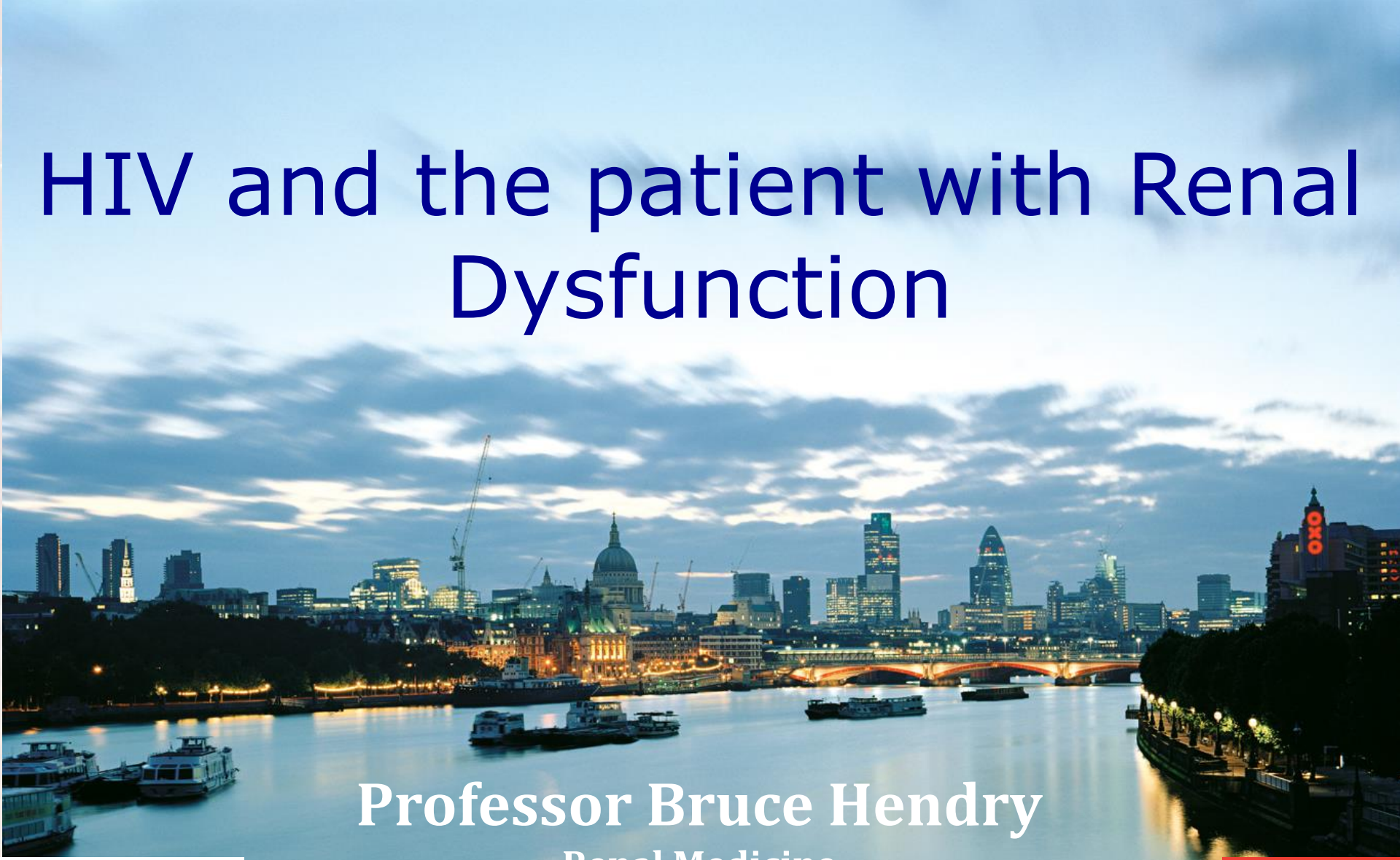
HIV and the patient with Renal Dysfunction



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HIV and Renal Dysfunction

Scheme of Lecture

- Basics of Chronic Kidney Disease in HIV care
- Toxicity of ART
- Creatinine Creep (falling eGFR)
- TAF: Pharmacology and Clinical Data

Chronic kidney disease (CKD)

Kidney damage or abnormal kidney function for >3 months

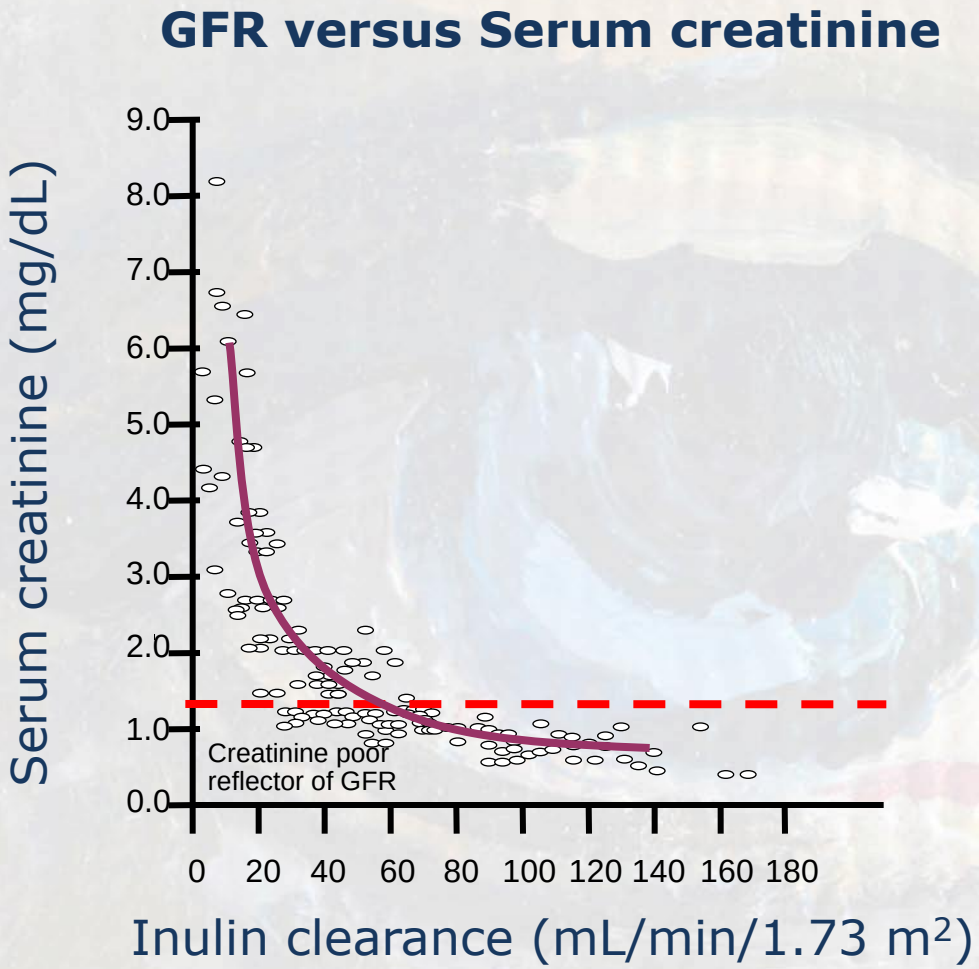
Kidney damage: Abnormal renal pathology or a surrogate marker (proteinuria, abnormal urinalysis or abnormal renal sonogram)

Abnormal kidney function: GFR < 60 mL/min/1.73 m^2

Stage	Description	eGFR (mL / min / 1.73m^2)
I	Kidney damage with normal or increased GFR	≥ 90
II	Kidney damage with mildly decreased GFR	60–89
III	Moderately decreased GFR	30–59
IV	Severely decreased GFR	15–29
V	Kidney failure	< 15 (or dialysis)

Levey AS et al. Ann Intern Med 2003;139(2):137-47

Serum creatinine is a poor reflection of GFR



Johnson R et al. Comprehensive Clinical Nephrology. 2000. Mosby. St. Louis. 4.15.1–4.15.15.

Considerations for estimated GFR

- **Cockcroft-Gault**
  - Validated in patients with *normal* GFR
  - Overestimates GFR at normal function
  - Easy to calculate
- **MDRD**
  - Validated in patients with *altered* GFR
  - In normal ranges, tends to underestimate GFR
  - Normalized to average BSA
  - More difficult to calculate
- **Both**
  - Still dependent on serum creatinine
  - Not validated in elderly, chronic disease states, HIV

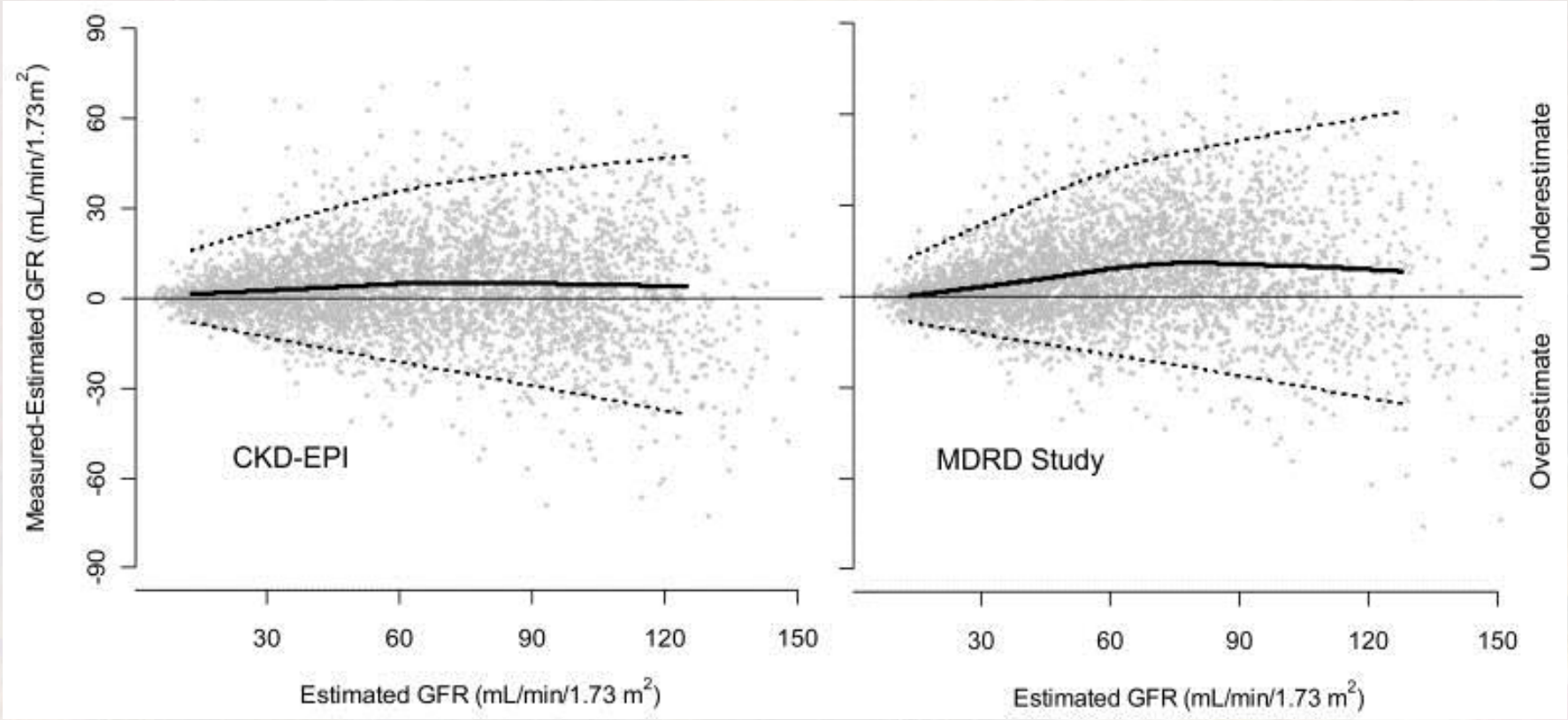
Cockcroft-Gault Equation (CG):

$$\text{CLcr (ml/min)} = \frac{[140 - \text{Age (yrs)}] \times \text{Wt (kg)} \times (0.85 \text{ if female})}{72 \times \text{Serum creatinine (mg/dL)}}$$

Modification of Diet in Renal Disease

$$\text{GFR (mL/min/1.73m2)} = 186 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if African American})$$

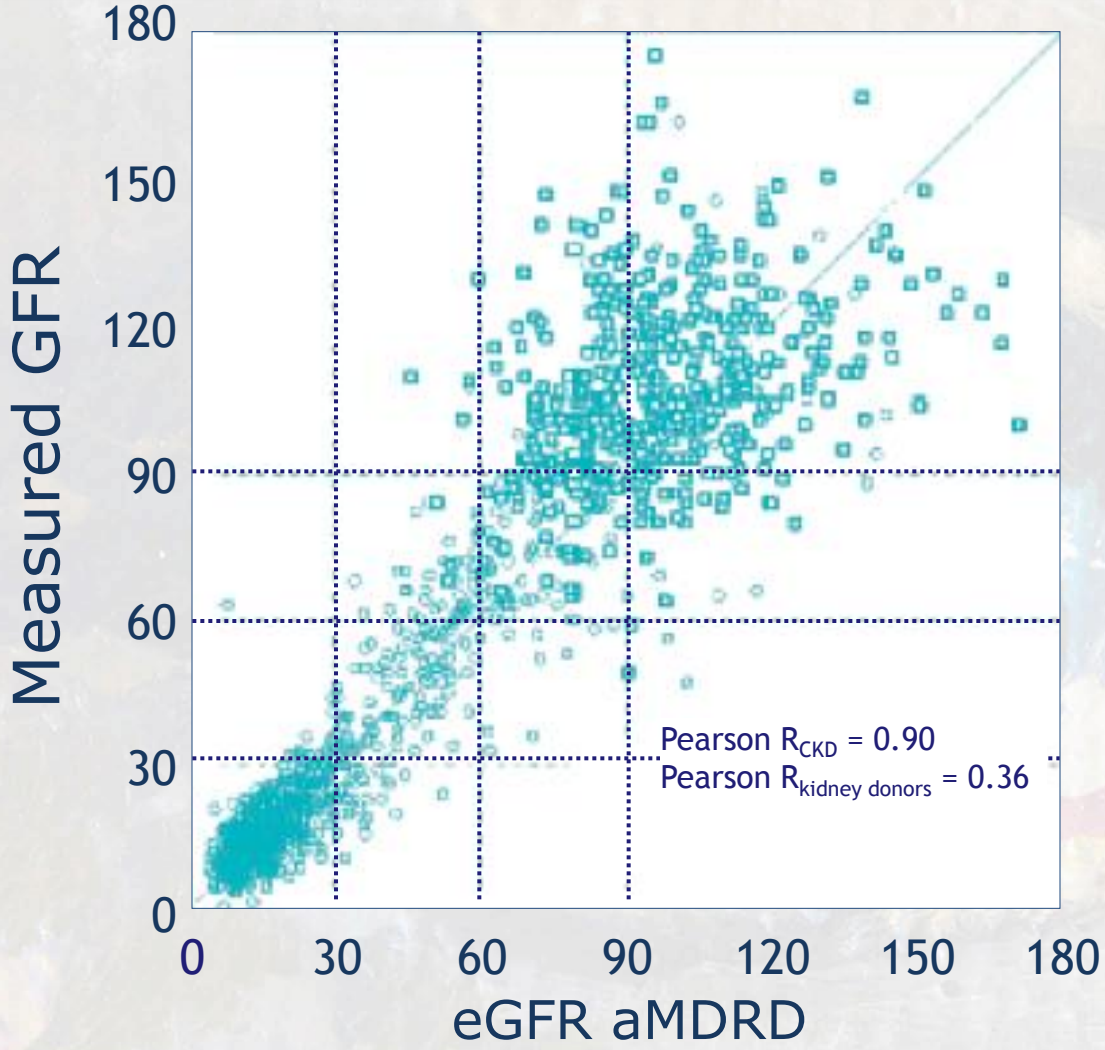
Plasma eGFR vs true GFR



- eGFR (MDRD) generally provides an underestimate of the true GFR
- Significant discordance between calculated and measured GFR may be observed throughout the GFR range
- The CKD-EPI equation may provide a more accurate estimate of the GFR

Levey AS et al. Ann Intern Med 2009; 150: 604-612

Plasma eGFR vs.. true GFR



Levy AS et al. Ann Intern Med 1999; 130: 461-470

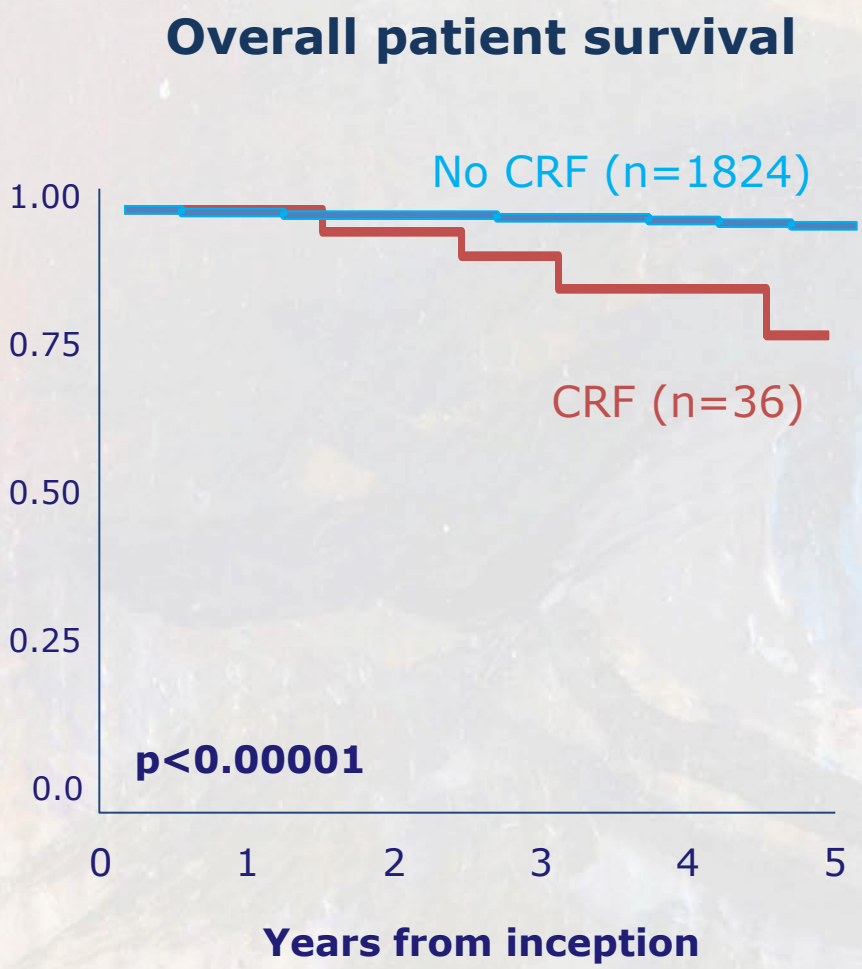
Chronic kidney disease

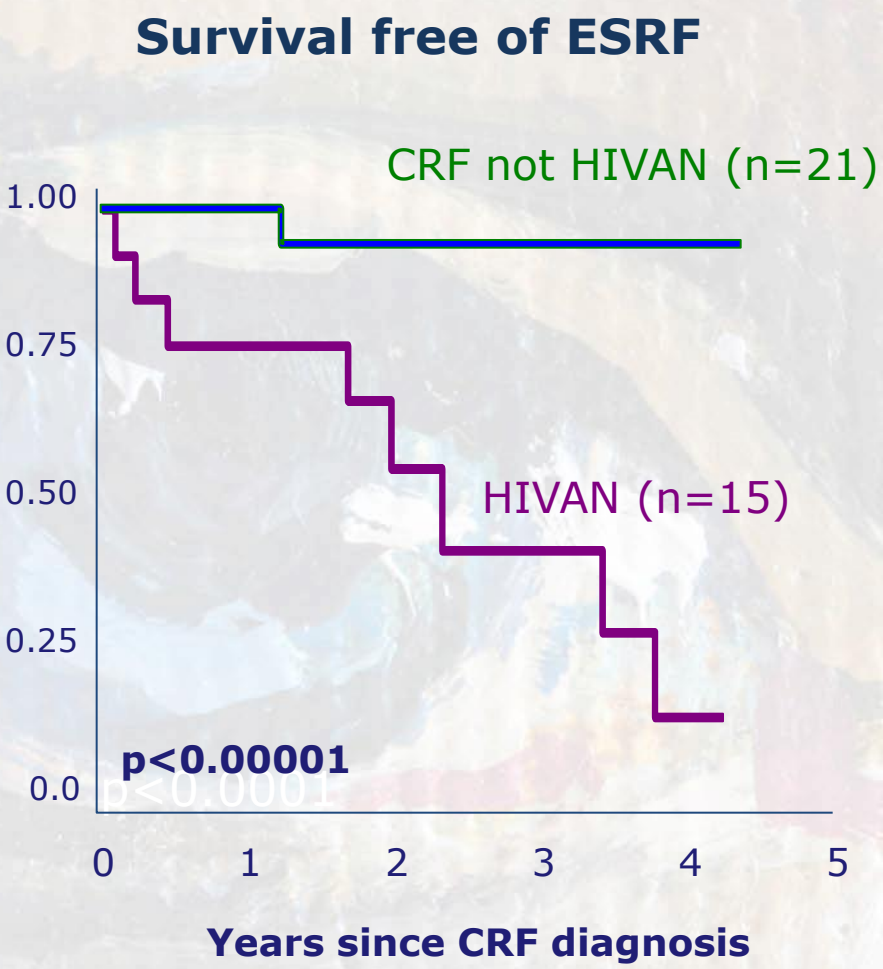
Identify patients with eGFR <60 ml/min

This is stage 3-5 CKD and they have 4 key issues:

1. Premature cardiovascular death
2. Progression to end-stage kidney disease requiring dialysis
3. Need to adjust drug doses
4. Increased risk of drug toxicity

HIV: Survival and dialysis-free survival





CRF = CKD stage 3-5

Campbell LJ et al. HIV Medicine 2009; 10(6): 329-336

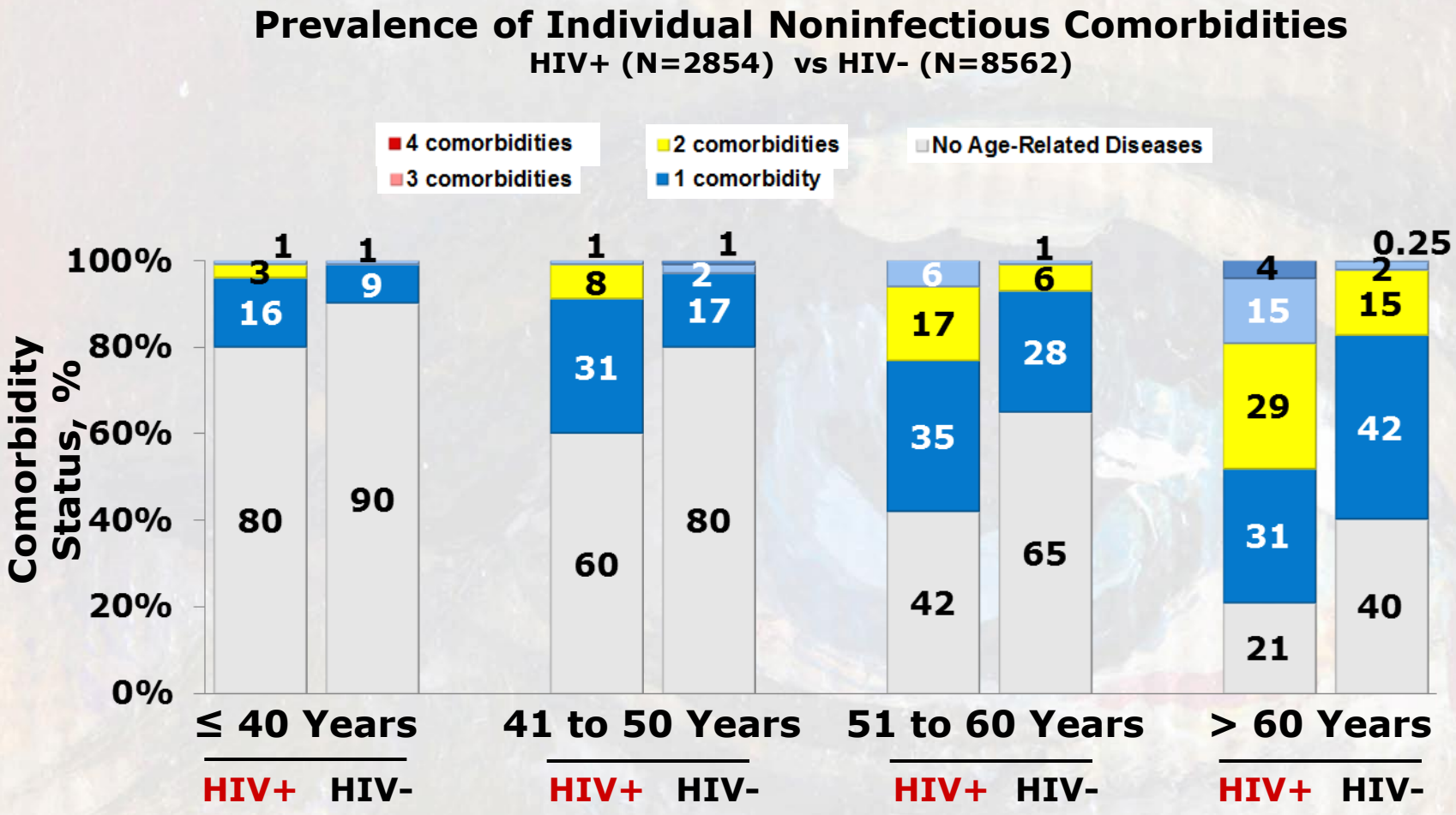
Chronic kidney disease

Key causes

- Diabetes mellitus
- Hypertension and Vascular Disease

- Interstitial Renal Disease (drugs including ART)
- Chronic pyelonephritis and obstructive nephropathy
- Glomerulonephritis
- Genetic- ADPKD
- History of Acute Kidney Injury (AKI)
- HIV-Associated Nephropathy

HIV+ vs HIV-
Onset of Age-Related Comorbidities

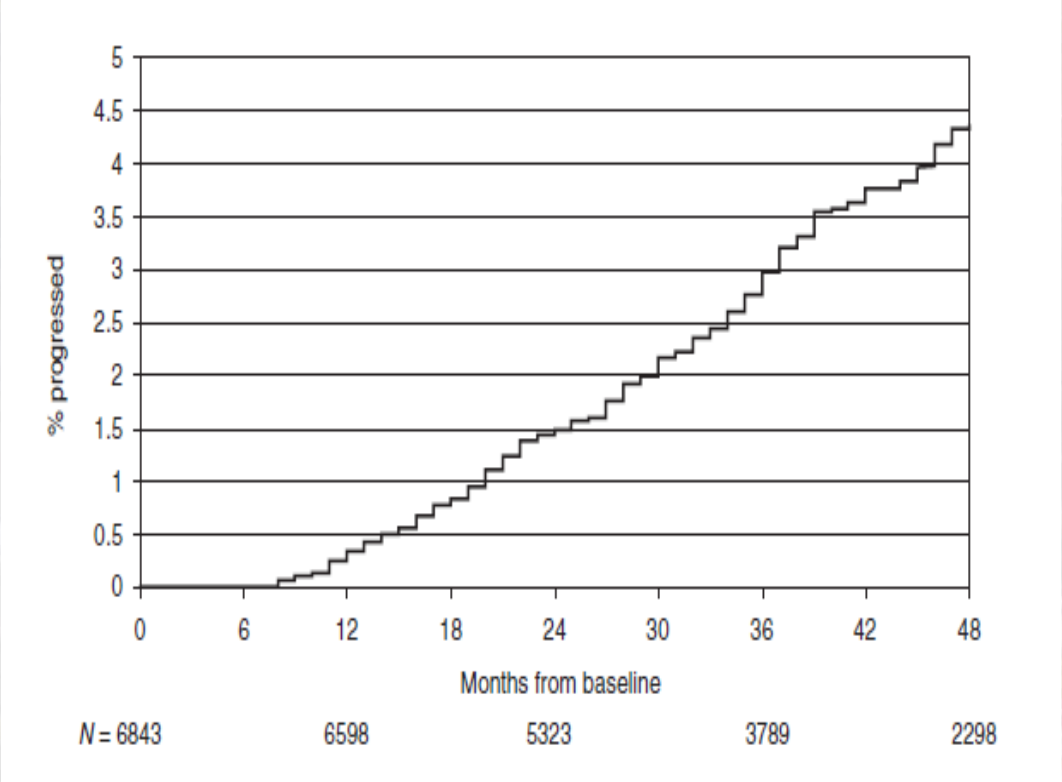


HIV+ individuals vs age-matched HIV- controls have more individual noninfectious comorbidities and at an earlier age (all P < 0.001)

Guaraldi G, et al. *Clin Infect Dis.* 2011;53:1120-1126.

Incident CKD in EuroSIDA

- CKD defined as:
  - Confirmed eGFR <60 if baseline eGFR >60
  - >25% decline if baseline eGFR <60
- 21,482 PYFU
  - median 3.7 years
- 225 (3.3%) progressed to CKD
  - Incidence 1.1 (0.9-1.2) per 100py

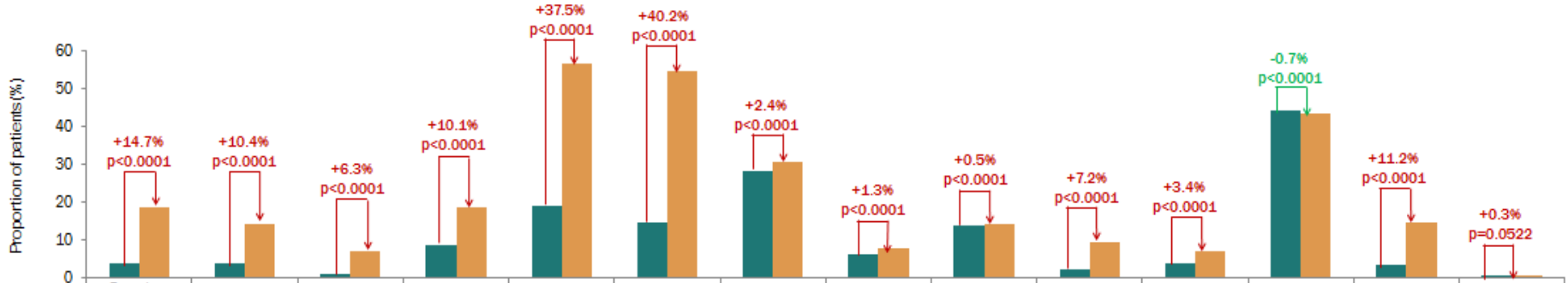


Mocroft A et al. AIDS 2010; 24: 1667-78

HIV PATIENTS TODAY AND 10 YEARS AGO: DO THEY HAVE THE SAME NEEDS? ANRS CO3 AQUITAINE COHORT

The objective of this study was to describe the evolution of chronic non-HIV related diseases and their risk factors, in patients included in the French ANRS CO3 Aquitaine prospective cohort, 10 years apart, observed both in 2004 and in 2014

- Significant improvement in HIV markers over time, in a population getting older
- High prevalence of comorbidities, (dyslipidaemia, hypertension) with increased associated risk factors and renal and cardiovascular risk scores more pronounced

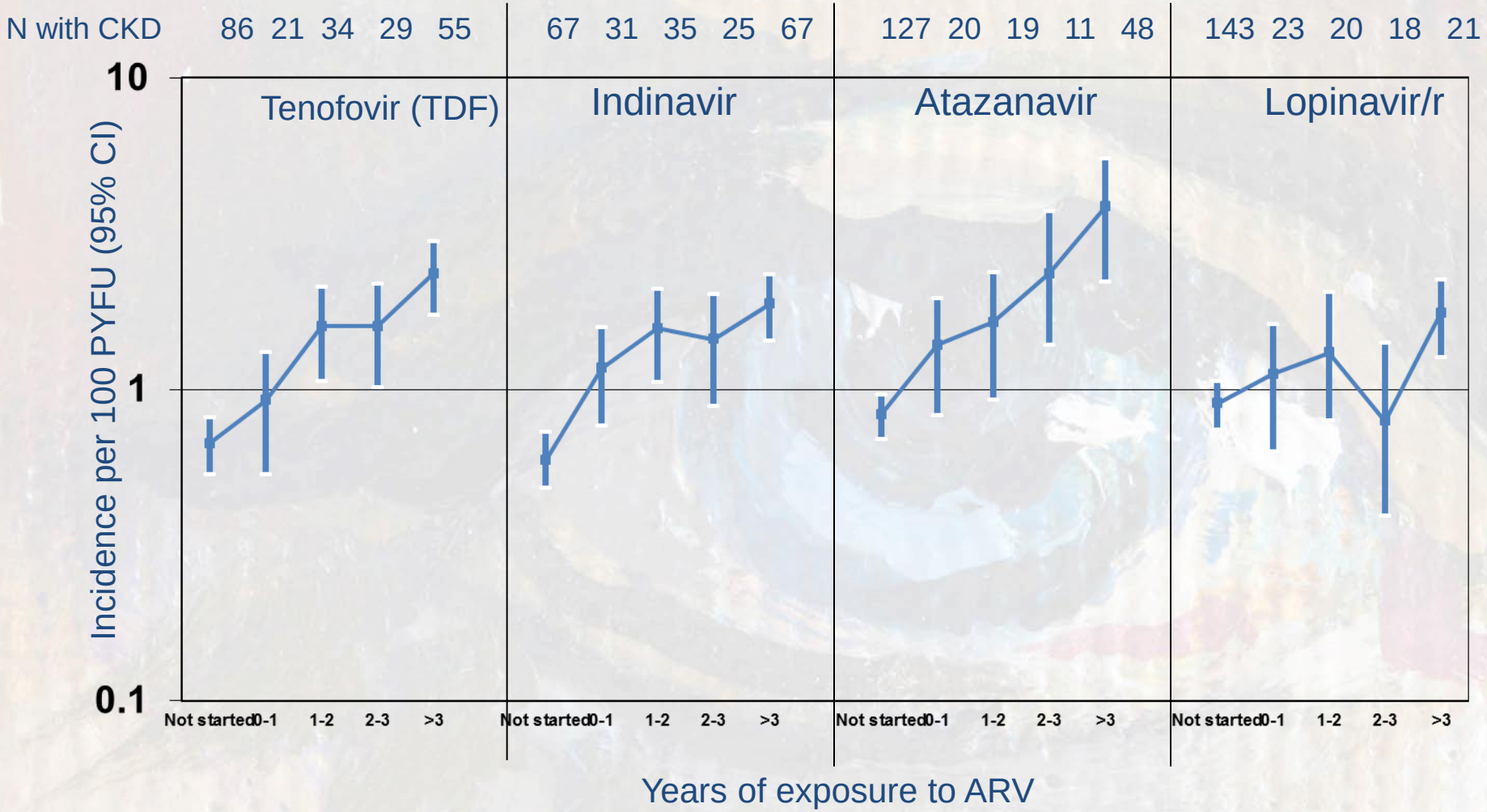


	Prevalent Chronic Kidney Disease	Cardiovascular event*	Fractures (anywhere)	Diabetes*	Hypertension*	Dyslipidaemia	Hepatitis C virus infection	Hepatitis B virus infection	Depression*	Cancer (non-AIDS related)	Obesity	Current tobacco consumption	Current alcohol abuse (regular)	Active injecting drug user
2004 (n=2,138)	3.6	3.6	0.7	8.4	18.8	14.3	28.2	6.2	13.5	2.2	3.6	44.0	3.1	0.2
2014 (n=2,138)	18.3	14.0	7.0	18.5	56.3	54.5	30.6	7.5	14.0	9.4	7.0	43.3	14.3	0.5

Figure 1 – Comorbidities and risk factors, in 2004 and 2014

- Careful HIV management including regular monitoring, screening for comorbidities and adequate selection of ART can promote continuous improvement in health related outcomes for PLWHIV

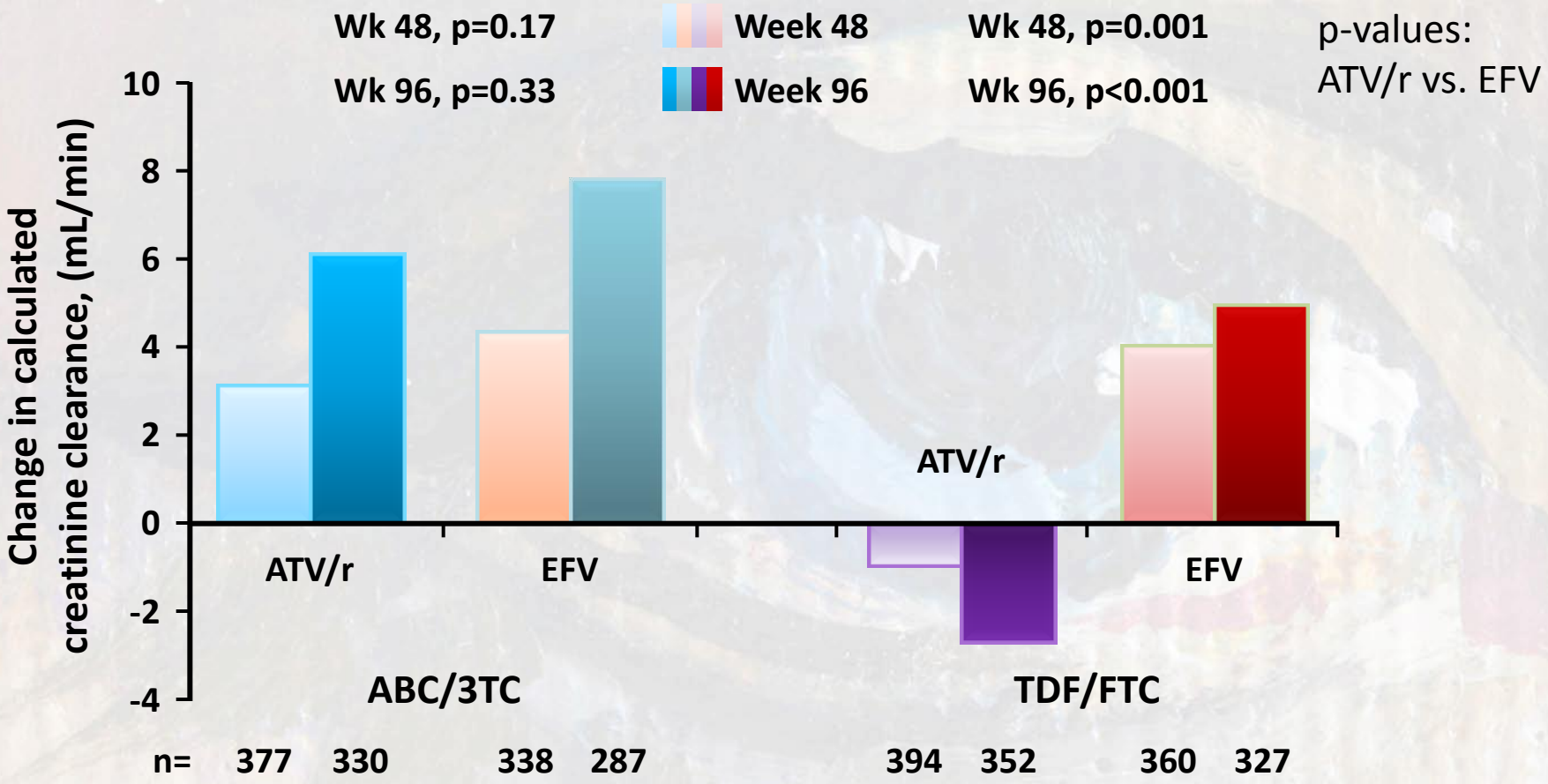
Crude incidence rate of CKD and increasing exposure to ARVs



CKD, confirmed (persisting for >3 months) decrease in eGFR ≤ 60 mL/min/1.73m^2 if eGFR at baseline >60 mL/min/1.73m^2 or confirmed 25% decrease in eGFR if baseline eGFR≤60 mL/min/1.73m^2

EuroSIDA: Kirk et al, CROI 2010

ATV/r vs. EFV
median change in creatinine clearance



PI and renal risk
Risk of CKD: multivariate analysis

	Hazard Ratio (95% CI)	P value
ATV/r	**1.52 (1.14-2.03)**	**0.004**
DRV/r	1.31 (0.94-1.81)	0.108
LPV/r	**1.61 (1.1-2.6)**	**0.017**
EFV	1	

- Patients on ATV/r or LPV/r were significantly more likely to develop eGFR<60 ml/min/1.73m^2 compared with EFV.
- DRV/r was not significantly associated with renal impairment.

*Adjusted for gender, age at start of HAART, baseline eGFR, Hep B SAg, prior exposure to TFV and IND and total duration of TFV exposure.

Rockwood N, et al. Oral presentation IAS; 2011. Rome.

Incidence of new CKD in HIV Care: Updated D:A:D Study 2016

In patients with baseline eGFR >90ml/min the incidence of new CKD (stages 3-5) was 1.76 per 1000 patient years. Increased adjusted hazard was associated with cumulative exposure to:

- TDF Tenofovir (HR 1.14 per year exposure)
- Atazanavir/r (HR 1.20 per year exposure)
- Lopinavir/r (HR 1.11 per year exposure)

Most HIV patients who develop CKD 3-5 have a baseline eGFR below 90

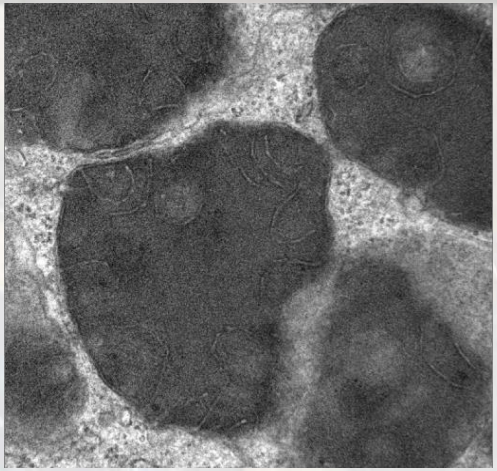
Mocroft et al Lancet HIV 2016; 3: e23–32

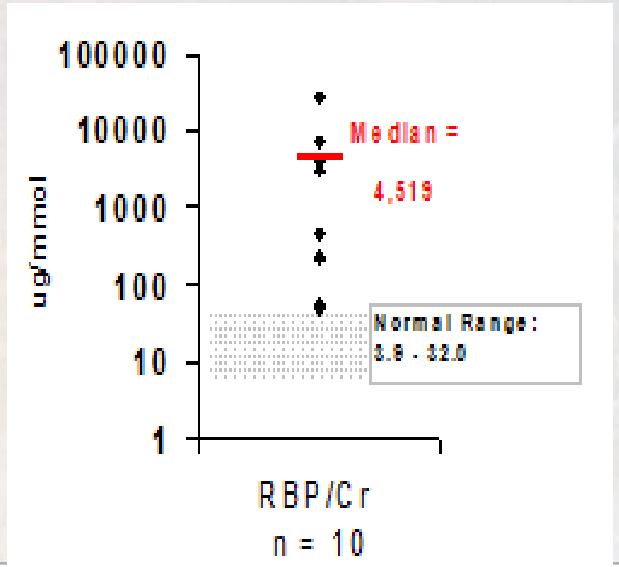
Fanconi syndrome (Proximal Renal Tubulopathy PRT)

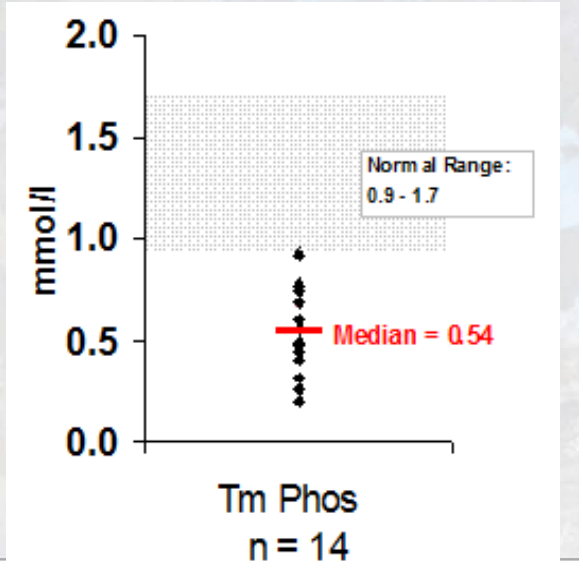
PRT Prevalence: 0.5-1.0% of patients receiving Tenofovir as TDF

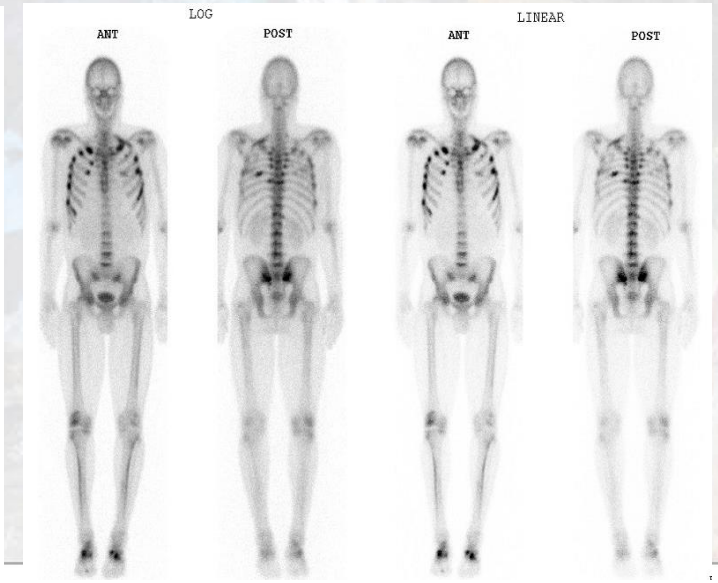
Bone pain, phosphate wasting, osteomalacia

Almost exclusively when tenofovir as TDF is co-administered with a (boosted) PI



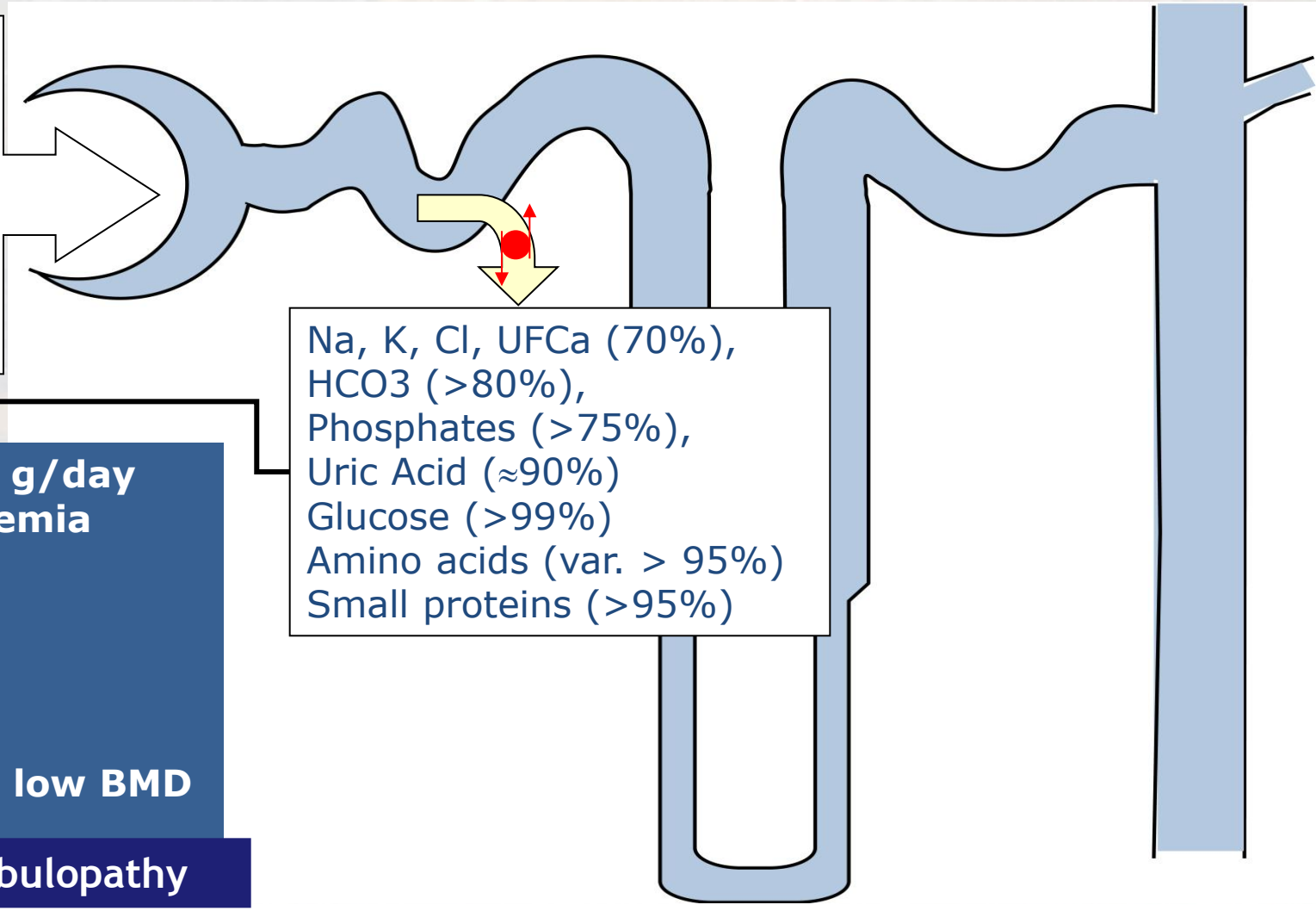






Woodward, HIV Med 2009

The critical question: Is it Fanconi syndrome?



Na, K, Cl,
HCO3,
Phosphates,
UFCa,
Glucose,
Amino Acids,
Uric Acid,
Small proteins

Na, K, Cl, UFCa (70%),
HCO3 (>80%),
Phosphates (>75%),
Uric Acid (≈90%)
Glucose (>99%)
Amino acids (var. > 95%)
Small proteins (>95%)

Proteinuria ≤ 2 g/day
Hypophosphatemia
Acidosis
Glycosuria
Hypokalemia
Aminoaciduria
Hypouricemia
If chronic then low BMD

Proximal Tubulopathy

The information portrayed on this slide is attributed to presenter's expert opinion

Creatinine Creep (falling eGFR)

When is this clinically significant?

- eGFR falls below 60 ml/min
- eGFR falls >25% and is < 90 ml/min
- Proteinuria (uPCR > 50 mg/mmole) (0.5g/d)
- Features of Fanconi Syndrome (PRT) present

Creatinine Creep (falling eGFR)

Actions if clinically significant eGFR fall?

- Check proteinuria, BP and diabetes
- Review medications
- Establish renal diagnosis (clinical, lab, renal U/S, renal biopsy?)
- Consider stopping TDF if no other renal explanation

Stage 3-5 CKD: Reducing Progression

Consider all risk factors for the progression of renal insufficiency

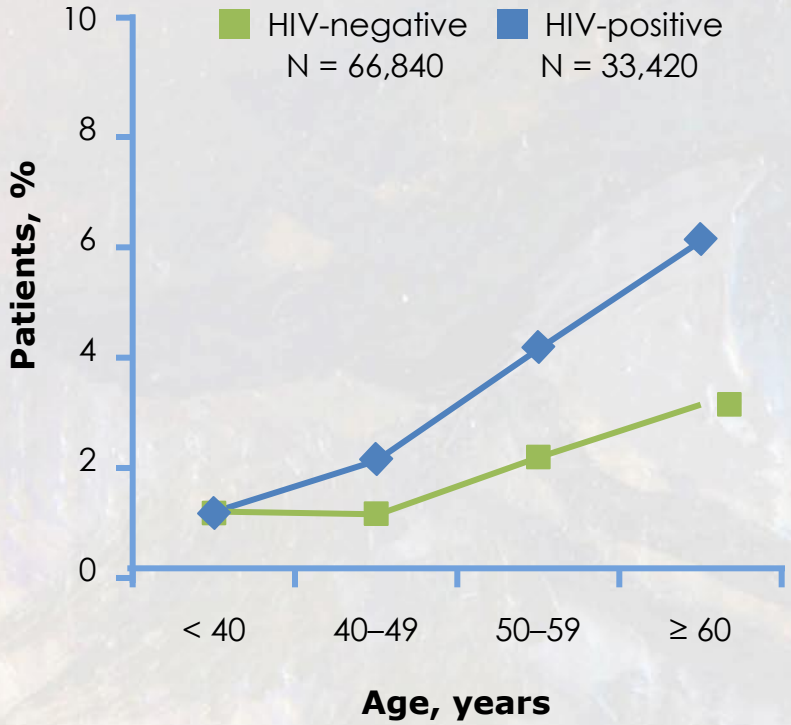
- Smoking
- Hypertension
- Dyslipidaemia
- Anaemia
- Diabetes

- Hyperuricaemia
- Metabolic syndrome
- Nephrotoxic drugs
- Vascular disease

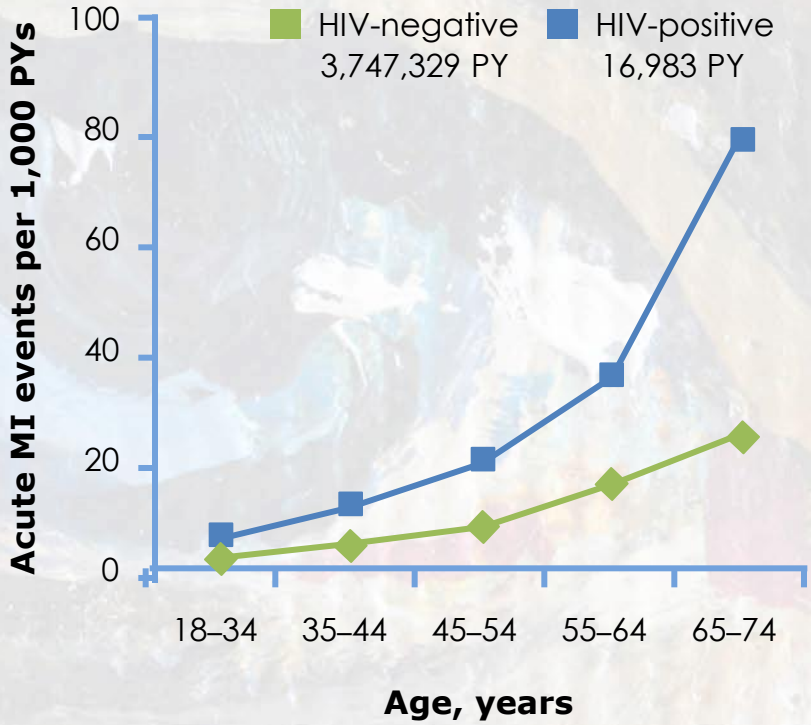
The information portrayed on this slide is attributed to presenter's expert opinion

Prevalence of CKD and MI increases with advancing age and HIV infection

Rate of CKD in patients according to HIV status and age group[1]



Rate of MI in patients (1996–2004) according to HIV status and age group[2]

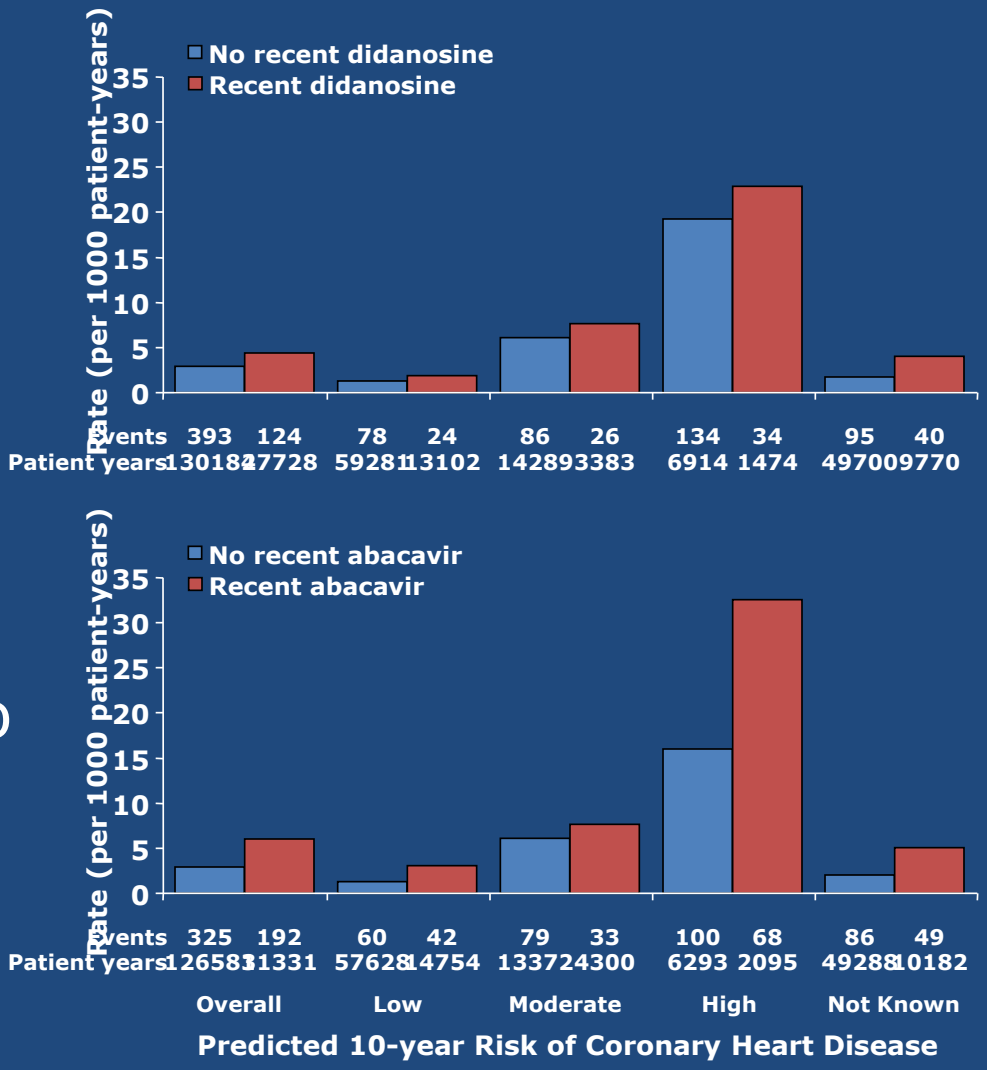


PY = patient-year.

1. Adapted from Goulet J, et al. Clin Infect Dis 2007; 45:1593–1601; 2. Adapted from Triant VA, et al. J Clin Endocrinol Metab 2007; 92:2506–2225.

NRTIs and MI Risk in D:A:D

- Increased risk associated with ABC and ddI most marked in those at "high" risk (6% of subjects in D:A:D)
- Associations between ABC and MI have also been observed in other cohorts (SMART, ANRS, VHA)



D:A:D Study Group. Lancet 2008;371:1417-1426
Stein JH, Currier JS. Lancet 2008;371:1391-1392

Renal risk and TDF limitations

- TDF-containing regimens are not recommended if eGFR is <75 ml/min per 1.73 m^2
- In patients with eGFR <75 ml/min per 1.73 m^2 managing high cardiovascular risk with regimens containing NRTIs is difficult
- TDF is associated with rates of PRT around 1% and requires additional monitoring (blood and urine tests)
- Increasing exposure to TDF is associated with higher incidence of CKD[1]
  - Incidence rate ratio (IRR) per year 1.16, 95% CI 1.06–1.25, P<0.0001

CKD, chronic kidney disease, eGFR, estimated glomerular filtration rate; PRT, proximal renal tubulopathy; TDF, tenofovir disoproxil fumarate.

1. Mocroft A, et al. AIDS 2010; 24:1667-78

EACS 2015 Guidelines: Recommended Regimen Options in Treatment-Naive Adults

Class	Regimen[a]		Limitations
Integrase Inhibitor	**ABC/3TC/DTG[a,b]**		HLA-B*5701 negative
	E/C/F/TDF[c,d,e]		Pre-ART eGFR ≥70 mL/min
	DTG	**FTC/TDF[c,d]**	-
	RAL (BID)	**FTC/TDF[c,d]**	-
NNRTI	**RPV/FTC/TDF[c]**		CD4 count >200 cells/μL and HIV VL <100,000 copies/mL
Boosted PI	**DRV + RTV**	**FTC/TDF[c,d]**	-

[a] ABC contraindicated if HLA B*5701 positive. Even if HLA B*5701 negative, counselling on HSR risk still mandatory. ABC should be used with caution in persons with a high CVD risk (>20%).

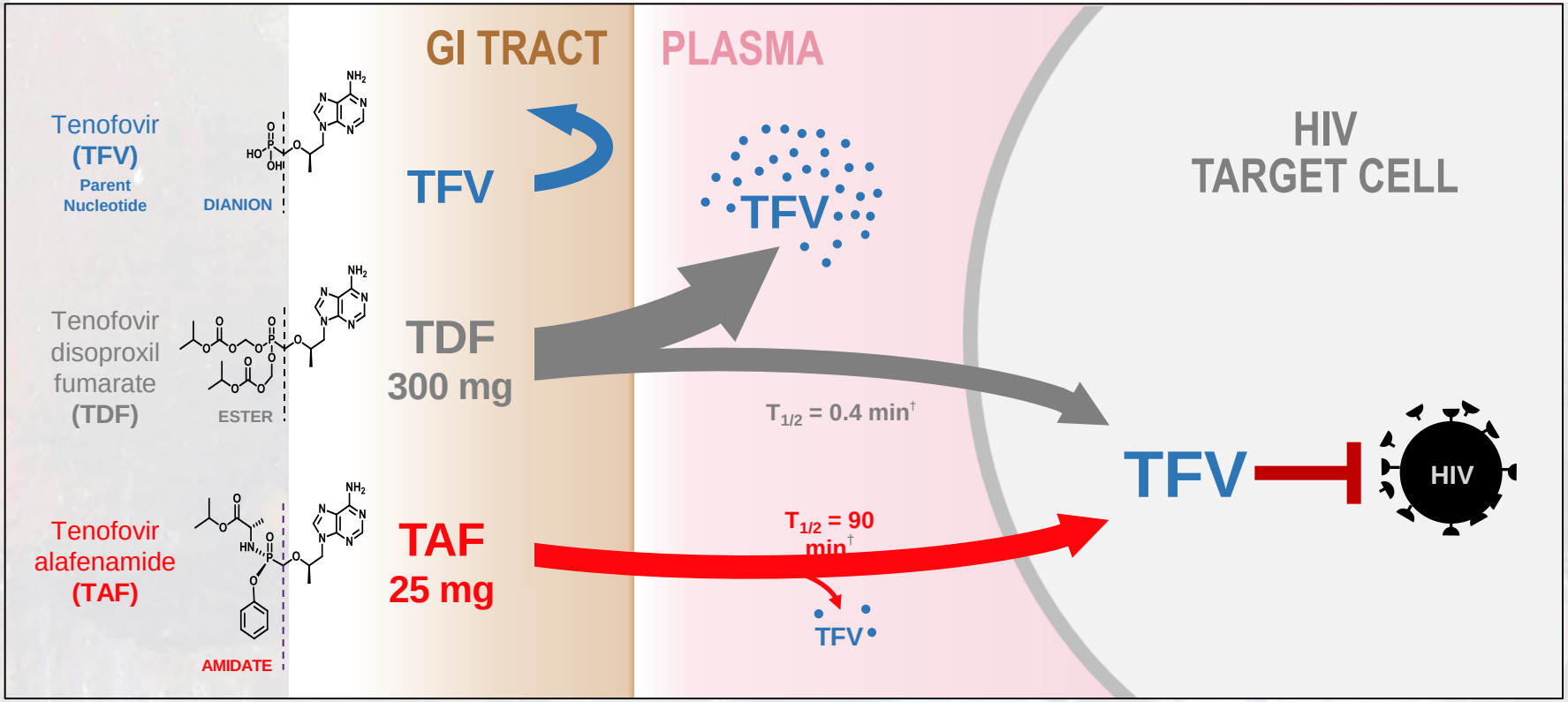
[b] Use this combination only if HBs Ag negative.

[c] Avoid TDF if osteoporosis, renal monitoring required.

[d] If TDF/FTC is not available, one alternative could be TDF+3TC as separate entities.

[e] TDF/FTC/EVG/c use only if eGFR ≥ 70 mL/min. It is recommended that TDF/FTC/EVG/c is not initiated in persons with eGFR < 90 mL/min unless this is the preferred treatment.

Tenofovir alafenamide (TAF): novel prodrug of tenofovir



- TAF is more stable in plasma compared with TDF[1]
- Intact TAF transits directly into target cells where it is intracellularly activated to tenofovir disphosphate (TFV-DP)[1–3]
- TAF at an equivalent dose of 25 mg (10 mg in boosted regimens) has 91% lower circulating plasma TFV levels compared to TDF 300 mg[4–6]

† $T_{1/2}$ based on *in vitro* plasma data.

1. Lee W et al. Antimicr Agents Chemo 2005;49(5):1898–1906; 2. Birkus G et al. Antimicr Agents Chemo 2007;51(2):543–550; 3. Babusis D et al. Mol Pharm 2013;10(2):459–66;
4. Ruane P et al. J Acquir Immune Defic Syndr 2013; 63:449–5; 5. Sax P et al. JAIDS 2014;67(1):52–8; 6. Sax P, et al. Lancet 2015 Apr 15 [Epub ahead of print]

E/C/F/TAF switch in eGFR 30-70

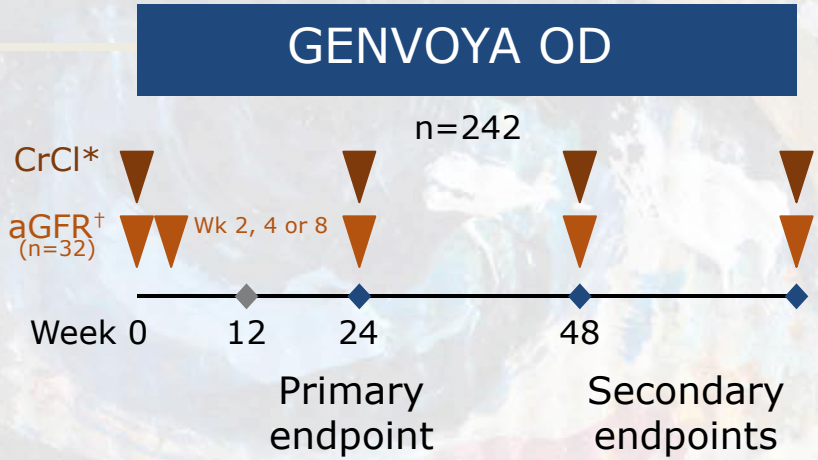
- STUDY 112 – PATIENTS WITH MILD-TO-MODERATE RENAL IMPAIRMENT

Inclusion criteria:
– HIV-suppressed adults with renal impairment (CrCl 30–69 mL/min)
– HIV-1 RNA <50 copies/mL for ≥6 months
– CD4 ≥50 cells/mm^3

Primary endpoint:
– Change from baseline in CrCl at Week 24**

*Creatinine clearance (CrCl) measured using the Cockcroft-Gault formula in all patients
†Actual GFR measured using iohexol plasma clearance in a subset of patients at 3 time points: baseline; Week 2, 4 or 8; and Week 24

- Phase III, 96-week, single-arm, open-label study of virologically suppressed adults changing from TDF- or non-TDF-based regimens to GENVOYA[1]



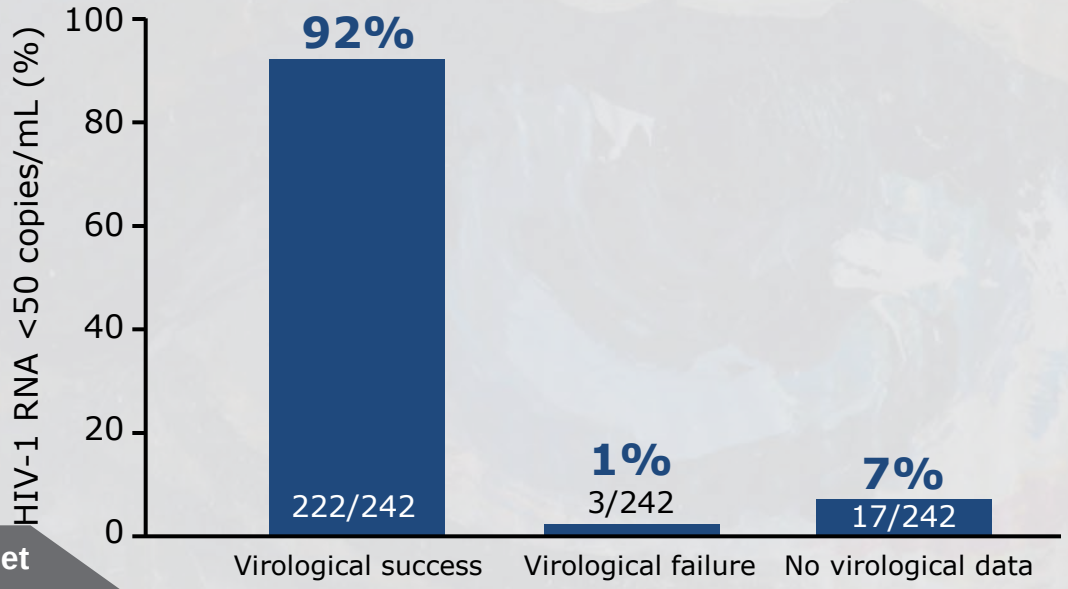
**Median (Q1, Q3) change in CrCl from baseline to Week 24 was -0.4 (-4.8, 4.5) mL/min

1. Pozniak A, et al. CROI 2015. Seattle, WA, USA. Poster 795

E/C/F/TAF SWITCH IN eGFR 30-70

GENVOYA MAINTAINS VIROLOGICAL SUCCESS IN ADULT PATIENTS AT 48 WEEKS

GENVOYA maintains a high rate of virological suppression in over 200 adult patients at Week 48[1]

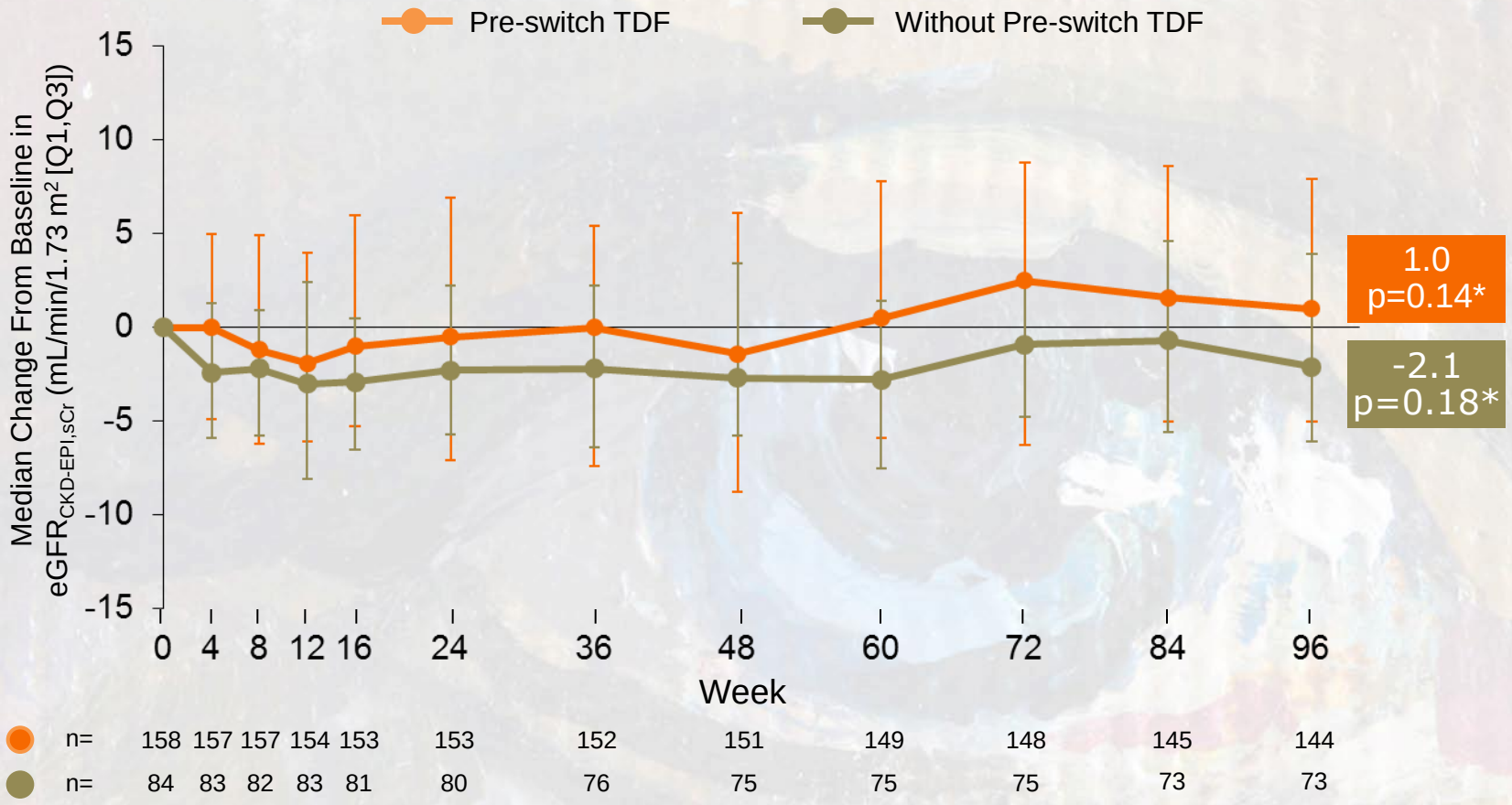


The primary endpoint was met
– Change from baseline in CrCl at Week 24*

*Median (Q1, Q3) change in CrCl from baseline to Week 24 was -0.4 (-4.8, 4.5) mL/min

1. Pozniak A, et al. CROI 2015. Seattle, WA, USA. Poster 795

Study 112: Suppressed Adults with Renal Impairment Switched to E/C/F/TAF

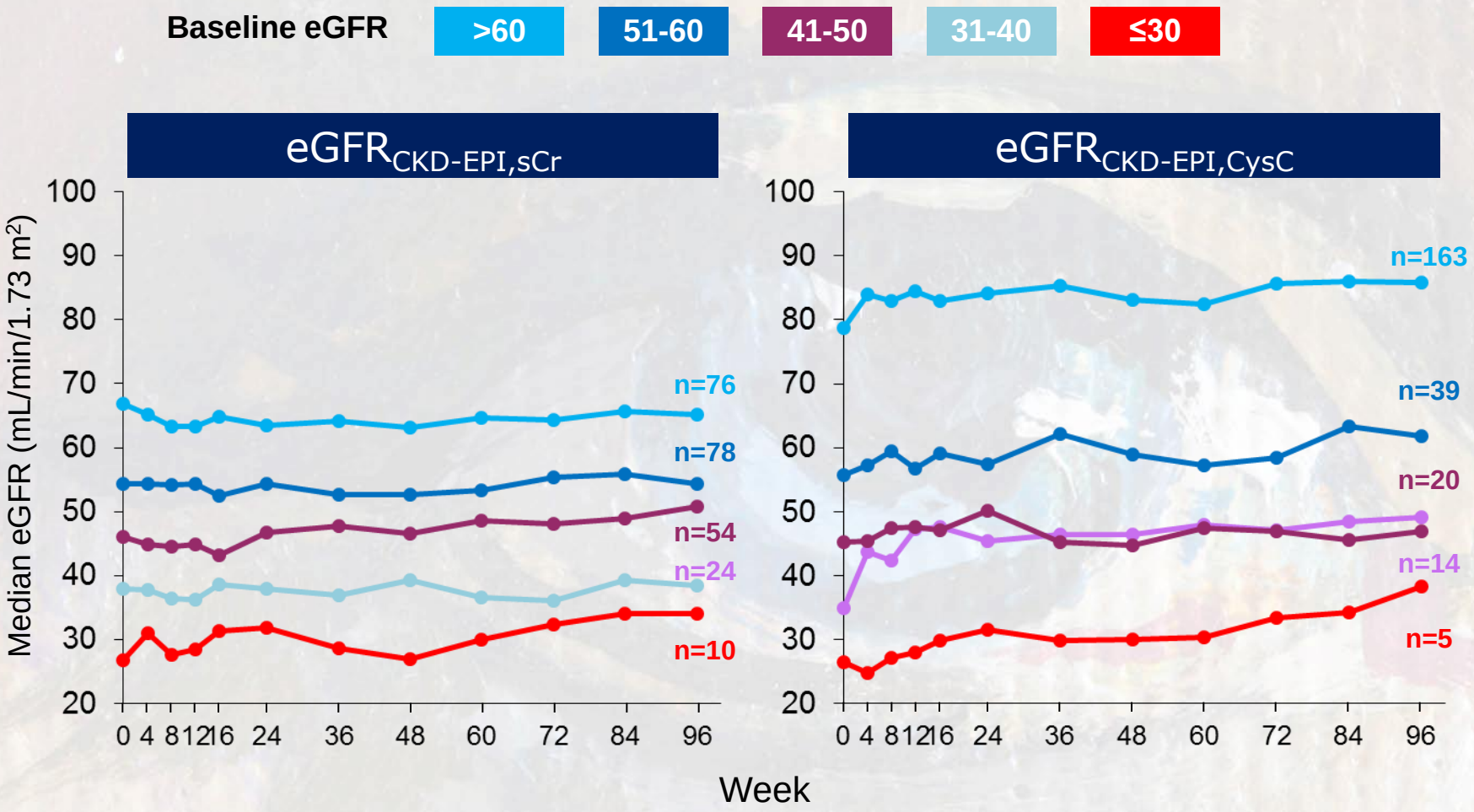


Median, mL/min/1.73 m^2 (Q1, Q3)	Baseline	Week 96
Pre-switch TDF	55.8 (48.9, 64.6)	58.3 (51.6, 67.5)
Without Pre-switch TDF	50.2 (39.9, 55.8)	49.7 (40.9, 55.5)

Post F, *et al.* CROI 2016, Boston, MA, USA. Poster 680.

*P-values for differences between baseline and Week 96 based on the two-sided Wilcoxon signed-rank test

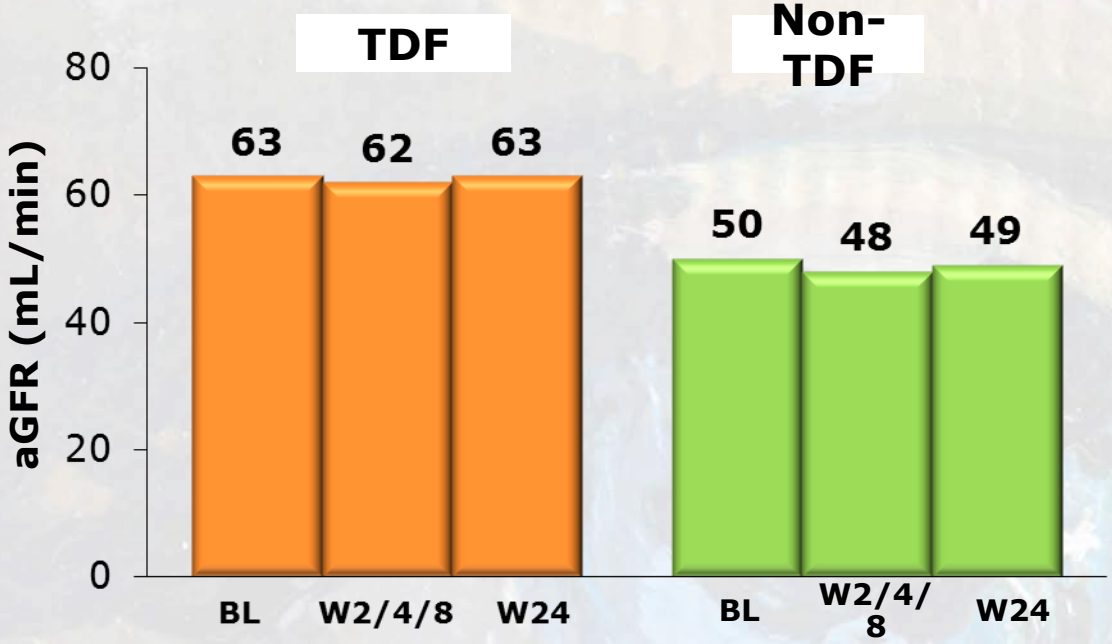
eGFR stratified by baseline



One patient was excluded due to missing cysC data at baseline.

Study 112: Renal Impairment in Adults: Sub-Group Analysis by Pre-Switch ARV Regimen (TDF vs. Non-TDF)

True GFR by Ioxehol clearance



		GLSM Ratio, % (90% CI)*
TDF (n=21)	Week 2, 4, or 8 vs baseline	98 (94, 102)
	Week 24 vs baseline	100 (96, 105)
Non-TDF (n=10)	Week 2, 4, or 8 vs baseline	96 (86, 108)
	Week 24 vs baseline	98 (87, 111)

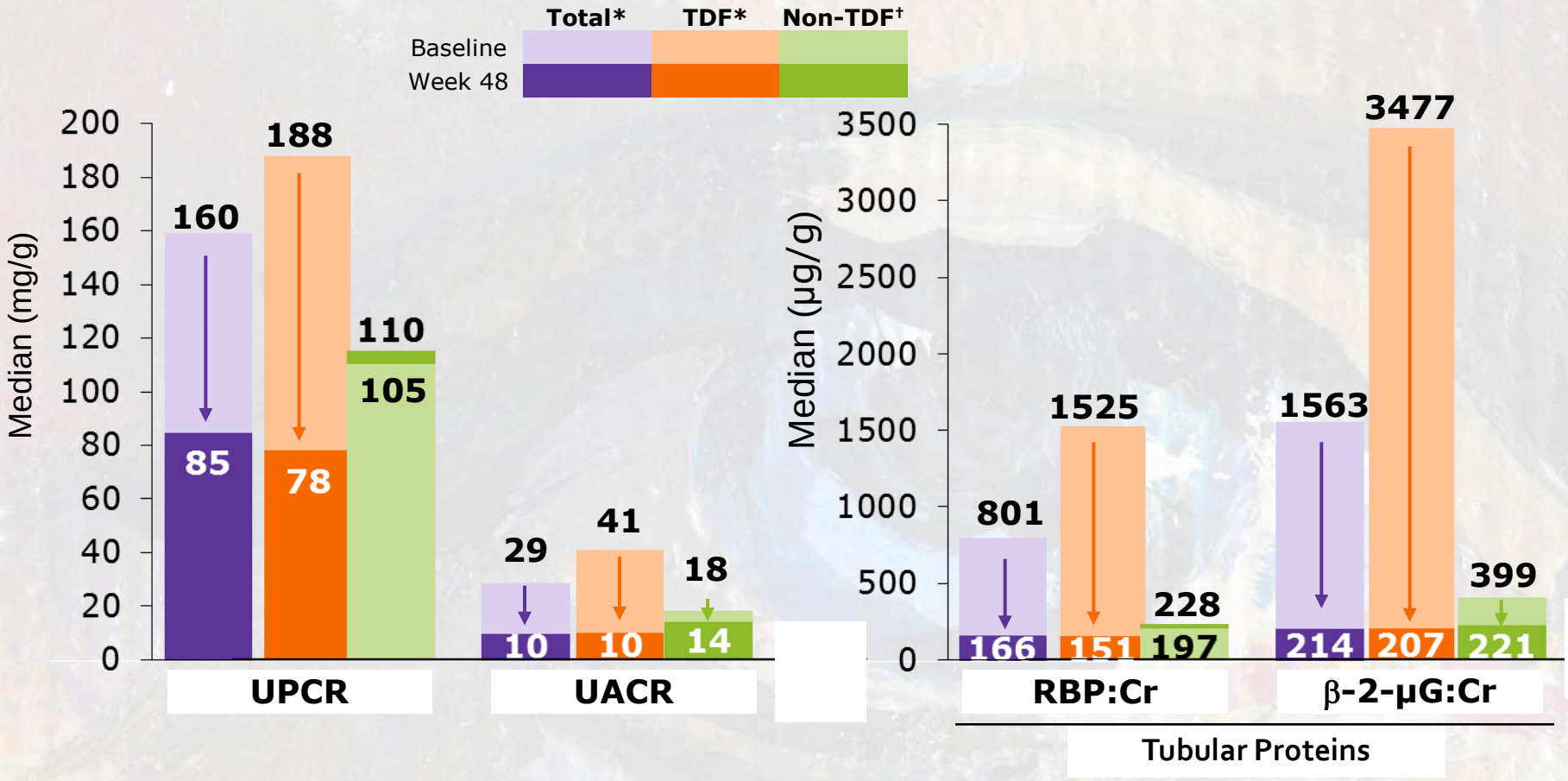
*Lack of alteration boundary: 80–125% (GLSM).

Actual GFR remained stable after E/C/F/TAF switch, regardless of previous regimen

Gupta S, et al. IAS 2015, Vancouver, Canada. Oral # TUAB0103

Study 112: Suppressed adults with renal impairment switched to E/C/F/TAF
Sub-group analysis by pre-switch ARV regimen (TDF vs. Non-TDF)

Change in proteinuria from baseline to week 48



Significantly less proteinuria in patients switching to E/C/F/TAF from a TDF-based regimen

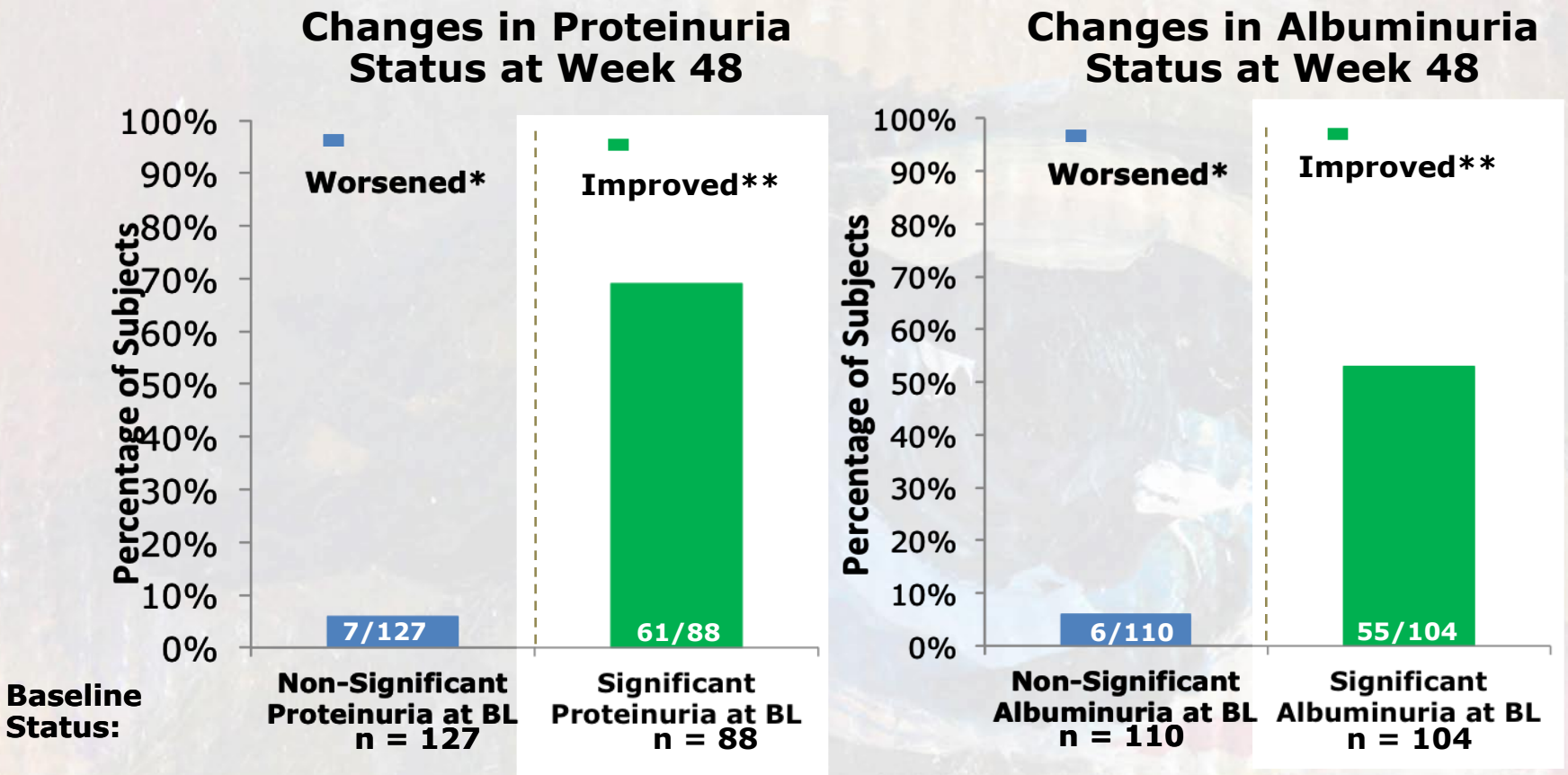
UPCR= Urine Protein:Creatinine Ratio
UACR= Urine Albumin: Creatinine Ratio
RBP:Cr= Retinol Binding Protein: Creatinine Ratio
β-2-µG:Cr: β-2-microglobulin:Creatinine Ratio

*All Total and TDF Wk 48 vs. baseline changes statistically significant
†All non-TDF Wk 48 vs. baseline changes not statistically significant.

Gupta S et al. IAS 2015, Vancouver, Canada. Oral # TUAB0103

Study 112: Suppressed Adults with Renal Impairment Switched to E/C/F/TAF

Changes in Proteinuria and Albuminuria Status at Week 48



***Worsened = change from nonsignificant to clinically significant UPCR (>200 mg/g) or UACR (≥30 mg/g)**

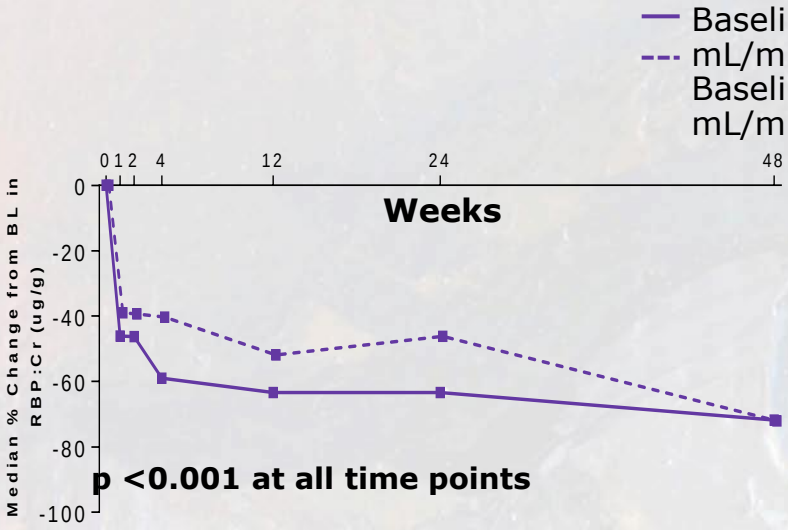
****Improved = change from clinically significant to nonsignificant UPCR <200 mg/g) or UACR (<30 mg/g)**

UPCR, urine protein to creatinine ratio; UACR, urine albumin to creatinine ratio

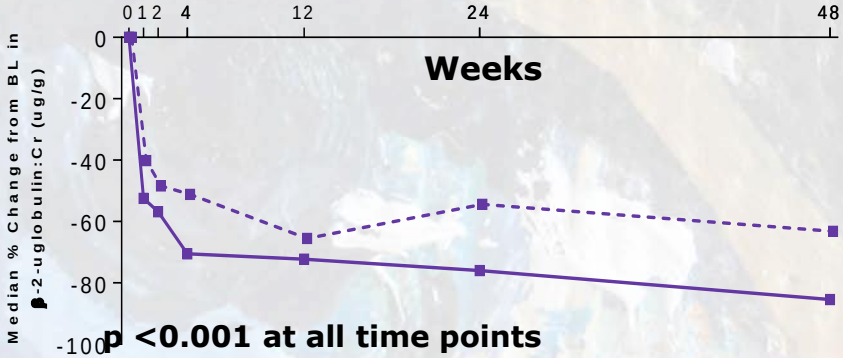
†Change from baseline was statistically significant (P < 0.001)

Changes in Markers of Tubular Function

Retinol Binding Protein:Cr



ß-2 µglobulin:Cr*



Immediate and significant improvements in Retinol Binding Protein and ß-2 µglobulin through Week 48

ß-2 µglobulin, beta-2 microglobulin

E/C/F/TAF AND THE KIDNEY- HOW DOES THIS AFFECT PATIENTS

- E/C/F/TAF is an STR-containing N(t)RTI that has not been associated with any significant demonstrable renal or cardiovascular toxicity in clinical trials[1,2,3,4]
- Patients on E/C/F/TAF do not require any additional renal monitoring; the regime may be used if eGFR is above 30ml/mim.[5]*
- Renal issues arising in PLWHIV on E/C/F/TAF should be amenable to clear and timely diagnosis and treatment with no confounding actions of TDF identified to date[1,2,3,4]
- The urinary biomarker profile of E/C/F/TAF is likely to be associated with better renal outcomes over the long term[1,2,3,4]

*Note: FDA require ART-specific monitoring

Sax P et al. Lancet. 2015;385:2606–15; 2. Mills A et al. Lancet Infect Dis 2016;16(1):43-52;
3. Pozniak A, et al. CROI 2015; Seattle, WA. #795; 4. Gupta S et al. IAS 2015, Vancouver, Canada. Oral # TUAB0103
5.http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004042/smops/Positive/human_smop_000885.jsp&mid=WC0b01ac058001d127

TAF use in patients with a history of PRT

- TAF has not been associated with PRT or the biomarker signals of PRT
- There are case reports of the use of TAF in patients with a history of PRT (1,2)
- At KCL a clinical trial has started of the use of TAF in patients with previous TDF-induced PRT (PI Frank Post)
- In certain patients this option may be considered if there are clinical indications for tenofovir

1. Mikula et a, Antiviral Therapy 2016, 10:3851
2. Garcia & Le Moal, AIDS 2016, 30:1487–1493

Thanks

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