The Double-Edged Sword: Nephrotoxicity of Anti-retroviral Therapy

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Disclosure of Interests

- Gilead: subcontract Research Grant to the Institution

Objectives

- Review classes of Antiretroviral treatment (ART)
- Evaluate patterns of renal injury with ART
- Outlines current renal guidelines on ART use/management

Deferred treatment

Early treatment

cART toxicities

Metabolic derangements

HIVAN

Initial Regimens: First-Line

DHHS Guidelines, July 2016

INSTI based	▪ DTG/ABC/3TC; only if HLA-B*5701 negative (AI) ▪ DTG (QD) + TDF/FTC (AI) or TAF/FTC (AII) ▪ EVG/COBI/TAF/FTC ▪ EVG/COBI/TDF/FTC; only if pre-ART CrCl >70 mL/min (AI) ▪ RAL + TDF/FTC (AI) or TAF/FTC (AII)
PI based	▪ DRV/r (QD) + TDF/FTC (AI) or TAF/FTC (AII)

Note:
3TC can be used in place of FTC and vice versa; TDF: caution if renal insufficiency

July 2016 Updates on Recommended Regimens for First-line ART

1. DHHS Guidelines. July 2016.
2. Günthard HF, et al. JAMA. 2016;316:191-210.

Regimen	DHHS[1]	IAS-USA[2]
DTG/ABC/3TC	■	■
DTG + TAF/FTC	■	■
DTG + TDF/FTC	■	■
EVG/COBI/TAF/FTC	■	■
EVG/COBI/TDF/FTC	■	■
RAL + TAF/FTC	■	■
RAL + TDF/FTC	■	■
DRV + RTV + TAF/FTC	■	■
DRV + RTV + TDF/FTC	■	■

■ Preferred/recommended ■ Alternative

DHHS[1]

- Recommended regimens include 3 INSTIs and 1 boosted PI
- Primary change since Jan 2016 update is addition of TAF/FTC

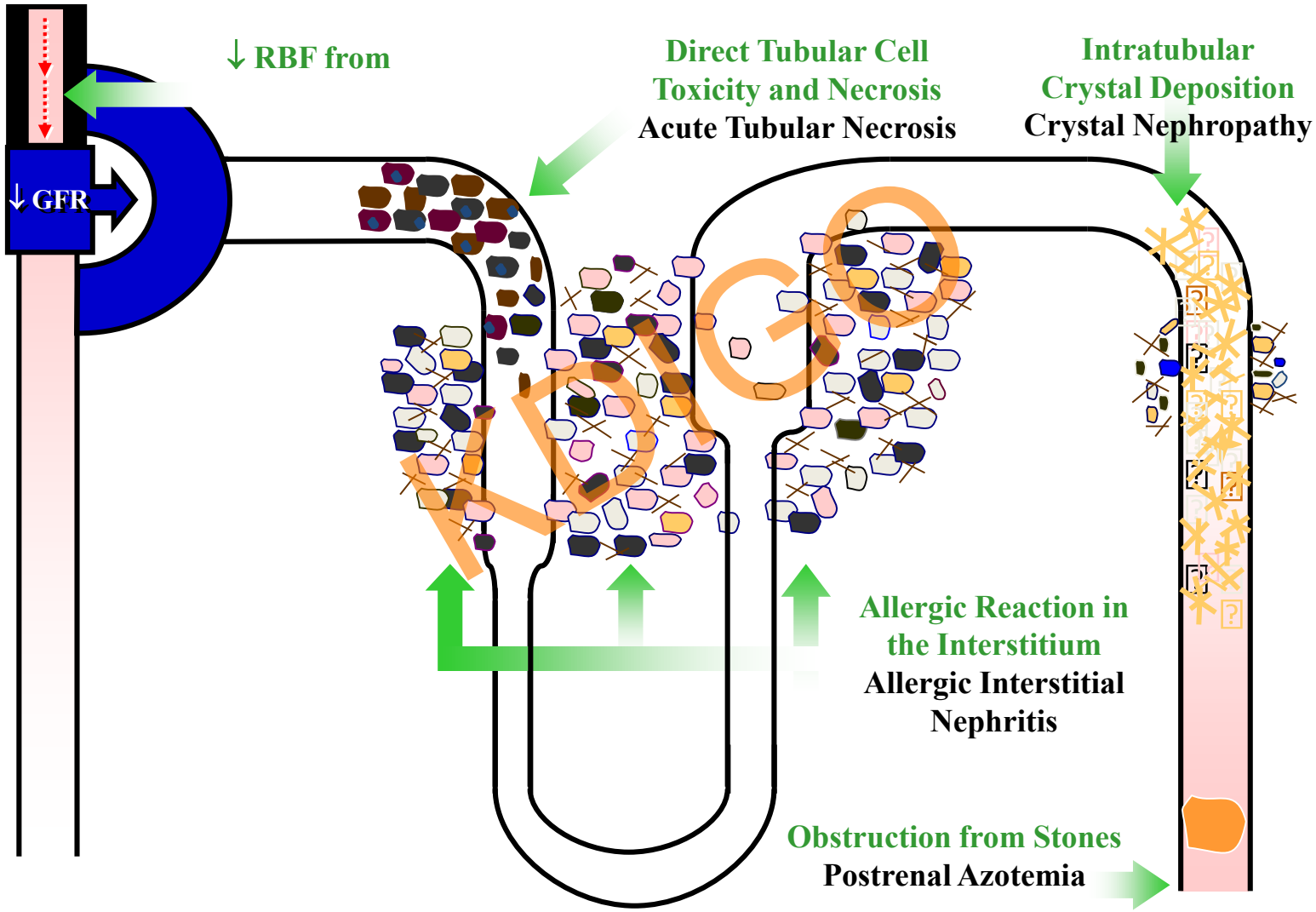
IAS-USA[2]

- All recommended regimens include INSTI + TAF/FTC or ABC/3TC
- Major changes since 2014 update include removal of NNRTIs, boosted PIs, and TDF

ART AND AKI

Causes of Acute Renal Failure

Valeri A, Neusy AJ. *Clin Nephrol*. 1991;35(3):110-118.
Rao TKS, Friedman EA. *Am J Kidney Dis*. 1995;25(3):390-398.
Perazella MA. *Am J Med Sci*. 2000;319(6):385-391.



ART associated with AKI

Protease inhibitors

Crystal-induced nephropathy, AIN

Tenofovir

AKI; Fanconi syndrome; nephrogenic DI

Integrase inhibitors

Rhabdomyolysis/pigment nephropathy

NNRTIs

Nephrolithiasis

NRTIs

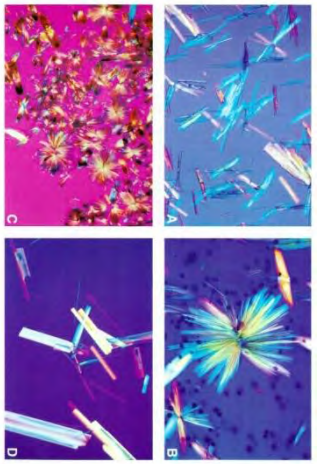
Nephrolithiasis; AIN; rhabdomyolysis

Crystalluria and Stone Formation

❑Indinavir

240 Patients:

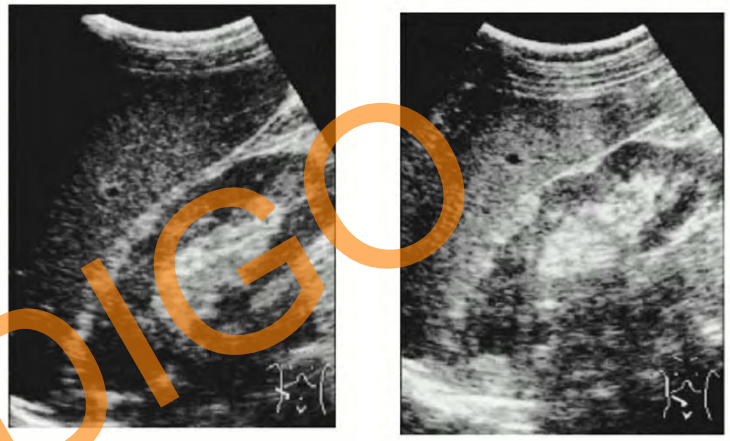
- **20 %: crystalluria**
- **3 %: uroliths**



Indinavir

Annals of Internal Medicine, 15 July 1997. 127:119-125

Week 20 Indinavir Week 76 Indinavir



NEJM, Hanabusa et al., February 1999

Risk factors:

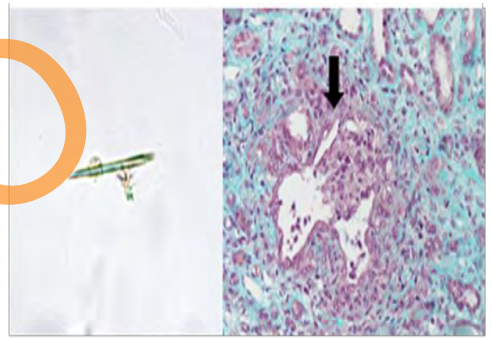
- Alkaline urine pH>6,
- low body mass,
- dose of 1000 mg or more twice daily,
- warm weather

Urolithiasis in HIV positive patients treated with atazanavir

Couzigou et al. CID 2007:45 (15 October)

Prevalence:

- 0.97% (11/1134) patients who were treated with ATV from March 2004 through February 2007



Risk factors:

- Alkaline pH: ≥6
- Duration on treatment

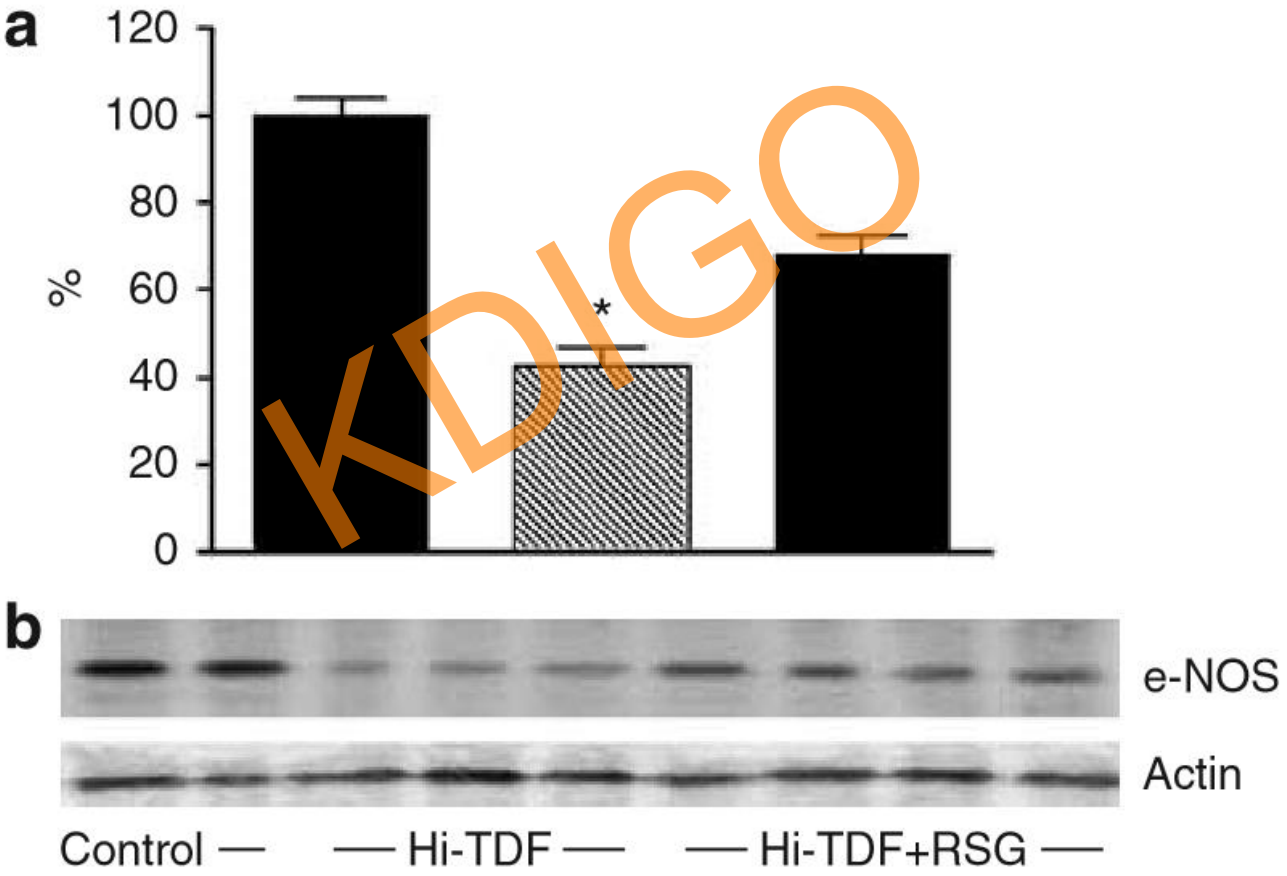
Tenofovir renal toxicity

- Reported in up to 15% of patients treated for 2-9 years.
  - Acute renal failure
  - Fanconi syndrome
  - Nephrogenic diabetes insipidus
  - Chronic kidney disease

Atta M. et al. Seminars in Nephrology 2008;6
Izzedine et.al. AJKD 2005;45
Winston, et.al. HIV Med 20067

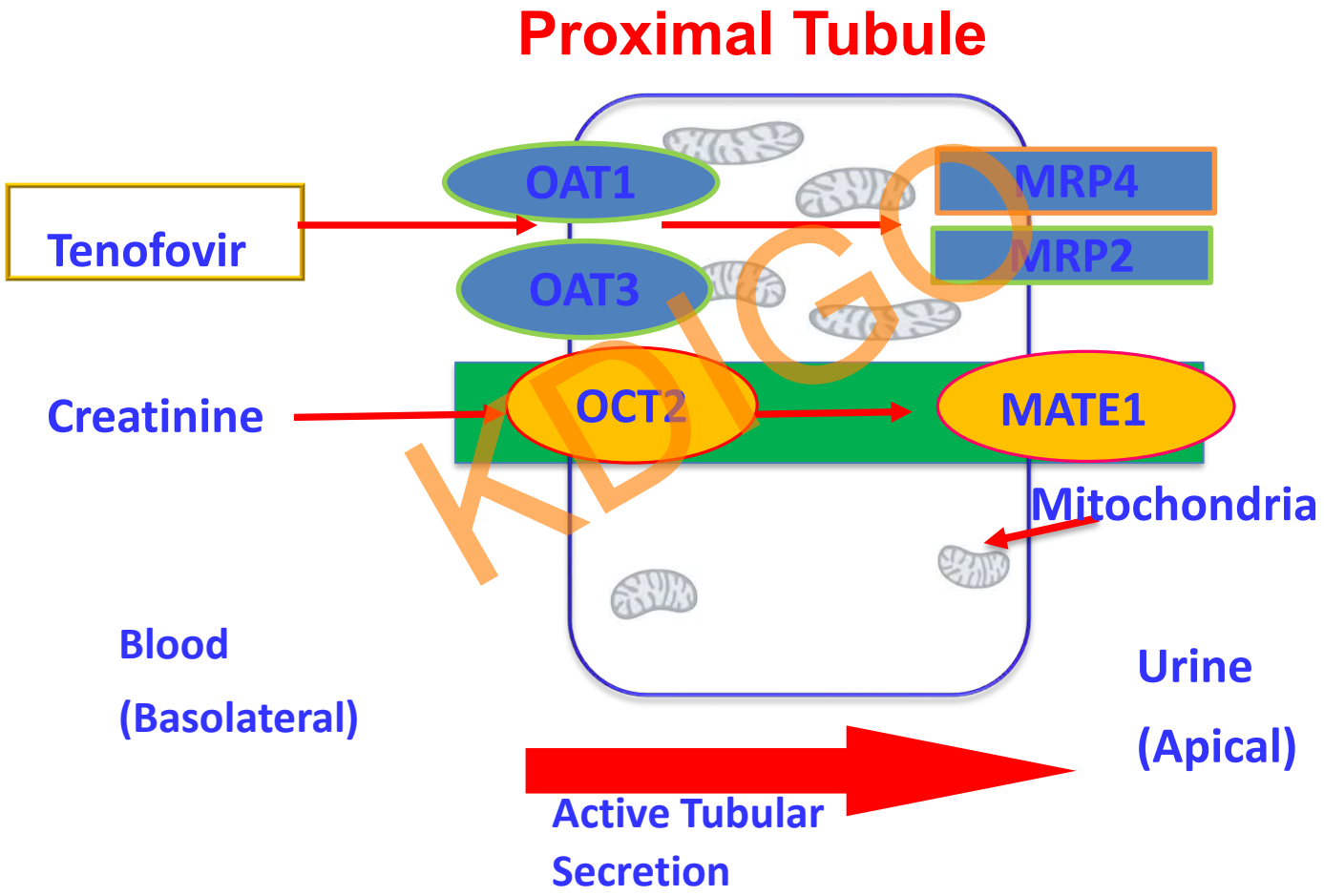
Rosiglitazone reverses tenofovir-induced nephrotoxicity

Kidney International (2008) 74, 910–918

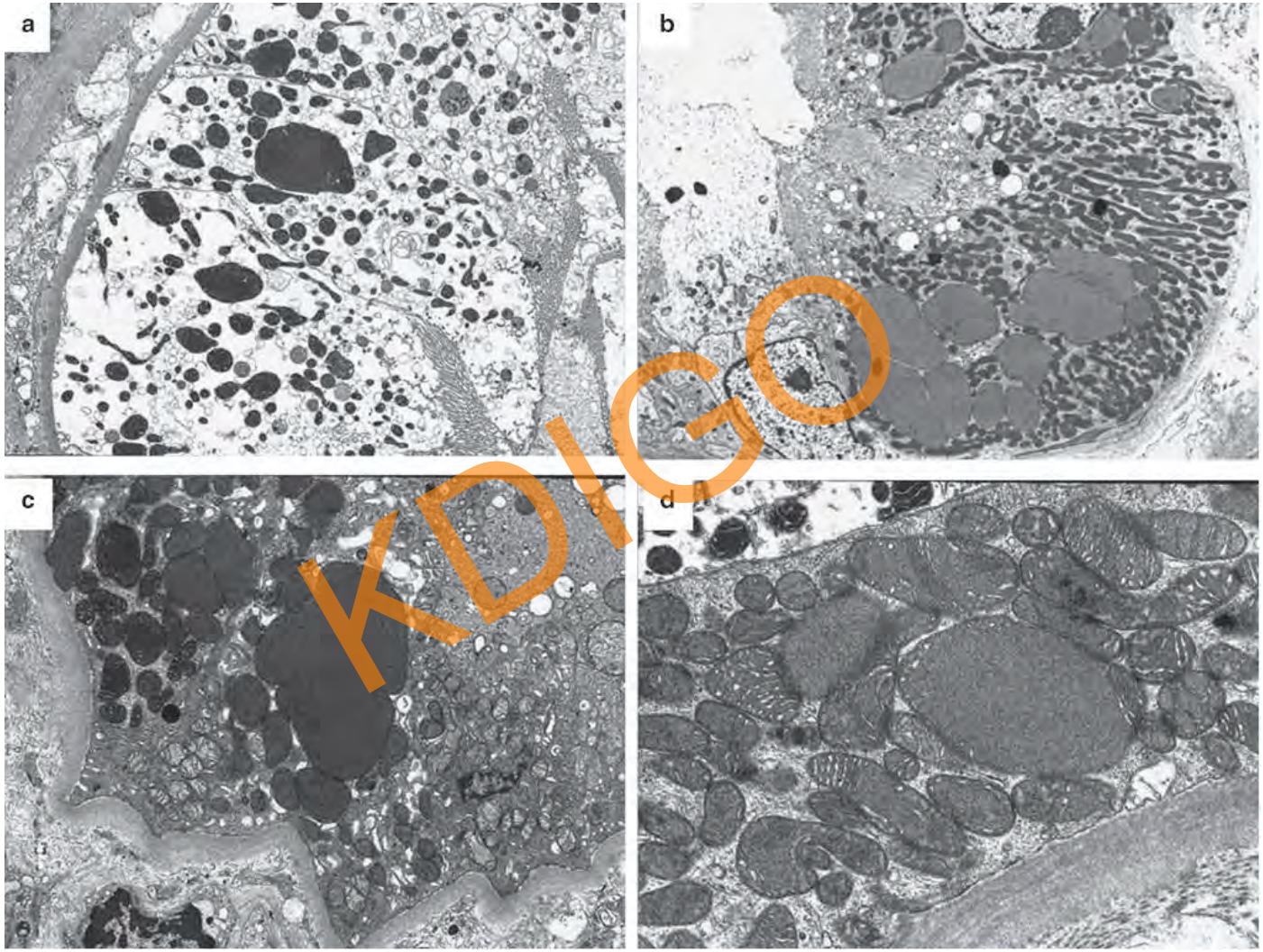


Model for TDF transport in the proximal tubule

Adapted from Mitema and Atta *Current Drug Metabolism*, 2015



Herlitz et al KI 2010



Increased risk of abnormal proximal renal tubular function with HIV infection and antiretroviral therapy

Dauchy et al. Kidney International 2011;80:302–309

PRTD was defined on the basis of the presence of at least 2/5 criteria (399 patients):

- ↑ in FE phos, with low sr. phos. <0.80 mmol/l
- Non-diabetic glucosuria
- Metabolic acidosis (pH <7.34 and sr. bicarb. <22 mmol/l)
- Ratio B2-microglobulinuria/ur. cr. >40.3 mg/l
- Low sr. uric acid with ↑ FE uric acid >15%

Increased risk of abnormal proximal renal tubular function with HIV infection and antiretroviral therapy

Dauchy et al. Kidney International 2011;80:302–309

- **Prevalence: 6.5%**

	Final model		
	OR	(95% CI)	P-value
Age	1.28	(1.05–1.58)	0.017
TDF	1.23	(1.02–1.47)	0.028
ATV	1.28	(1.04–1.58)	0.021

Prevalence of TDF renal tubular dysfunction

Ezinga et al. Antiviral Therapy 2014

- 161 patients (mean age 46, 85% men, mean TDF exposure 40 months)
- RTD: urine α1-microglobulin/Cr. >15mg/10mmol, FEPO4>20% with low serum PO4, FEUric acid >10% with low serum, glucosuria
- 62.7% had one criteria,
  10.6% had 2 or more criteria

Hamzah et al. AIDS 2015

- 293 men (mean age 48, 94% White, median TDF exposure 2.1 years)
- RTD: retinol-binding protein/creatinine ratio (RBPCR) or FEPO4>20% with low serum PO4
- 22.5% had RBPCR-defined RTD, 6.5% >5 fold increase, and 12.3% had FEPO4-defined RTD

Clinical course of Proximal tubular dysfunction

Waheed et al. Clinical Kidney Journal, 2015, vol. 8, no. 4, 420–425

15 patients (73% male) with FEPO2>20% (mean age 56, 80% White ethnicity, mean TDF exposure 64 months).

Mean FEPO4 34%.

Mean eGFR at TDF start 104 mL/min/1.73m2 with a gradual decline to 69 mL/min/1.73m2 by the time of TDF discontinuation.

None returned to baseline eGFR after discontinuation.

Predictors of Kidney Tubular Dysfunction in HIV-Infected Patients Treated with TDF: A Pharmacogenetic Study

Rodrı´guez-No´voa et al. CID 2009:48 (1 June)

115 HIV-infected patients were examined, of whom 19 (16.5%) had RTD:

Adjusted analysis:

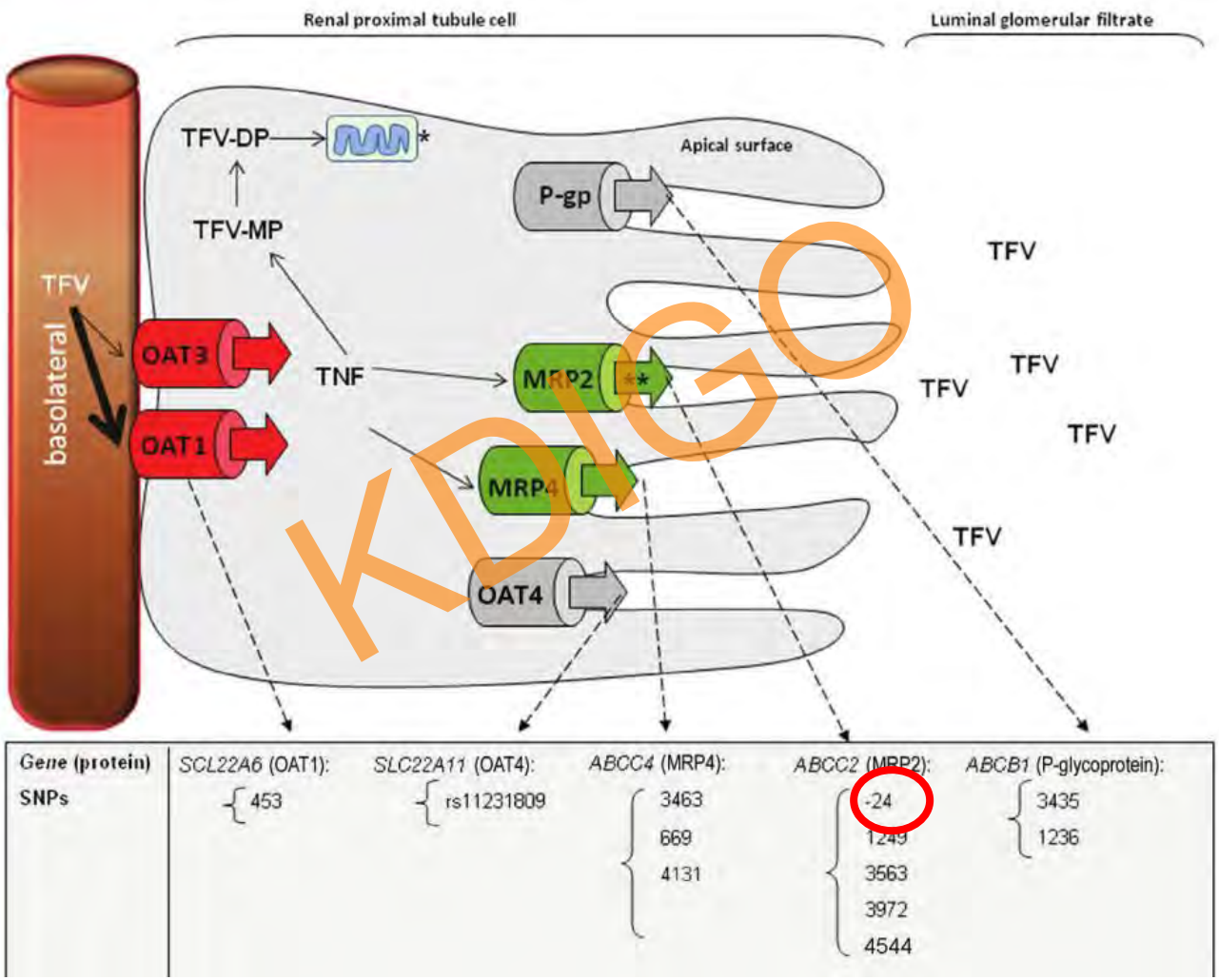
Older age per 1y (OR,1.1; 95% CI,1.0–1.2; *p=024)*

Lower body weight/1kg (OR,0.9;* 95% CI, 0.8–0.9; *p=048)

Genotype CC at ABCC2 position 24 (OR, 5; 95% CI, 1.2–21; p=027)

Polymorphisms associated with renal adverse effects of antiretroviral therapy in a Southern Brazilian HIV cohort

da Rochaa et al. Pharmacogenetics and Genomics 2015

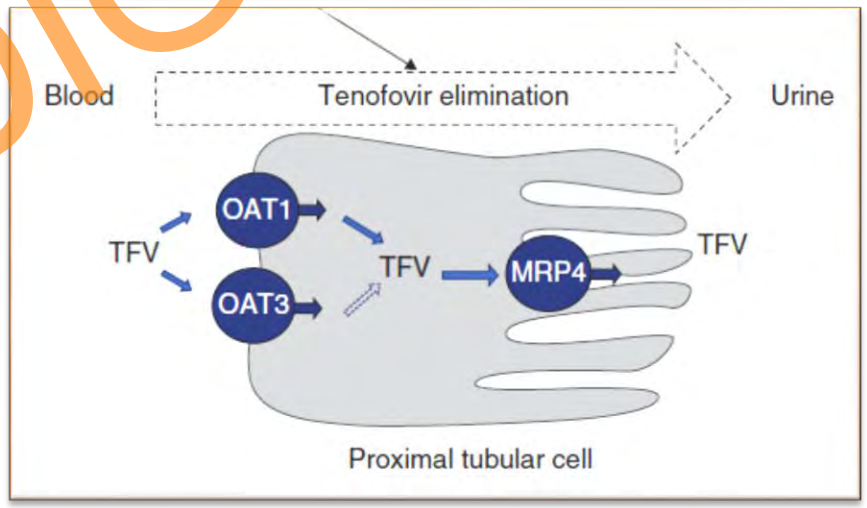


Risk Factors influencing TDF elimination

Risk Factors

- Low body weight
- Underlying kidney disease
- Use of DDI
- Use of nephrotoxic drugs
- Low CD4 count
- HCV coinfection
- DM

Older age
SNPs in transporter proteins
Drugs

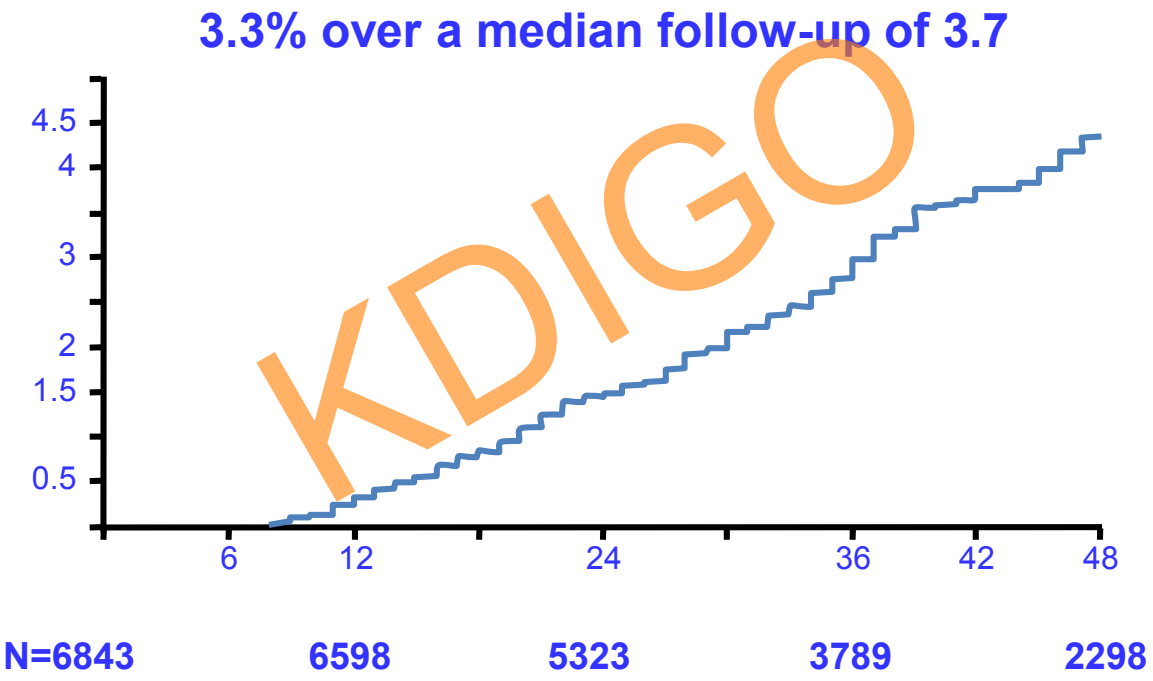


Adapted from Expert Opin. Drug Saf. 2010;9:545-559

ART AND CKD

Chronic kidney disease and antiretroviral drug use in HIV-positive patients

Mocroft et al. AIDS 2010, EuroSIDA Study Group



Hazard of CKD incidence

Mocroft et al. AIDS 2010, EuroSIDA Study Group

Tenofovir	1.16	1.06-1.25
Indinavir	1.12	1.06-1.18
Atazanavir	1.21	1.09-1.34
Lopinavir/r	1.08	1.01-1.16

Tenofovir exposure and risk of outcomes

Scherzer et al. AIDS 2012

- **10,841 HIV-infected VA patients 1997-2007**
- **Median follow-up: 3.9 years (proteinuria), 5.5 years (CKD)**

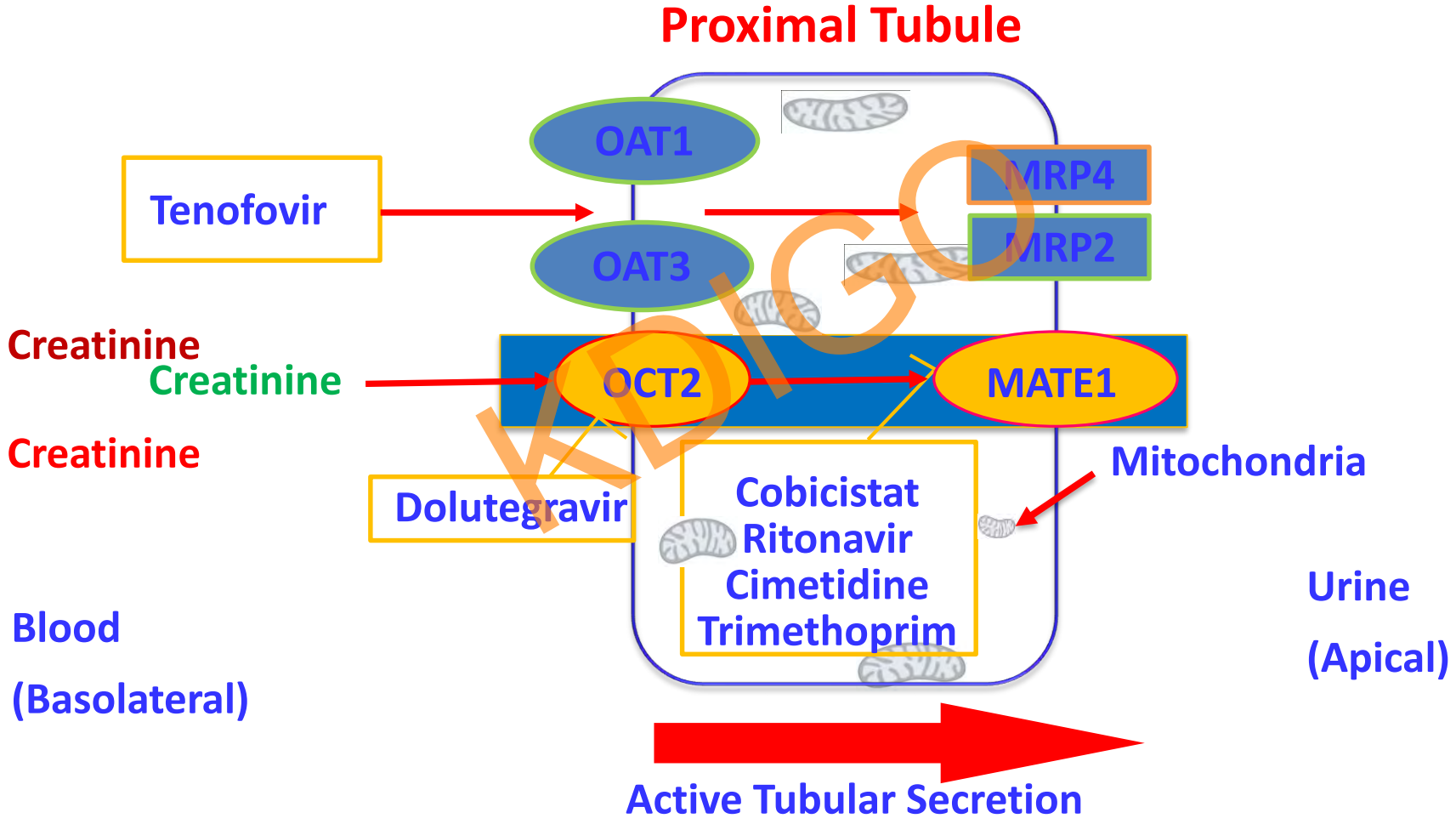
	Hazard ratio (95% CI)		
	Proteinuria (n=3400 events)	Rapid decline (n=3078 events)	CKD (n=1712 events)
Cumulative exposure to tenofovir (per year)			
	1.34 (1.25–1.45)***	1.11 (1.03–1.18)*	1.23 (1.12–1.35)***
Ever exposure to tenofovir (versus never)			
	1.68 (1.52–1.85)***	1.36 (1.23–1.50)***	1.38 (1.20–1.57)***

NEW AGENTS

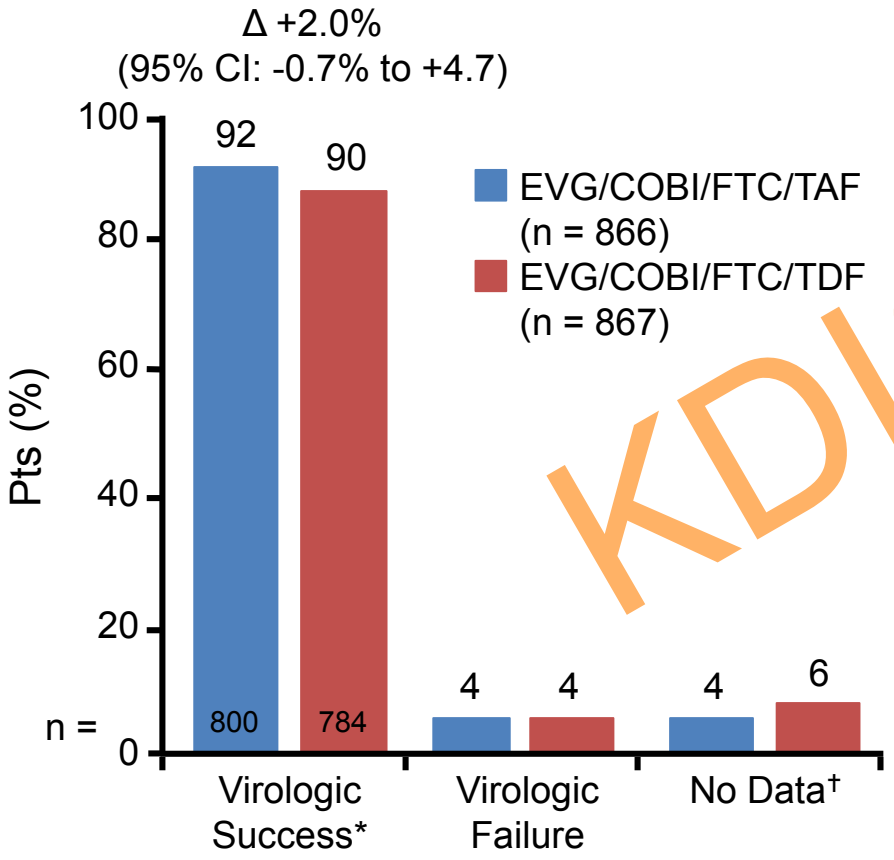
Dolutegravir: Integrase inhibitor
Cobicistat: Pharamcoenhancer

Model of organic anion transporters in proximal tubule

Adapted from Mitema and Atta *Current Drug Metabolism*, 2015



Tenofovir Alafenamide (TAF) vs TDF in Treatment-Naive Pts



*HIV-1 RNA < 50 c/mL as defined by FDA Snapshot algorithm.
†Discontinued for AE, death, or missing data.

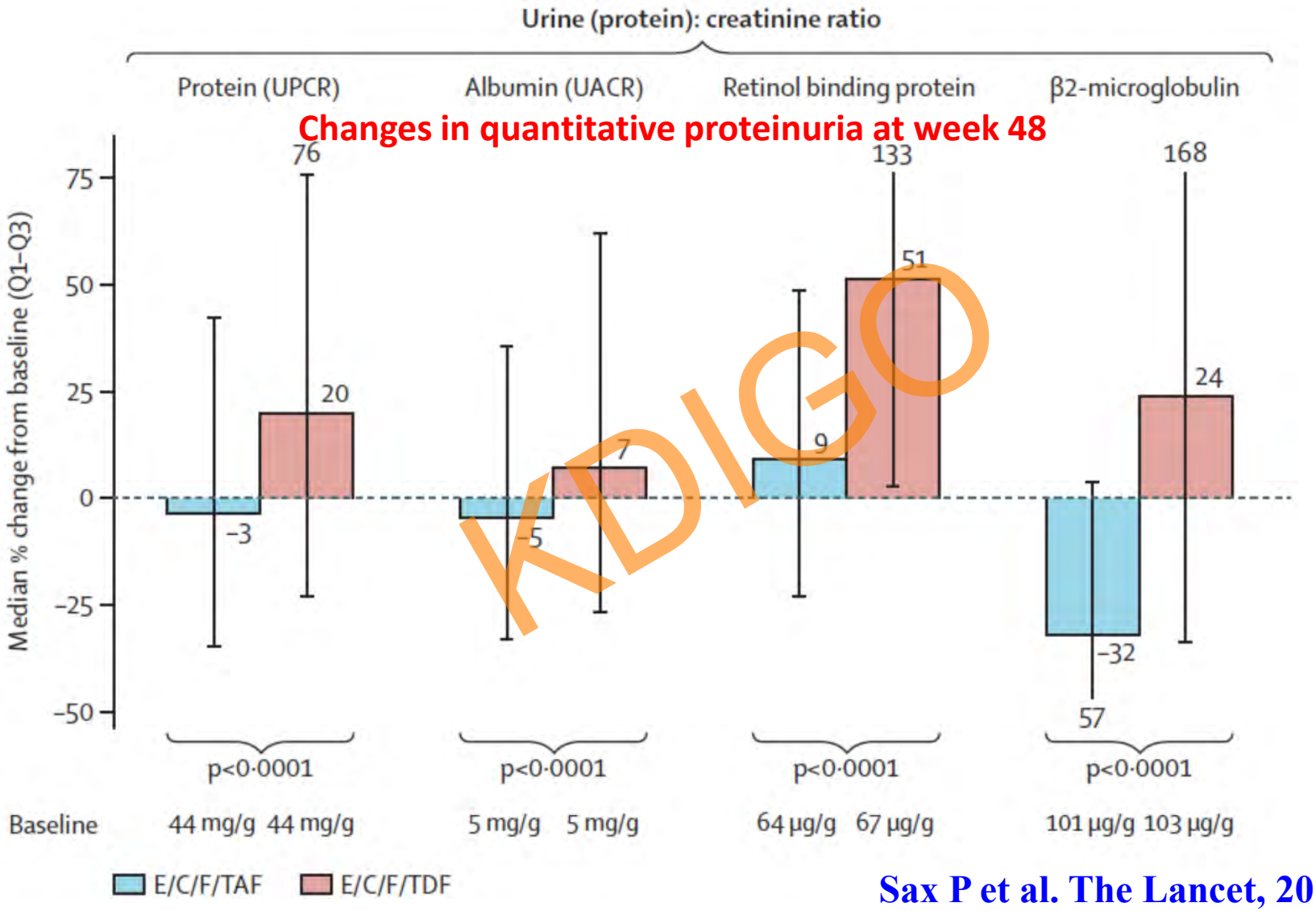
Parallel, randomized, double-blind, active-controlled phase III studies

Primary endpoint: HIV-1 RNA at Week 48

eGFR ≥ 50 mL/min

Sax P et al. The Lancet, 2015

Changes in quantitative proteinuria at week 48



Sax P et al. The Lancet, 2015

Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Patients With Renal Impairment: 48-Week Results From a Single-Arm, Multicenter, Open-Label Phase 3 Study

Anton Pozniak, MD, Jose R. Arribas, MD,† Joseph Gathe, MD,‡ Samir K. Gupta, MD,§ Frank A. Post, MD,|| Mark Bloch, MD,¶ Anchalee Avihingsanon, MD,# Gordon Crofoot, MD,** Paul Benson, MD,†† Kenneth Lichtenstein, MD,‡‡ Moti Ramgopal, MD,§§ Ploenchan Chetchotisakd, MD,|||| Joseph M. Custodio, PhD,¶¶ Michael E. Abram, PhD,¶¶ Xuelian Wei, PhD,¶¶ Andrew Cheng, MD, PhD,¶¶ Scott McCallister, MD,¶¶ Devi SenGupta, MD,¶¶ and Marshall W. Fordyce, MD,¶¶ for the GS-US-292-0112 Study Team*

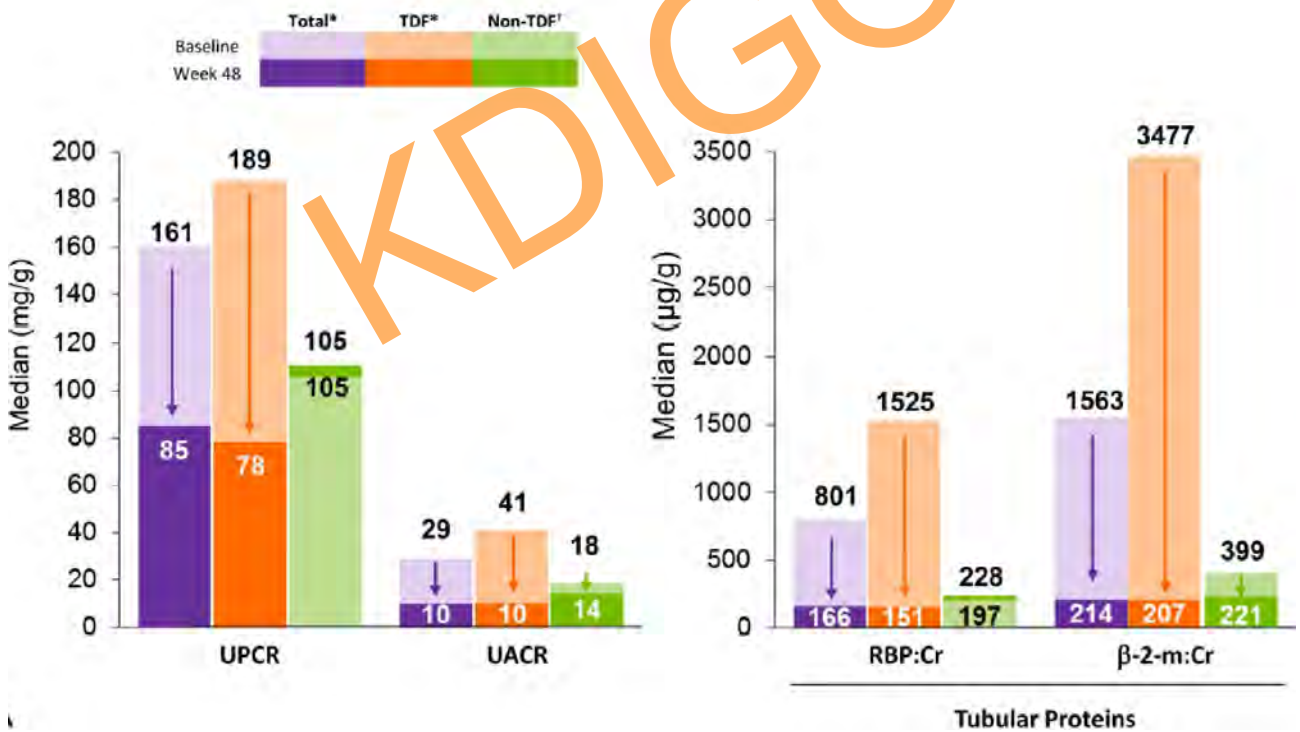
J Acquir Immune Defic Syndr Volume 71, Number 5, April 15, 2016

N= 242, Cr. Cl. 30-69; <50=80, >50 162

Primary endpoint: Change in GFR from baseline

TABLE 2. Estimated GFR: Change From Baseline to Weeks 24 and 48

Median Change (Q1, Q3) (mL/min)*	Total, N = 242	<50 mL/min, n = 80	≥50 mL/min, n = 162	TDF Containing, n = 158	Non-TDF Containing, n = 84
Change at week 24					
$eGFR_{CG}$	−0.4 (−4.8, 4.5)	+1.2 (−3.9, 5.6)	−0.9 (−4.9, 3.6)	+0.6 (−4.5, 5.5)	−0.9 (−4.8, 2.4)
$eGFR_{CKD\text{-}EPIsCr}$	−1.8 (−6.1, 4.9)	+0.3 (−4.1, 7.2)	−2.2 (−8.1, 3.7)	−0.5 (−7.1, 6.9)	−2.3 (−5.7, 2.2)
$eGFR_{CKD\text{-}EPIcysC}$	+3.8 (−4.8, 11.2)	+3.8 (−4.8, 12.2)	+3.8 (−3.8, 10.7)	+4.8 (−3.0, 13.4)	+1.5 (−5.9, 8.9)
Change at week 48					
$eGFR_{CG}$	−0.6 (−5.4, 5.4)	+0.6 (−3.4, 6.9)	−1.4 (−6.3, 4.0)	+0.2 (−5.8, 6.3)	−1.8 (−4.5, 4.0)
$eGFR_{CKD\text{-}EPIsCr}$	−1.8 (−7.9, 4.1)	+1.4 (−5.3, 6.1)	−3.1 (−8.9, 2.7)	−1.5 (−8.8, 6.0)	−2.7 (−5.8, 3.4)
$eGFR_{CKD\text{-}EPIcysC}$	+1.6 (−7.4, 11.9)	+1.1 (−5.3, 11.3)	+1.8 (−8.9, 12.2)	+2.7 (−6.2, 14.1)	−1.4 (−8.5, 5.2)



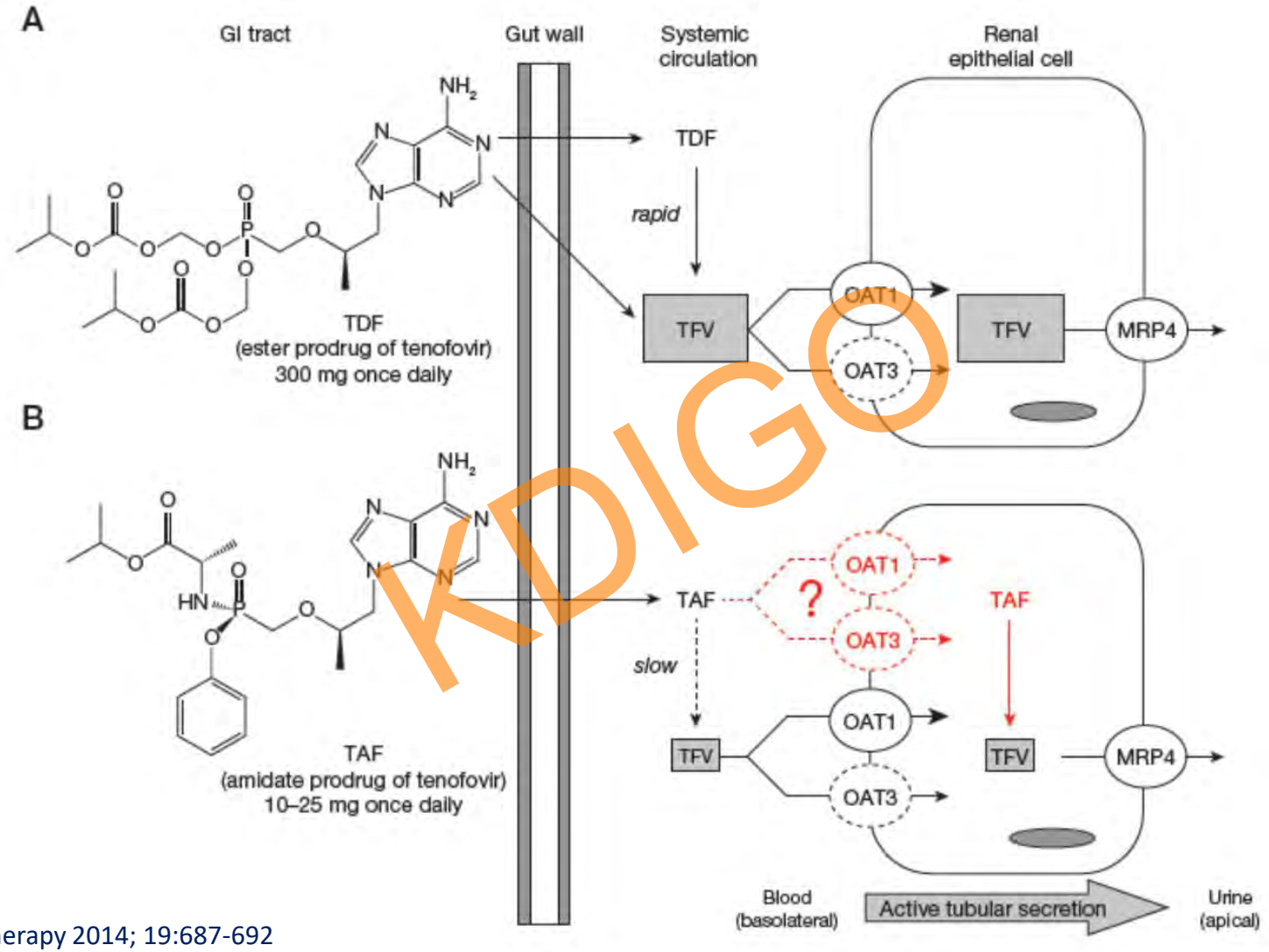
TDF vs TAF

TDF	TAF
300 mg daily	10-25 mg daily
No systemic metabolism	Hepatic and mononuclear cell metabolism to TFV
Rapidly hydrolyzed in plasma	Prolonged stability in plasma
High circulating TFV	Reduced systemic exposure to TFV

For TAF:

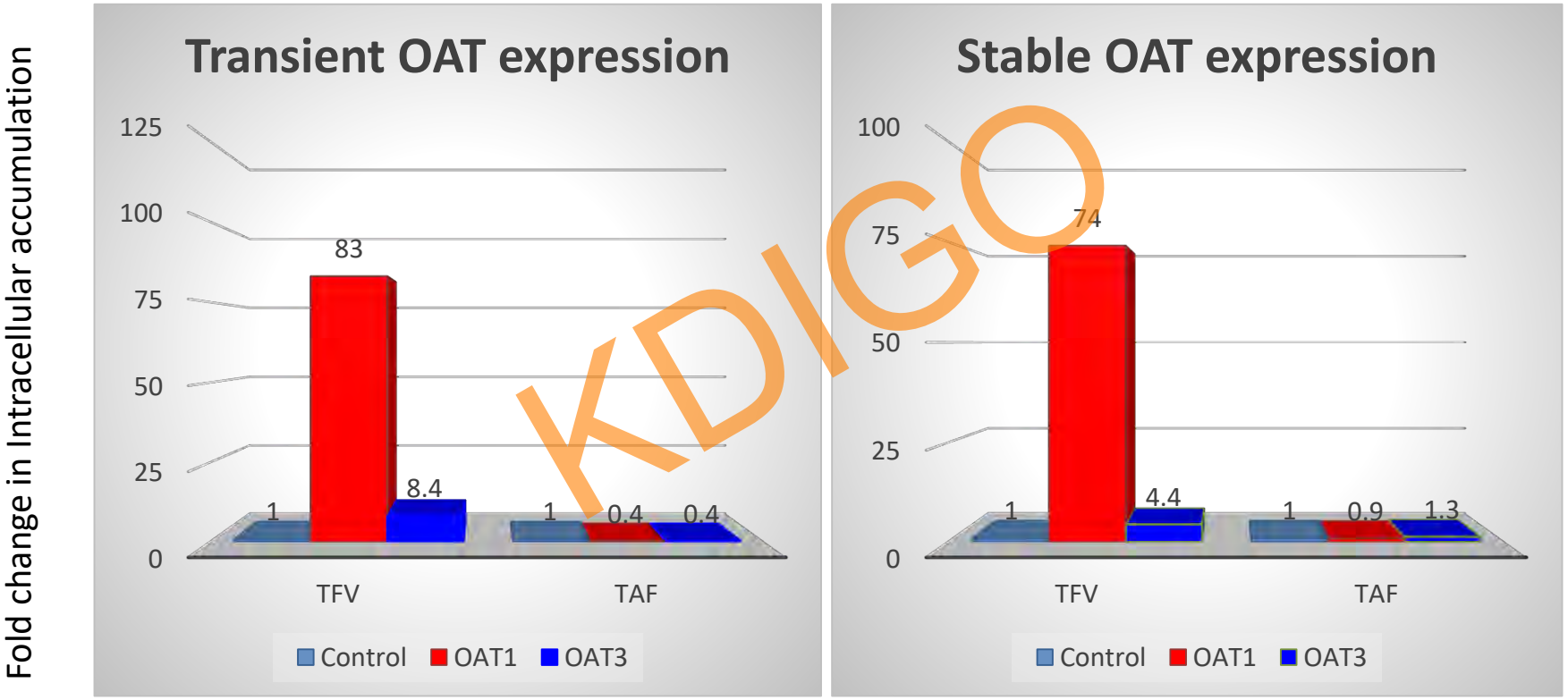
Hepatic impairment decreases AUC of active metabolite (TFV) by 11%.

AUC of active metabolite (TFV) increases by 5.7 fold with renal impairment (CrCl 15mL/min – 90mL/min)



Antiviral Therapy 2014; 19:687-692

Intracellular accumulation of TFV and TAF in cells expressing OAT transporters



March 24, 2017

WHAT SHOULD WE DO?

D:A:D: ARV Exposure and Risk Score of CKD

17,954 HIV+ individuals with eGFR > 60 ml/min/1.73 m^2

Enrolled in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D)

641 developed CKD during median follow-up of 6.1 years.

Risk for CKD:

- Older age, Female, IVDU, lower CD4 count nadir
- Lower baseline eGFR, HCV coinfection, HTN, DM, and CVD.

Mocroft A, Lundgren JD, Ross M, Law M, Reiss P, et al. (2015) Development and Validation of a Risk Score for Chronic Kidney Disease in HIV Infection Using Prospective Cohort Data from the D:A:D Study. PLoS Med 12(3): e1001809. doi:10.1371/journal.pmed.1001809
http://127.0.0.1:8081/plosmedicine/article?id=info:doi/10.1371/journal.pmed.1001809

Chronic Kidney Disease Tool

Gender:	○ Female ○ Male
Age at the time when eGFR was measured:	**Date of birth (yyyy-mm-dd)** **Date when eGFR was measured (yyyy-mm-dd)**
IDU:	○ Yes ○ No
HCV:	○ Yes ○ No
eGFR:	eGFR Calculator
Nadir CD4:	

Estimate Reset

If the answer to any of the questions below is unknown, please do not enter any further data; your risk-score for CKD will be calculated without using these variables.

Diabetes:	○ Yes ○ No
History of Cardiovascular Disease	○ Yes ○ No
Is the answer yes to at least one of the following 3 questions: – **Is the diastolic blood pressure >100 mm/Hg (10 mm/Hg or 13.33 kPa)?** – **Is the systolic blood pressure >150 mm/Hg (15 mm/Hg or 20.00 kPa)?** – **Is the person using anti-hypertensive medication or ACE inhibitors?**	○ Yes ○ No

Chronic Kidney Disease Tool

Gender:	◉ Female ○ Male
Age at the time when eGFR was measured:	50 **Date of birth (yyyy-mm-dd)** **Date when eGFR was measured (yyyy-mm-dd)**
IDU:	◉ Yes ○ No
HCV:	◉ Yes ○ No
eGFR:	70 eGFR Calculator
Nadir CD4:	200

If the answer to any of the questions below is unknown, please do not enter any further data; your risk-score for CKD will be calculated without using these variables.

Diabetes:	○ Yes ◉ No
History of Cardiovascular Disease	○ Yes ◉ No
Is the answer yes to at least one of the following 3 questions: – **Is the diastolic blood pressure >100 mm/Hg (10 mm/Hg or 13.33 kPa)?** – **Is the systolic blood pressure >150 mm/Hg (15 mm/Hg or 20.00 kPa)?** – **Is the person using anti-hypertensive medication or ACE inhibitors?**	◉ Yes ○ No

Chronic Kidney Disease Tool

Gender:	◉ Female ○ Male
Age at the time when eGFR was measured:	50 **Date of birth (yyyy-mm-dd)** **Date when eGFR was measured (yyyy-mm-dd)**
IDU:	◉ Yes ○ No
HCV:	◉ Yes ○ No
eGFR:	70 eGFR Calculator
Nadir CD4:	200

If the answer to any of the questions below is unknown, please do not enter any further data; your risk-score for CKD will be calculated without using these variables.

Diabetes:	○ Yes ◉ No
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Estimate | Reset

Basic result

Based on the information you have put into the CKD risk-score calculator, you are estimated to have a **86%** chance of developing CKD in the next 5 years.

Some antiretrovirals may be associated with higher risks of CKD, and adding or starting these may increase your risk of CKD, as shown below

ARV started or added to regimen	Chance of CKD over the next 5 years
Tenofovir	100%
Atazanavir with ritonavir	100%
Atazanavir without ritonavir	100%
Lopinavir with ritonavir	100%
Any other ritonavir boosted protease inhibitor	100%

When more than one of the potentially nephrotoxic antiretrovirals are added, the risk of CKD may increase even further. Please indicate if you are adding or starting more than one of these antiretrovirals at the same time

- ☐ Tenofovir
- ☐ Atazanavir with ritonavir
- ☐ Atazanavir without ritonavir
- ☐ Lopinavir with ritonavir
- ☐ Any other ritonavir boosted protease inhibitor

Selected IDSA recommendations 2014

CID 2014:59 (1 November)

Screen for kidney disease: **when ART is initiated or changed, and at least twice yearly in stable HIV-infected patients.**

In patients with e**GFR <60 mL/minute/1.73 m2, we recommend avoiding TDF** when feasible

In TDF-treated patients with **confirmed GFR decline by >25% or to<60 mL/minute/1.73 m2, we recommend substituting alternative ART for TDF**, particularly in those with evidence of PTD.

The necessity for differential dose adjustments of one or more components usually **precludes the use of fixed-dose combinations in patients with moderately to severely impaired kidney function**

ART and Kidney

- *Renal toxicities are rare with NNRTIs, Entry and Integrase inhibitors.*
- *Among PIs, renal toxicities have mainly been reported with IDV and ATZ.*
- *TDF is the most nephrotoxic used today.*
- *CKD 5-year risk score can be a helpful tool.*
- *TAF can be nephrotoxic in susceptible host.*

THANK YOU!