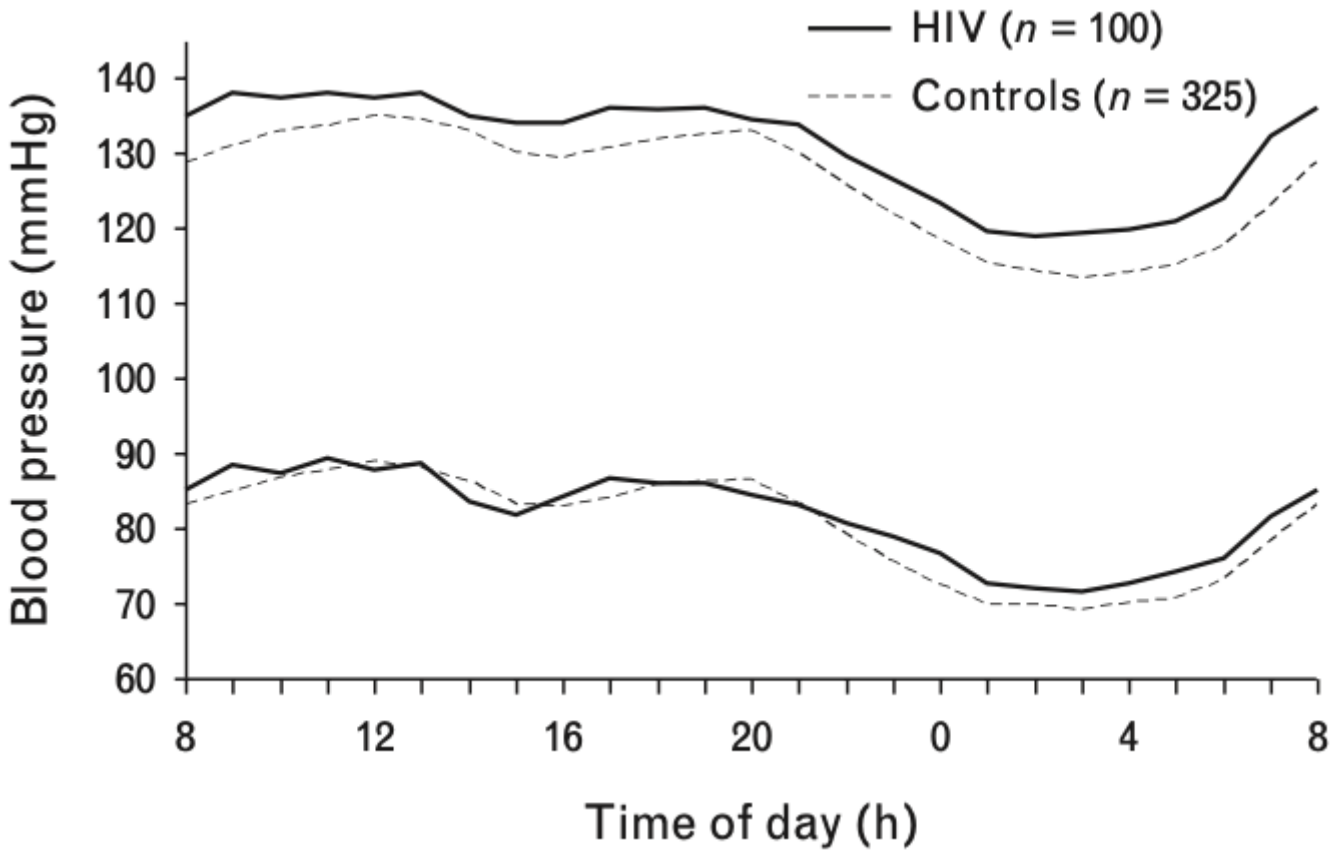
HIV-related kidney diseases



Diana NE et al, *Nat Rev Nephrol 2024*

Hypertension in PWH

PWH had a reduced nocturnal BP fall and a higher proportion of an abnormal circadian BP rhythm (‘nondipping’ pattern).



Schillaci G et al, *J Hyperten 2013*

Antiretroviral Therapy and the Prevalence and Incidence of Diabetes Mellitus in the Multicenter AIDS Cohort Study

Characteristic	MACS (n = 5622)	Current Study Population (N = 1278)	HIV-Seronegative (n = 710)	HIV-Infected Not Using HAART (n = 157)	HIV-Infected Using HAART (n = 411)	*P* Value†
White subjects, No. (%)	4681 (83)	1089 (85)	618 (87)	119 (76)	352 (86)	.53
College degree, No. (%)	3121 (56)	787 (62)	477 (67)	74 (47)	236 (57)	<.001
Age (IQR range), y	33 (28, 38)	48 (43, 53)	50 (45, 56)	46 (41, 50)	46 (42, 51)	<.001
Body mass index‡	23 (22, 25)	26 (24, 28)	26 (24, 29)	25 (23, 28)	25 (23, 27)	<.001
Waist-hip ratio	NA	0.95 (0.91, 0.99)	0.94 (0.90, 0.99)	0.94 (0.91, 0.97)	0.95 (0.91, 0.99)	.17
Total cholesterol level, mg/dL	NA	202 (176, 229)	201 (178, 227)	188 (158, 218)	210 (182, 239)	<.001
Glucose level, mg/dL	NA	90 (83, 98)	90 (83, 97)	88 (82, 98)	91 (84, 101)	.03
Nadir CD4 count, cells/mm^3	NA	NA	NA	318 (187, 432)	211 (108, 318)	NA
Duration of receiving HAART§	NA	NA	NA	NA	3.26 (2.63, 3.81)	NA

Patient Group	Diabetes Mellitus*	
	No. (%) of Patients	PR (95% CI)†
Overall (N = 1278)	**101** (8)	NA
HIV seronegative (n = 710)	33 (5)	1
HIV infected not using HAART (n = 157)	11 (7)	2.21 (1.12-4.38)
HIV infected using HAART (n = 411)	57 (14)	4.64 (3.03-7.10)

Brown TT et al, *Arch Intern Med 2005*

Weight Gain After Antiretroviral Therapy Initiation and Subsequent Risk of Metabolic and Cardiovascular Disease

Sara H. Bares,[1] Xingye Wu,[2] Katherine Tassiopoulos,[3] Jordan E. Lake,[4] Susan L. Koletar,[5] Robert Kalayjian,[6] and Kristine M. Erlandson[7]; for the A5322 Study Team

Table 5. Adjusted Cox Proportional Hazard Models of Weight Change at Week 48 and Subsequent Clinical Events Among Participants With >10% Weight Gain

Clinical Event	HR (95% CI)
Diabetes mellitus (n = 130)	**2.01 (1.30, 3.08)**
Metabolic syndrome (n = 360)	**2.02 (1.55, 2.62)**
Cardiometabolic event (n = 424)	**1.54 (1.22, 1.95)**
CV Event (n = 28)	0.60 (.22, 1.67)

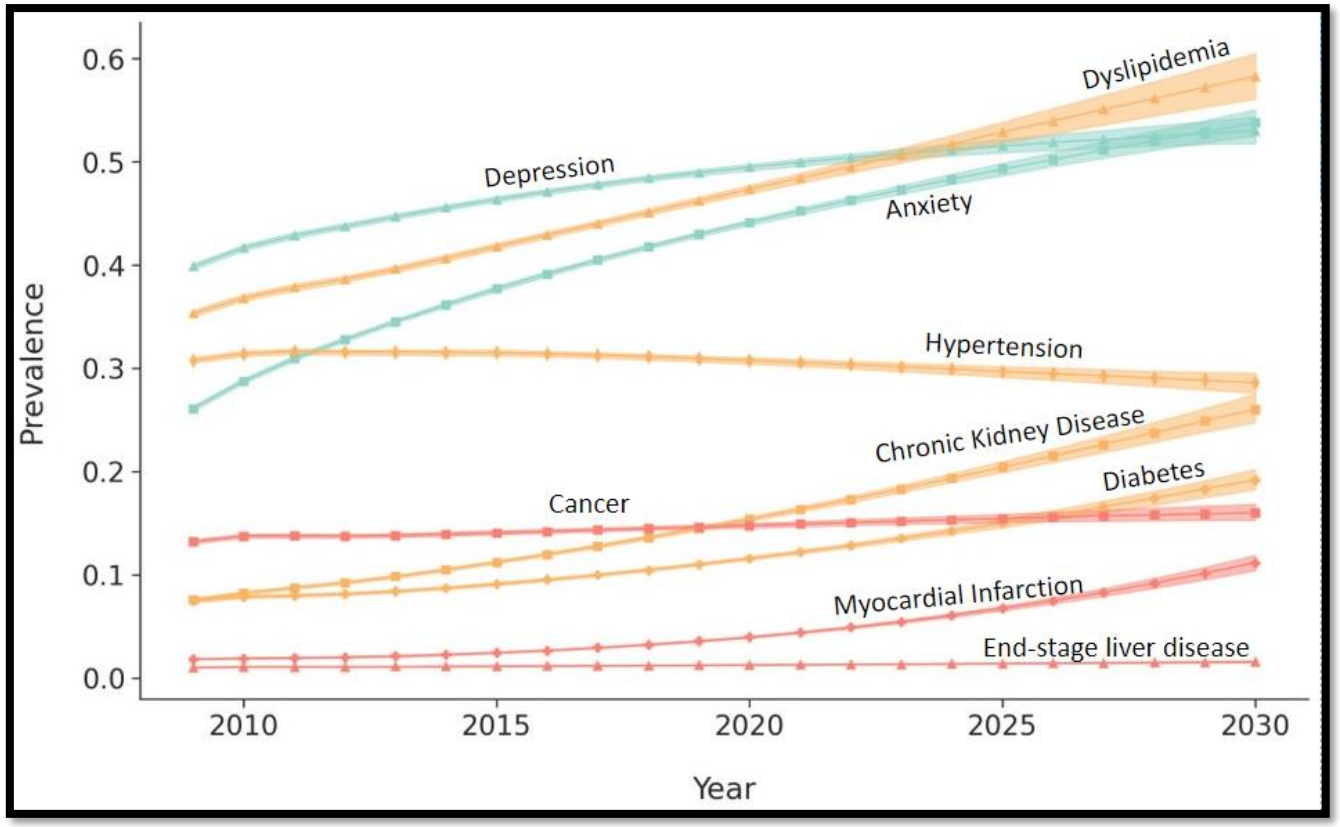
Clin Infect Dis 2024

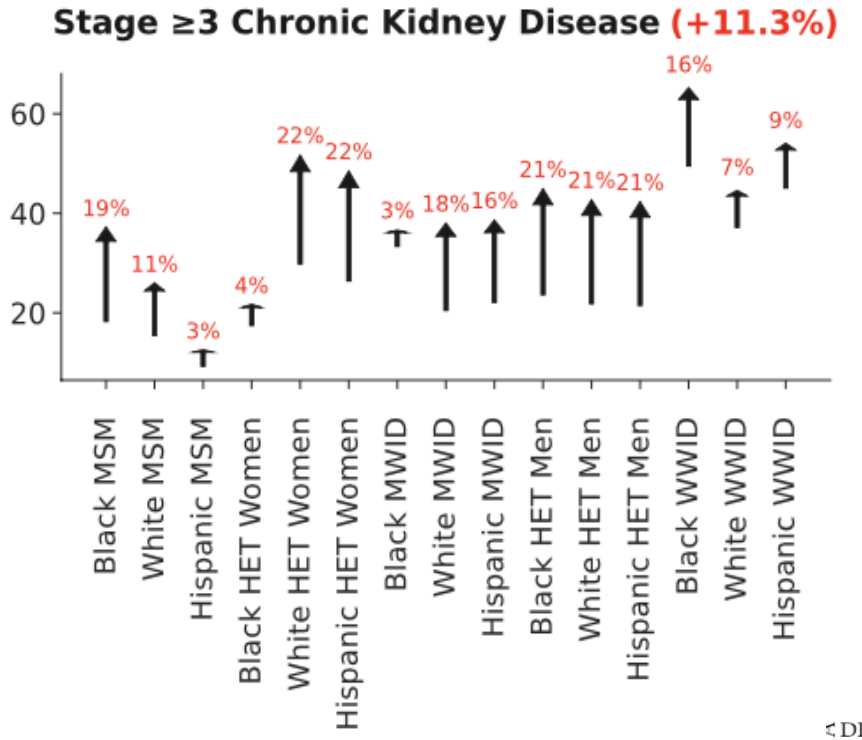
BONUS TRACK

WHAT LIES AHEAD? IS THE PROBLEM UNDER CONTROL?

CKD Rates are Increasing in PWH

- The objective of our study was to forecast the prevalence of comorbidities and multimorbidity among people with HIV(PWH) using antiretroviral therapy (ART) in the United States (US) through 2030.
- Simulations were informed by the US CDC HIV surveillance data of new HIV diagnosis and the longitudinal North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) data on risk of comorbidities from 2009 to 2017





Althoff KA et al, *PloS Med 2024*

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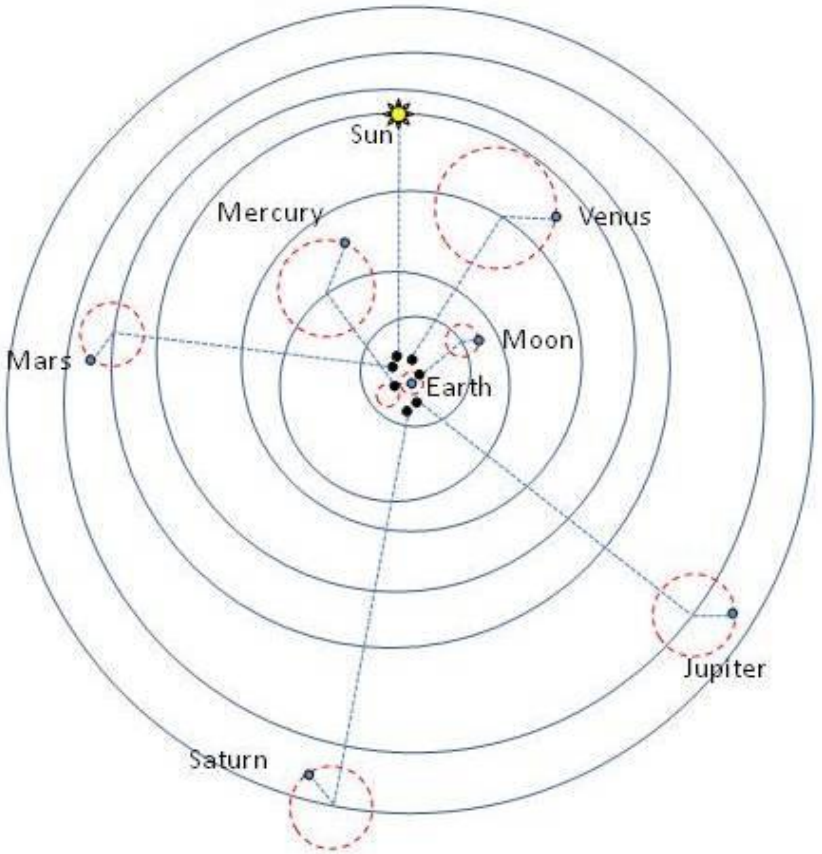
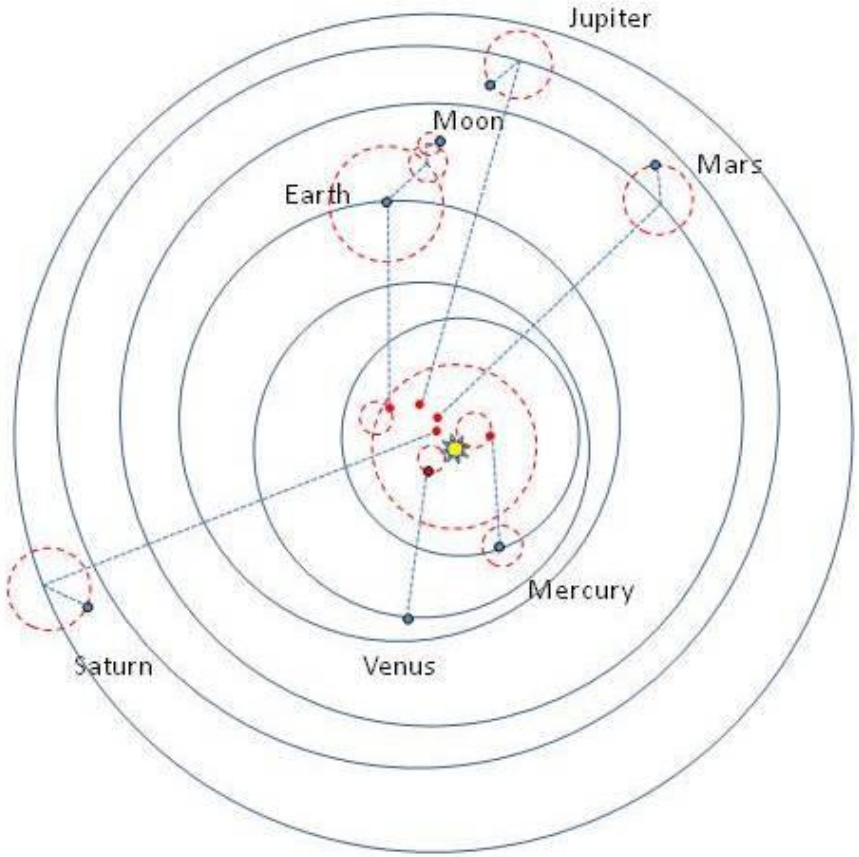
Inertia is the resistance of change



Ptolemaic Model



Copernican Model

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Quocumque modo faciemus

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