a multicentre study

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Chronic kidney disease and exposure to antiretroviral drugs in a large cohort with long-term follow-up: The EuroSIDA Study

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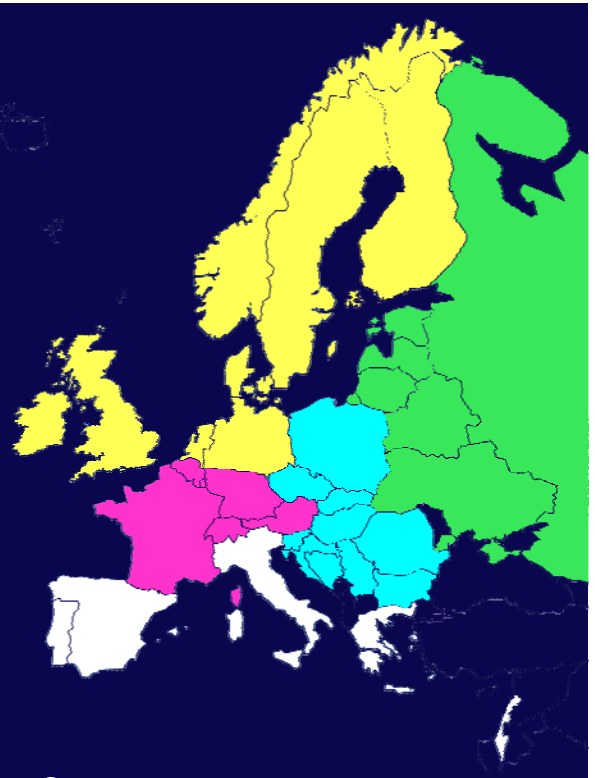
for the EuroSIDA Study Group

Background

- Renal impairment in HIV-positive persons might be caused by traditional and HIV-related factors
- Impact of long-term exposure to specific antiretrovirals (ARVs) remains poorly elucidated
- Chronic kidney disease (CKD)*: a persistent reduction in glomerular filtration rate (GFR) to below 60 ml/min/1.73m^2 and/or albuminuria

*: National Institute of Diabetes and Digestive and Kidney Diseases

Methods (I)



- The EuroSIDA study, 103 clinics in 35 countries
- Eligible patients: ≥3 serum creatinine and corresponding body weight measurements from 2004 and onwards
- CKD defined as confirmed:
  - eGFR ≤60 if baseline eGFR >60 mL/min/1.73m²
  - 25% decline if baseline eGFR ≤60 mL/min/1.73m²
- Primary analysis: Cockcroft-Gault formula
- Poisson regression used to determine factors (incl. ARVs) associated with CKD

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*: (2 measurements ≥3 months apart)

Methods (II)

- ARV exposure calculated as cumulative exposure on a monthly basis and modelled as time-updated variable

- Sensitivity analyses:
  - using MDRD and CKD-EPI formulas for assessment of eGFR
  - variety of censoring strategies
  - alternative means of categorizing ARV/cART status:
    - never used / ‹1 year / 1-2 years / 2-3 years / › 3 years)
    - never exposed / exposed but not currently taking / exposed and currently taking
    - on any cART regimen/ non-PI cART / non-boosted PI, non-ritonavir cART / non-boosted PI, ritonavir cART / ritonavir boosted cART

Results

Baseline characteristics (n=6843):

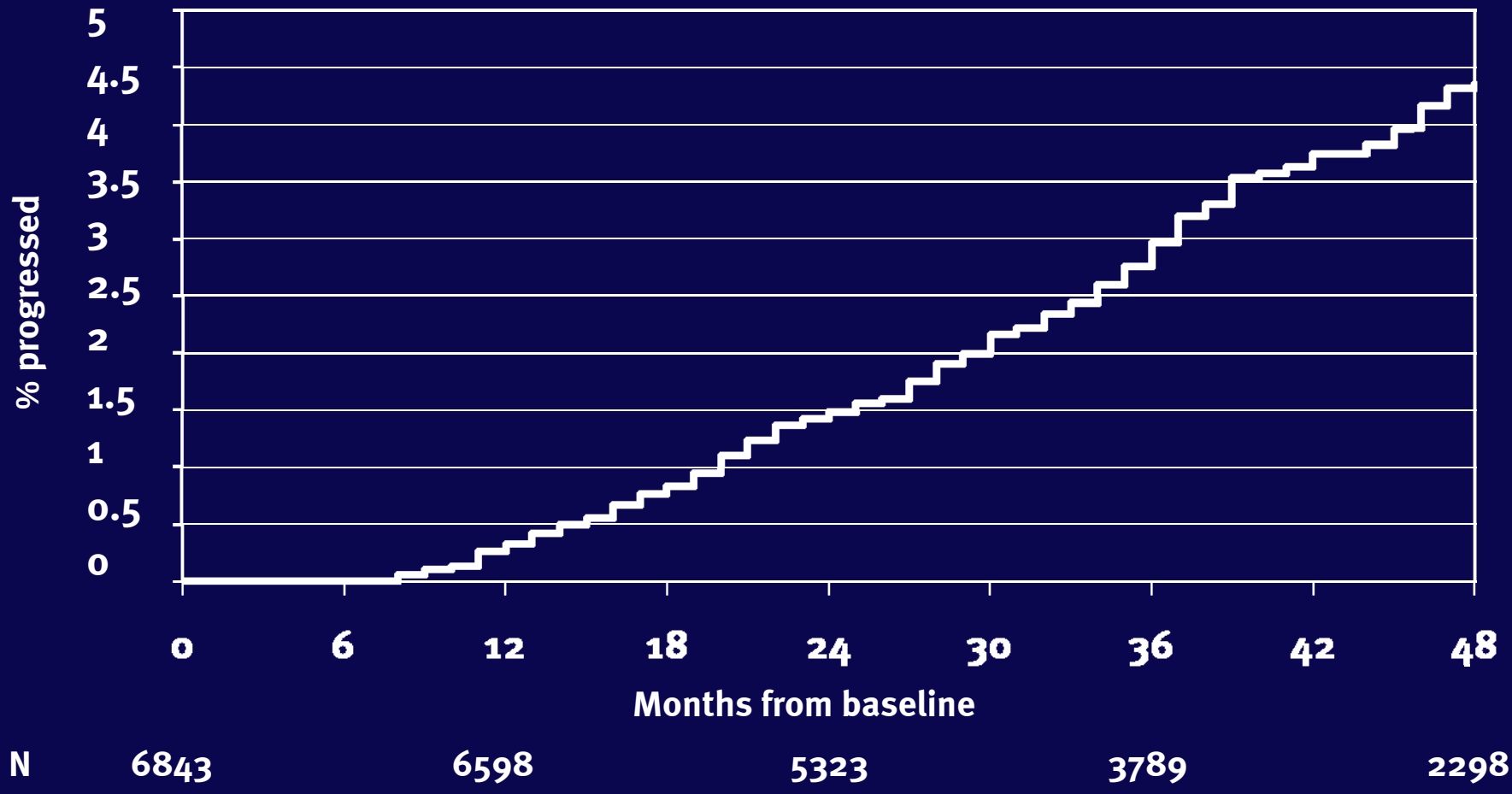
- 24.9% females
- 85.5% Caucasians
- 42.8% MSM
- 31.2% prior AIDS
- 23.1% HCV+ ab
- 89.8% exposed to cART
- 21.7% arterial hypertension
- 4.9% diabetes mellitus
- Median age: 42.8 (IQR: 37.5-50.0) years
- Median CD4 cell count: 450 (IQR: 305-638) cells/mm^3

Follow-up:

21,482 PYFU; median 3.7 (IQR: 2.8-5.7) years

- 225 (3.3%) progressed to CKD

Kaplan-Meier progression to CKD



CKD, confirmed (persisting for >3 months) decrease in eGFR < 60 mL/min/1.73m² if eGFR at baseline >60 mL/min/1.73m² or confirmed 25% decrease in eGFR if baseline eGFR<60 mL/min/1.73m²

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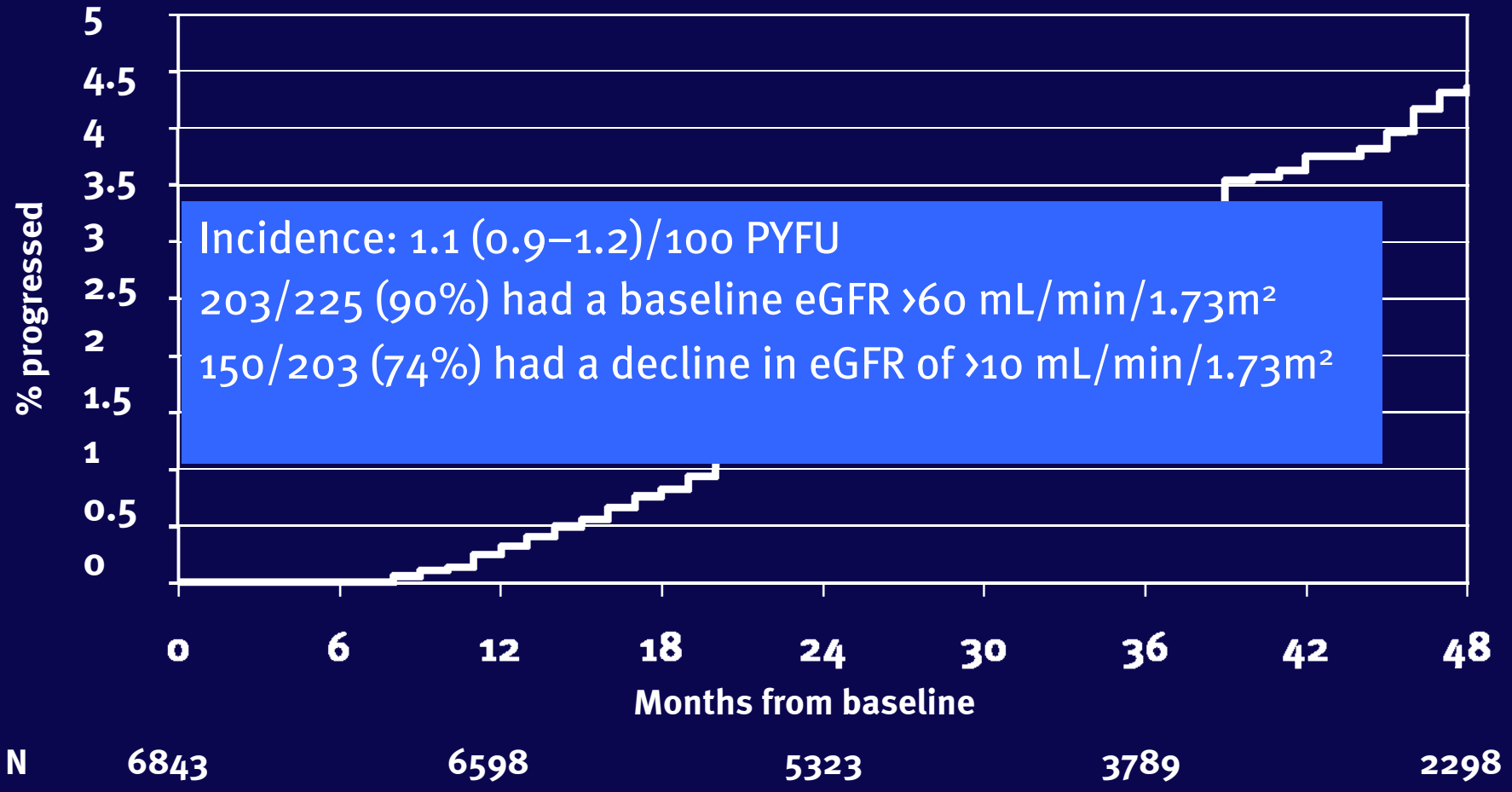
Kaplan-Meier progression to CKD



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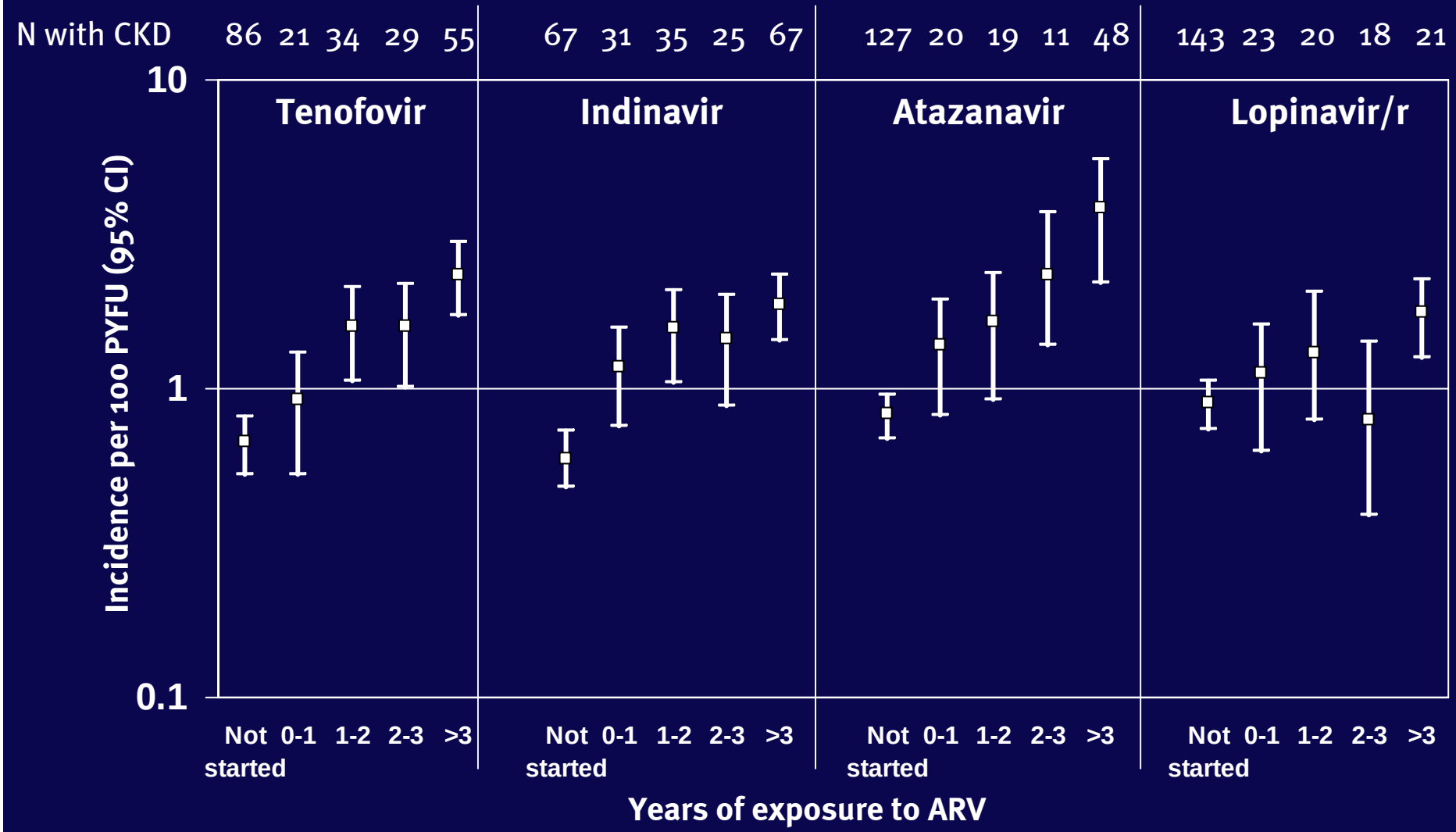
Crude incidence rate of CKD and increasing exposure to ARVs



CKD, confirmed (persisting for ›3 months) decrease in eGFR ‹ 60 mL/min/1.73m² if eGFR at baseline ›60 mL/min/1.73m² or confirmed 25% decrease in eGFR if baseline eGFR‹60 mL/min/1.73m²

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Poisson models
Cumulative exposure to ARVs and risk of CKD

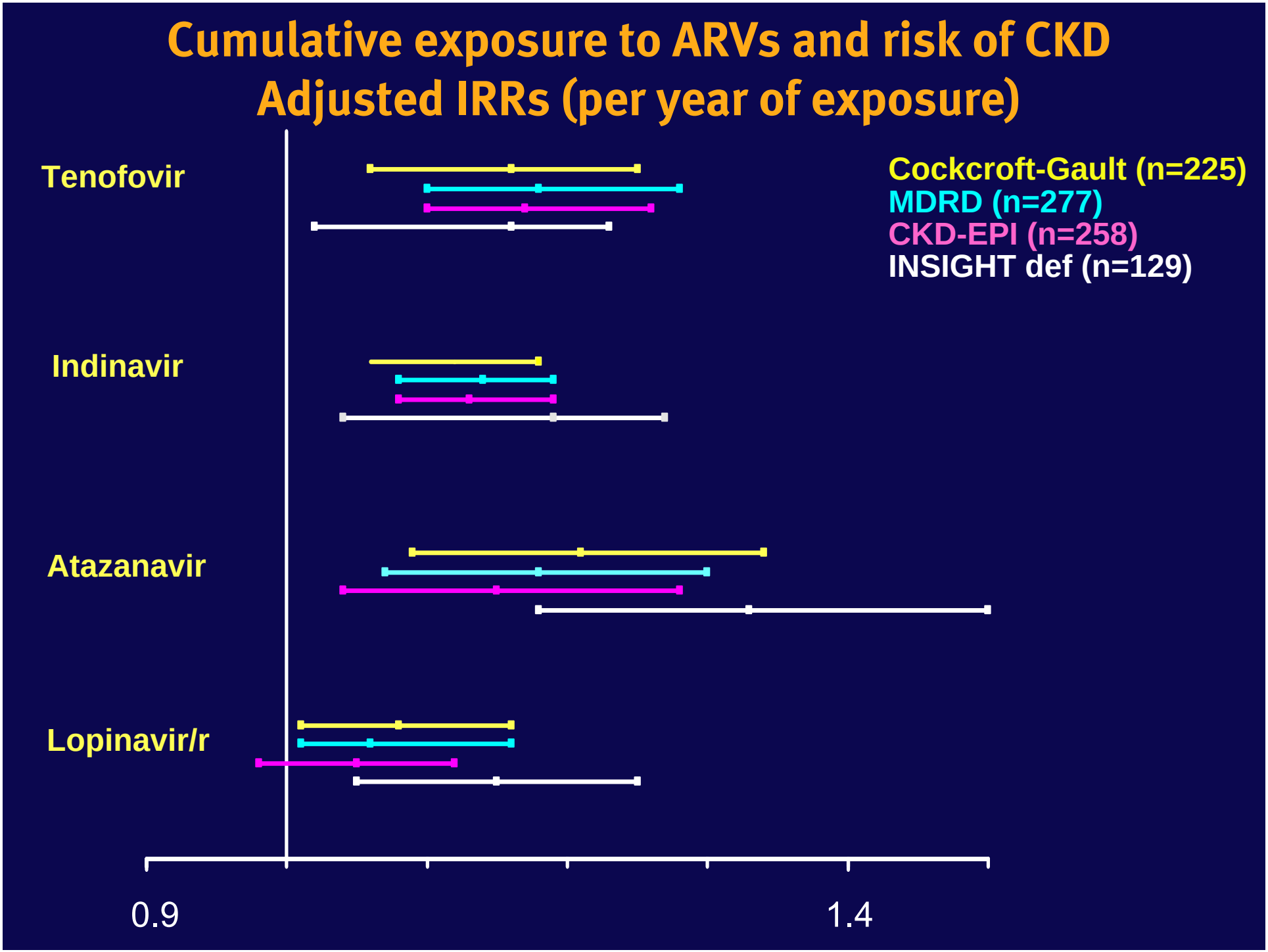
	Univariable			Multivariable¤		
	IRR*/ year	95%-CI	P-value	IRR*/ year	95%-CI	P-value
Tenofovir	1.32	1.21-1.41	<0.0001	1.16	1.06-1.25	<0.0001
Indinavir	1.18	1.13-1.24	<0.0001	1.12	1.06-1.18	<0.0001
Atazanavir	1.48	1.35-1.62	<0.0001	1.21	1.09-1.34	0.0003
Lopinavir/r	1.15	1.07-1.23	<0.0001	1.08	1.01-1.16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

¤: also included baseline eGFR and AIDS, AIDS during follow-up*, use of nephrotoxic drugs*, current CD_4 count*, age*, HIV-RNA*, any cardiovascular event*, arterial hypertension*, diabetes*, HCV antibody status*, non-AIDS malignancy*, and gender
*: variable included as time-updated

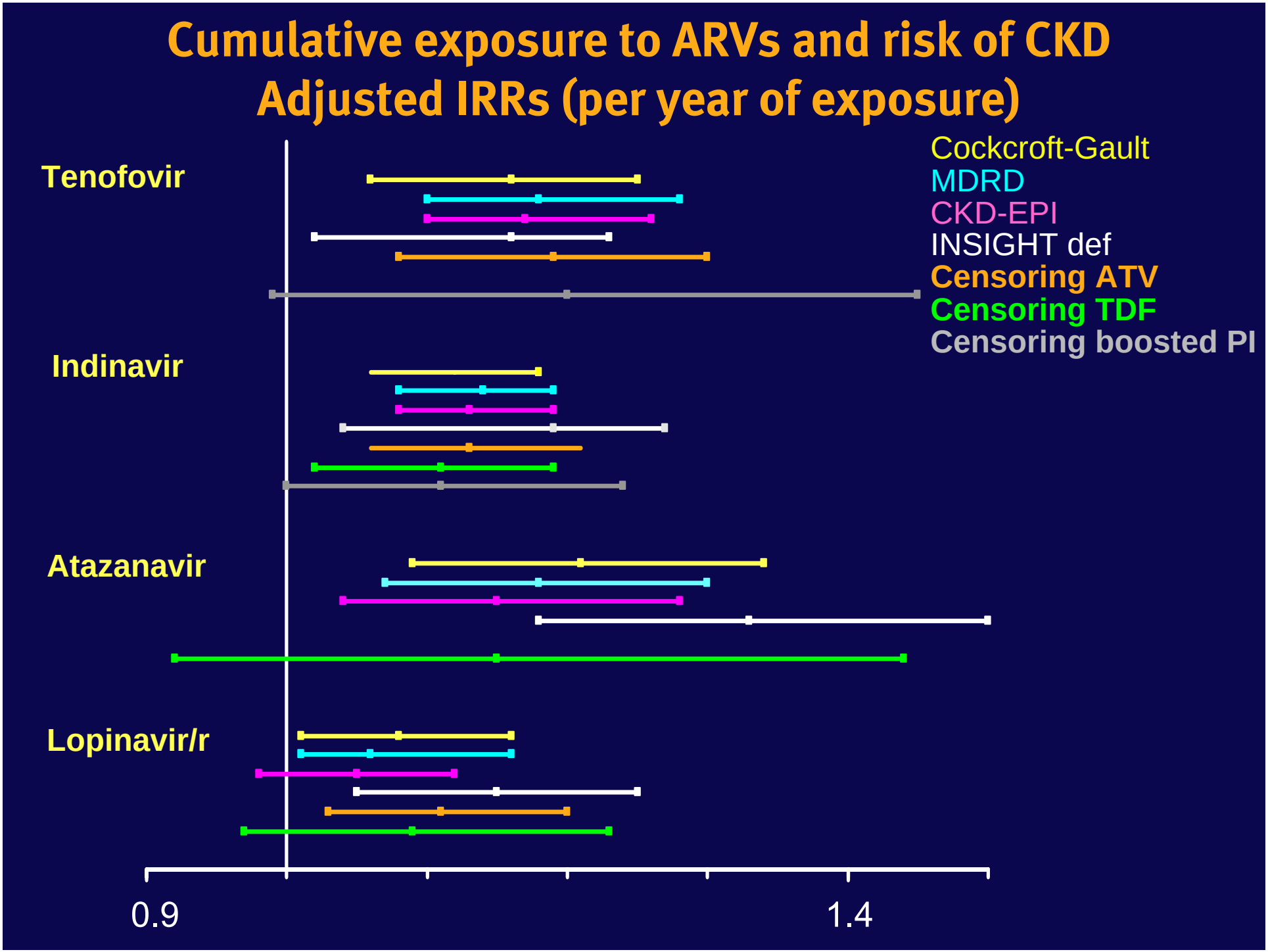
No other ARVs or types of regimens associated with CKD

*: Incidence rate ratio

Cumulative exposure to ARVs and risk of CKD
Adjusted IRRs (per year of exposure)



Cumulative exposure to ARVs and risk of CKD
Adjusted IRRs (per year of exposure)



Stopping ARVs and risk of CKD

- Among patients stopping tenofovir during prospective follow-up:
  - Within first 12 months: IRR: 4.05 (2.51-6.53) compared with patients never exposed to tenofovir
  - After 12 months: IRR: 1.12 (0.63-1.99)

- The risk of CKD among patients stopping atazanavir or lopinavir/r is similar to that of patients not exposed to the specific ARVs

Limitations and strengths

- Non-randomised study, but based on a well described large cohort
- Heterogeneous study population with high levels of co-morbidity (contrast to randomised trials)
- A median follow-up of nearly 4 years
- Robustness of results using a large variety of different methods and estimations of GFR
- Insufficient follow-up to exclude association with the more recently introduced ARVs (darunavir, tipranavir, etravirine, maraviroc, raltegravir)

Summary

- Prevalence and incidence rate of CKD consistent with other studies
- Traditional risk factors for CKD also present in our study
- AIDS, non-AIDS malignancies and coinfection with HCV were also independently associated with CKD
- Increasing exposure to tenofovir associated with a higher risk of CKD
- Association with CKD also identified for indinavir and atazanavir
- Results for lopinavir/r less clear

Perspectives

- We have identified several ARVs associated with progressive, long-term renal impairment/CKD
- This may be due to
  - glomerular and tubular dysfunction (tenofovir)
  - high renal excretion rates and crystalluria/ crystal nephropathy/ nephrolithiasis (PIs)
- Although biologically plausible, the exact pathogenesis behind these findings remains to be elucidated
- Further follow-up and data needed to establish whether the risk of CKD continues to increase with longer exposure to the specific ARVs
- Studies on the clinical implications of the findings and the long-term consequences are warranted

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Q&As on our findings available at

www.cphiv.dk

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Definitions

GFR (CG) = $\frac{(140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine} \times 72} \times 0.85$ (if female)

GFR (MDRD)=186 x serum creatinine$^{-1.154}$ x age$^{-0.203}$ x 0.742 (female) x 1.21 (black)

CKD-EPI: Algorithm depending on race, gender and serum-creatinine

Our definition of CKD: confirmed (persisting for >3 months) decrease in eGFR ≤ 60 mL/min/1.73m² if eGFR at baseline >60 mL/min/1.73m² or confirmed 25% decrease in eGFR if baseline eGFR ≤60 mL/min/1.73m²

INSIGHT definition: 25% decrease in eGFR to <60 for those with a baseline eGFR >60 mL/min/1.73m², or 25% decrease in eGFR if baseline eGFR ≤60 mL/min/1.73m²

Cockcroft-Gault (Cockcroft & Gault, *Nephron* 1976), MDRD (Levey, *Ann Intern Med* 1999), CKD-EPI (Levey, *Ann Intern Med* 2009)

Definitions

CKD-EPI: Algorithm depending on race, gender and serum-creatinine

Race and Sex	Serum Creatinine Level, *μmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

Levey, *Ann Intern Med* 2009