PERSIMUNE

CENTRE OF EXCELLENCE FOR PERSONALISED MEDICINE OF INFECTIOUS COMPLICATIONS IN IMMUNE DEFICIENCY

Exposure to antiretrovirals and development of chronic kidney disease

Amanda Mocroft, Jens Lundgren, Michael Ross, Christoph Fux, Peter Reiss, Olivier Moranne, Philippe Morlat, Antonella d'arminio Monforte, Ole Kirk, Lene Ryom on behalf of the D:A:D* study group

*The Data Collection on Adverse events of Anti-HIV Drugs

chip Centre for Health & Infectious Disease Research

FACULTY OF HEALTH AND MEDICAL SCIENCES UNIVERSITY OF COPENHAGEN

REGION H

Rigshospitalet

UCL

Disclosure

Amanda Mocroft has previously received honoraria, travel grants, and/or lecture fees from BMS, Gilead, Pfizer, Merck and GSK

Introduction

- Several studies show an association between the use of some antiretroviral drugs (TDF, ATV/r, LPV/r, other PI/r, ABC) and renal impairment[1-4]
- Continued controversy whether this association is either cumulative and risk increases as exposure to antiretrovirals increase or an '*early hit*' [5-7]
- Minimal data with long term exposure to antiretrovirals in persons with initially normal eGFR to show whether risk of renal impairment continues to increase or plateaus with longer term (>5 years) exposure

[1]Ryom JID 2013; [2]Mocroft AIDS 2010; [3]Scherzer AIDS 2012; [4]Hamada CID 2012; [5]Laprise CID 2013; [6]Arribas JAIDS 2008; [7]Yombi AIDS 2014.

Study Objective

- Determine if the reported association between antiretrovirals (TDF, ATV/r, LPV/r, other PI/r and ABC)[1-4] and CKD is cumulative among persons with an initially normal renal function (>90 mL/min/1.73m^2)

[1]Ryom JID 2013; [2]Mocroft AIDS 2010; [3]Scherzer AIDS 2012; [4]Hamada CID 2012

Methods

- Included persons with baseline eGFR > 90 mL/min/1.73m^2
- Baseline : first eGFR after 1/1/2004
- D:A:D participants followed from baseline until earliest of
  - CKD (confirmed [>3 months apart] eGFR <60 mL/min/1.73m^2)
  - last eGFR
  - 1/1/2013
  - last visit plus 6 months
- Exclusions
  - <2 eGFRs after baseline
- eGFRs calculated using Cockcroft Gault, standardised for body surface area

Statistical Methods

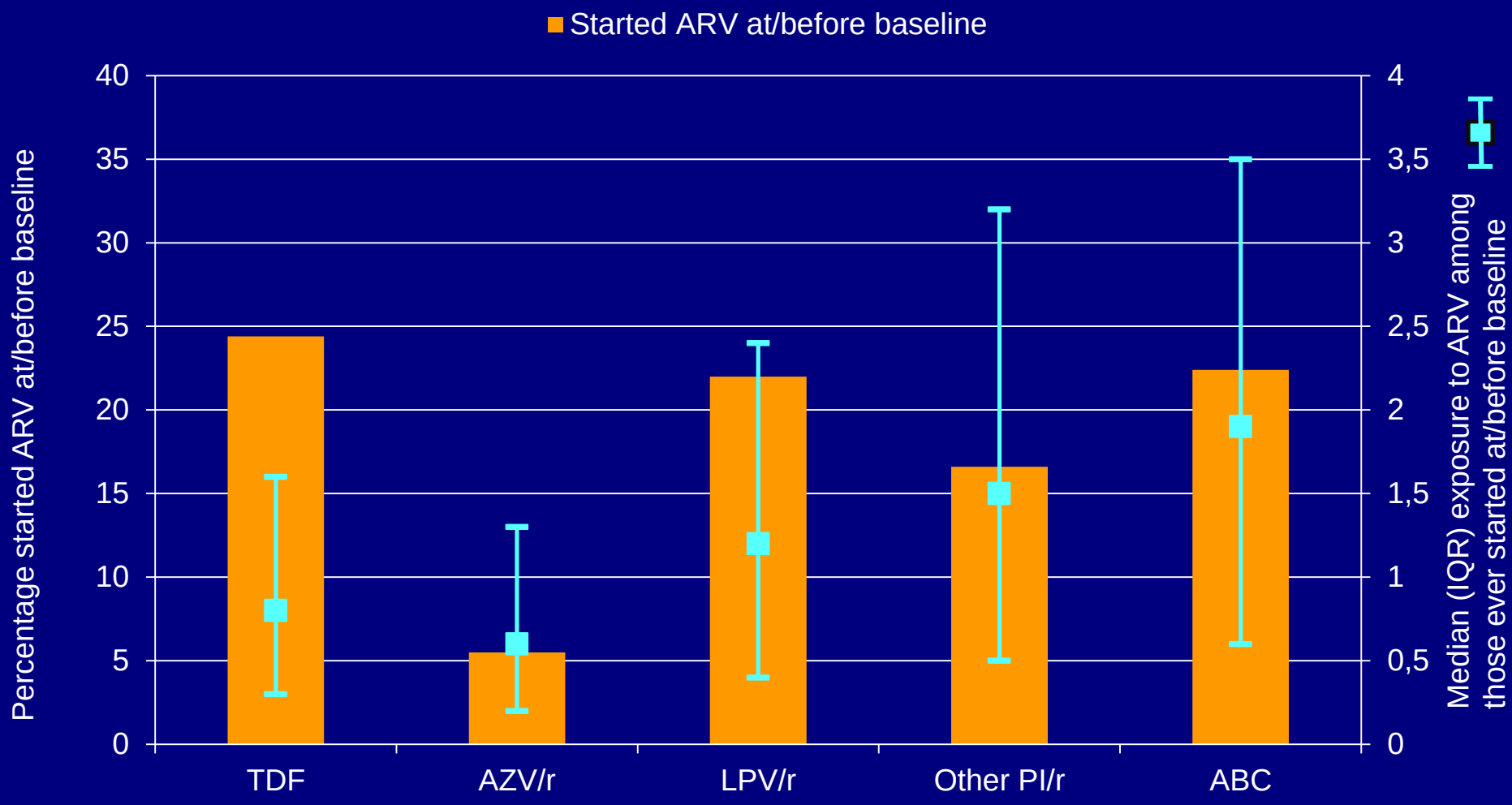
- Poisson regression was used to estimate the incidence of CKD associated with cumulative exposure to, or time since stopping,
  - Tenofovir (TDF)
  - Ritonavir-boosted atazanavir (ATV/r)
  - Lopinavir (LPV/r)
  - Other ritonavir-boosted protease inhibitors (other PI/r)
  - Abacavir (ABC)

Patient characteristics at baseline N=23560

		Did not develop CKD		Developed CKD	
		N	%	N	%
All		**23350**	**99.1**	**210**	**0.9**
Gender	Male	16982	72.7	147	70.0
Race	White	10647	45.6	123	58.6
HIV Risk	MSM / IDU	10495 / 3002	44.9 / 12.9	74 / 66	35.2 / 31.4
Hypertension[1]	Yes	1812	7.8	32	15.2
CVD[1]	Yes	106	0.5	3	1.4
HCV+	Yes	3057	13.1	61	29.1
AIDS	Yes	5096	21.8	76	36.2
Diabetes[1]	Yes	705	3.0	22	10.5
VL < 400	Yes	13142	56.3	133	63.3
		Median	IQR	Median	IQR
Age	Years	39	33 – 44	47	41 – 54
CD4	/mm^3	441	294 – 629	388	244 – 565
Nadir CD4*	/mm^3	240	119 – 380	160	57 – 279
eGFR	mL/min/1.73m^2	110	100 – 125	102	95 - 114

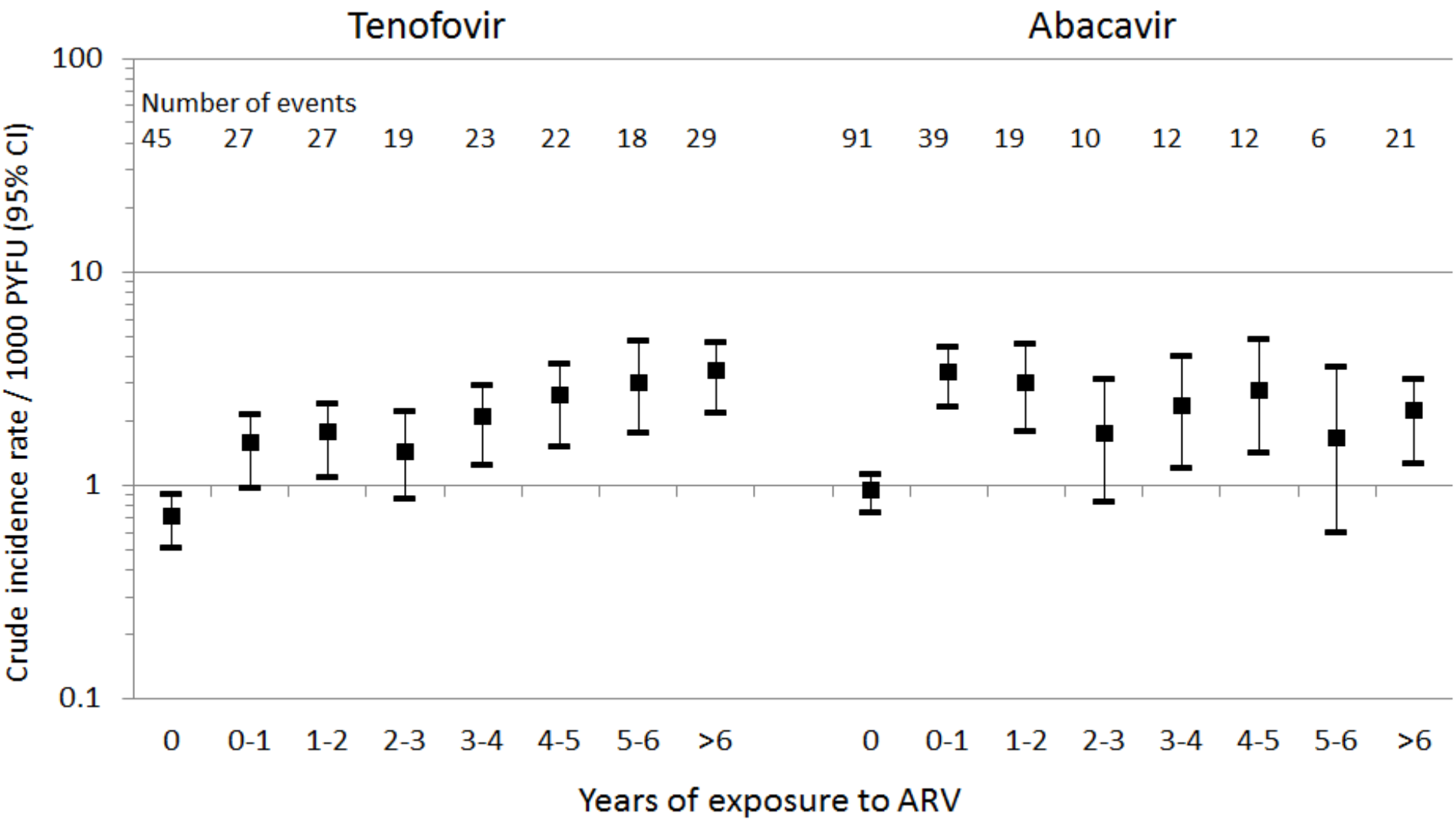
[1]Ryom et al, JID 2013; IQR interquartile range. Baseline : first eGFR after 1 January 2004. *Lowest CD4 prior to baseline

Exposure to antiretrovirals at/before baseline



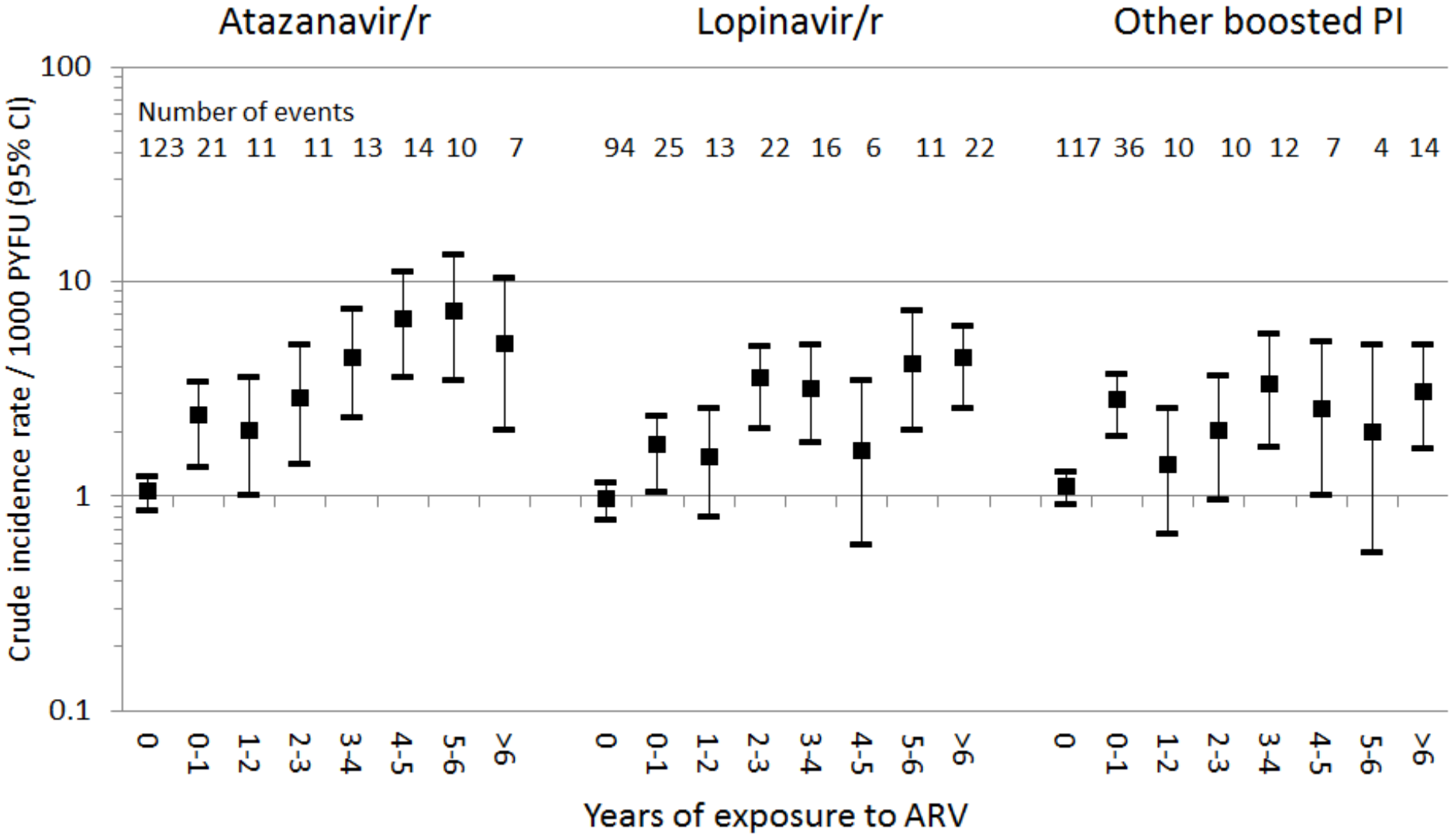
Ever started ARV at/before baseline					
N	5353	1298	5185	4376	5272
% stopped	12.9	21.1	35.5	67.1	38.6

Crude incidence rates of CKD and cumulative exposure to TDF and ABC



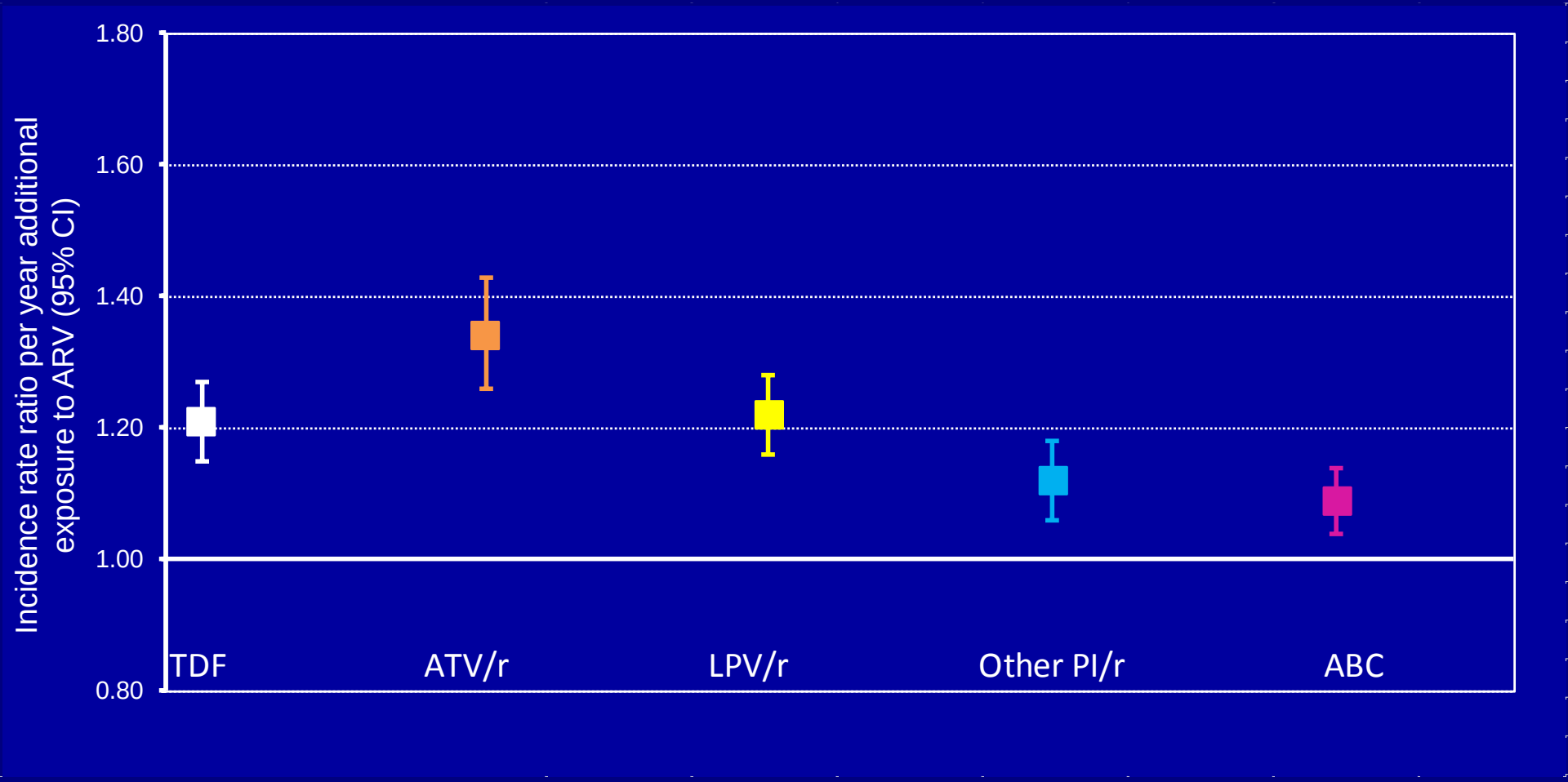
CKD; chronic kidney disease; confirmed (>3 months apart) eGFR < 60 mL/min/1.73m^2

Crude incidence rates of CKD and cumulative exposure to ATV/r, LPV/r and PI/r



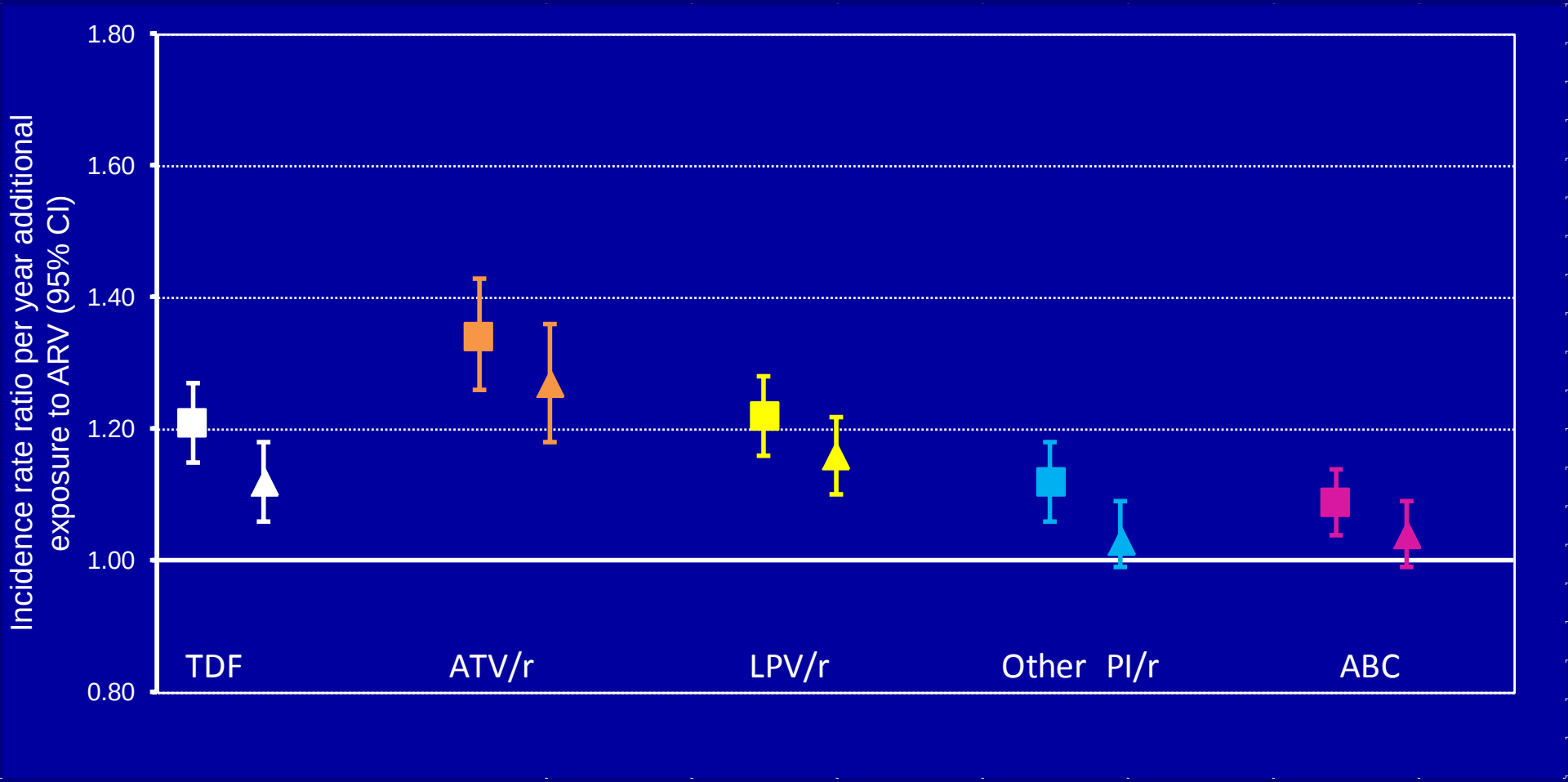
CKD; chronic kidney disease; confirmed (>3 months apart) eGFR < 60 mL/min/1.73m^2

Relationship between increasing exposure to ARVs and CKD



Relationship between increasing exposure to ARVs and CKD

Univariate *Multivariate**



*adjusted for gender, race, HIV exposure, study, prior CVD, age, baseline date, baseline eGFR and CD4 nadir as fixed variables at baseline. Hepatitis B and C status, smoking status, BMI, family history of CVD, HIV viral load, CD4 count, anaemia, diabetes, hypertension, starting cART, and an AIDS diagnosis within the previous 12 months was included as time-updated covariates. Models were additionally adjusted for cumulative exposure to indinavir and mutually adjusted for use of other ARVs

Cumulative effect of ARVs

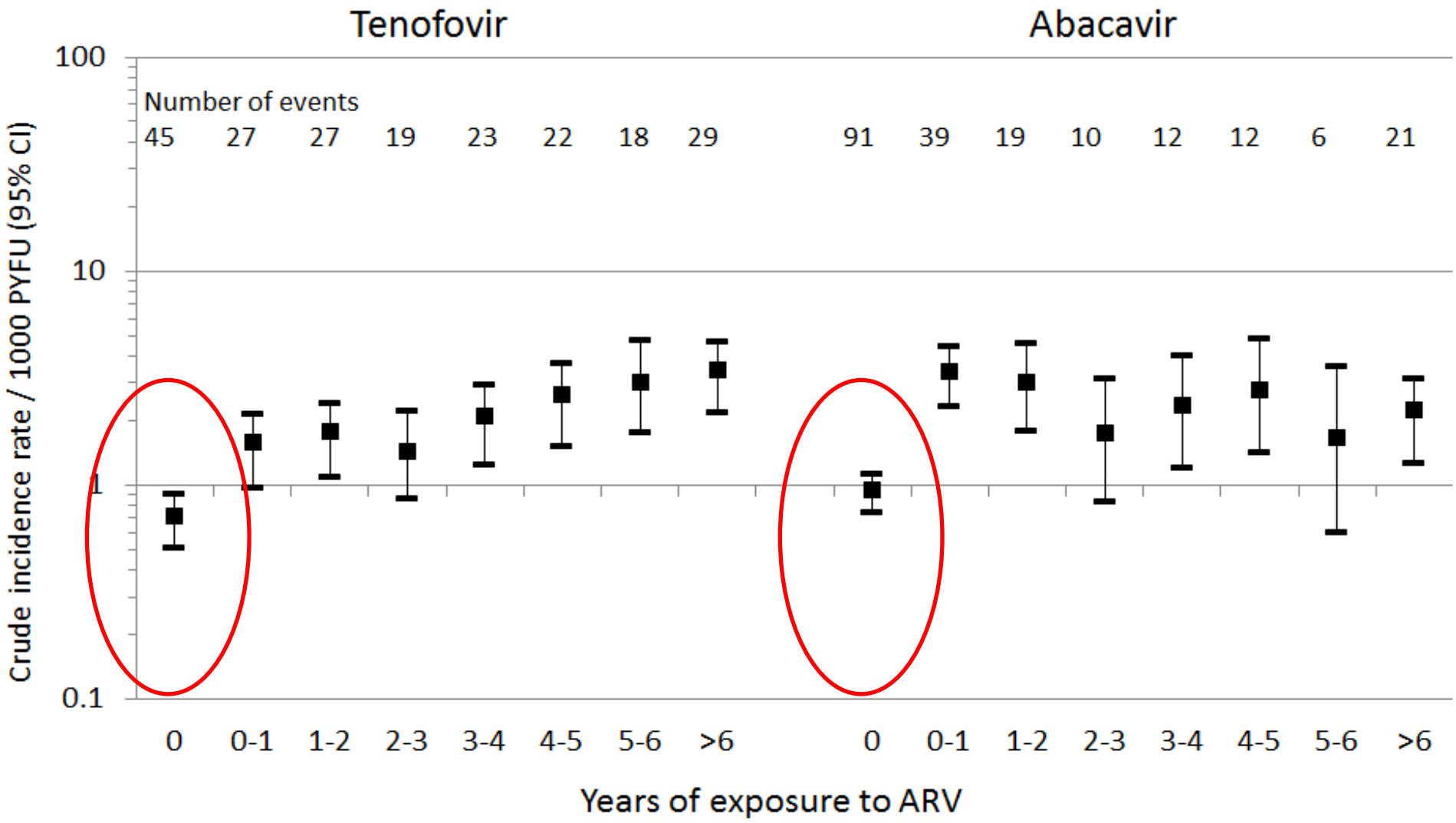
- Although a modest effect per year, risk is cumulative over time

	TDF	ATV/r	LPVr
1 year	1.12 (1.06 – 1.18)	1.27 (1.18 – 1.36)	1.16 (1.10 – 1.22)
2 years	1.25 (1.12 – 1.39)	1.61 (1.40 – 1.84)	1.35 (1.21 – 1.50)
5 years	1.74 (1.33 – 2.27)	3.27 (2.32 – 4.61)	2.11 (1.62 – 2.75)

- Underlying risk of CKD varies considerably[1] and increased risk will be most significant in those at highest risk of CKD

[1]Mocroft et al, PLoS Med 2015

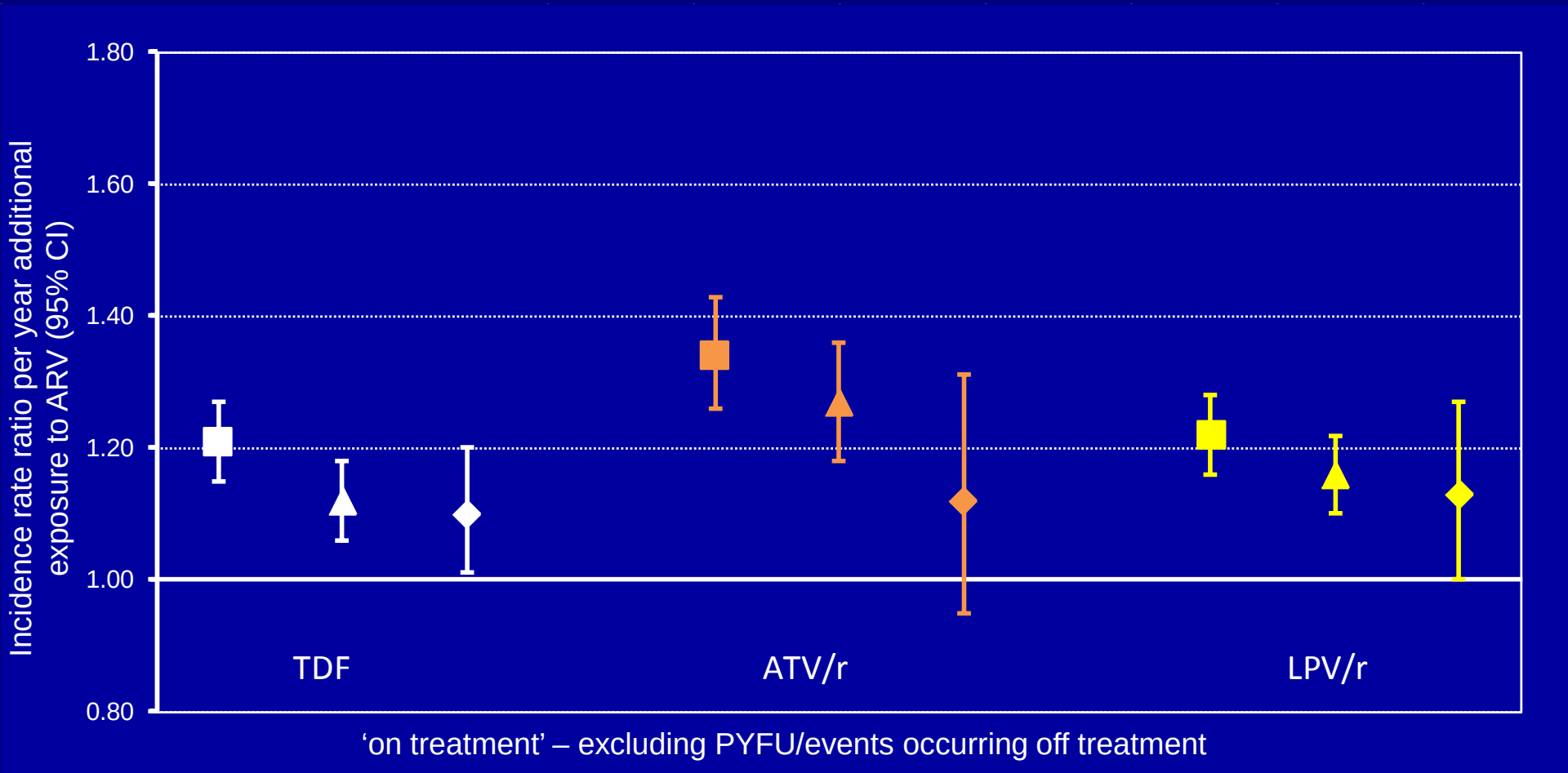
Crude incidence rates of CKD and cumulative exposure to TDF and ABC



CKD; chronic kidney disease; confirmed (>3 months part) eGFR < 60 mL/min/1.73m^2

Relationship between increasing exposure to ARVs and CKD

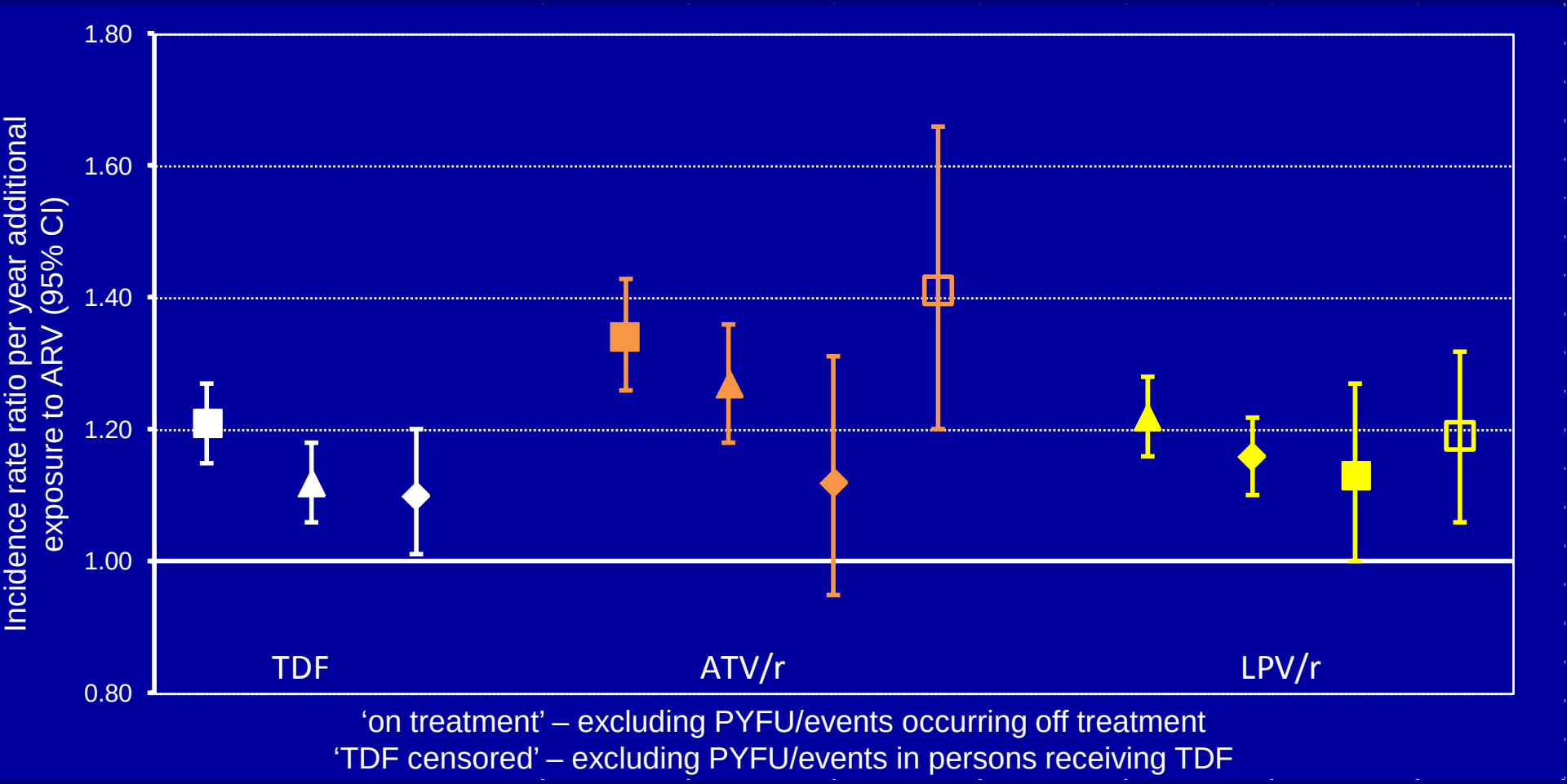
Univariate *Multivariate** *Multivariate (on treatment)*



*adjusted for gender, race, HIV exposure, study, prior CVD, age, baseline date, baseline eGFR and CD4 nadir as fixed variables at baseline. Hepatitis B and C status, smoking status, BMI, family history of CVD, HIV viral load, CD4 count, anaemia, diabetes, hypertension, starting cART, and an AIDS diagnosis within the previous 12 months was included as time-updated covariates. Models were additionally adjusted for cumulative exposure to indinavir and mutually adjusted for use of other ARVs

Relationship between increasing exposure to ARVs and CKD

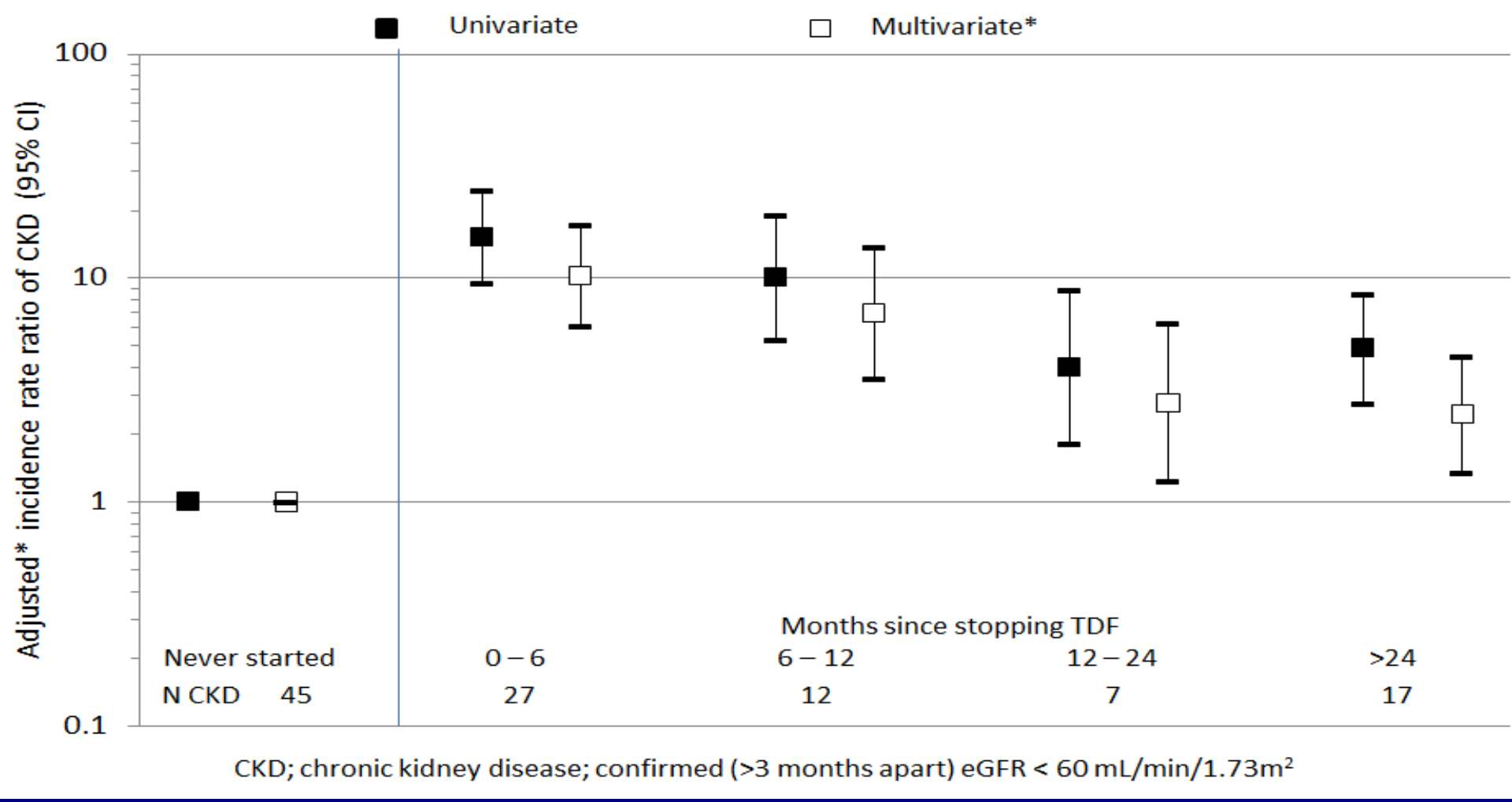
Univariate *Multivariate** *Multivariate (on treatment)* *Multivariate (TDF censored)*



'on treatment' – excluding PYFU/events occurring off treatment
'TDF censored' – excluding PYFU/events in persons receiving TDF

*adjusted for gender, race, HIV exposure, study, prior CVD, age, baseline date, baseline eGFR and CD4 nadir as fixed variables at baseline. Hepatitis B and C status, smoking status, BMI, family history of CVD, HIV viral load, CD4 count, anaemia, diabetes, hypertension, starting cART, and an AIDS diagnosis within the previous 12 months was included as time-updated covariates. Models were additionally adjusted for cumulative exposure to indinavir and mutually adjusted for use of other ARVs

Time since stopping ARVs and development of CKD



CKD; chronic kidney disease; confirmed (>3 months apart) eGFR < 60 mL/min/1.73m^2

*adjusted for gender, race, HIV exposure, study, prior CVD, age, baseline date, baseline eGFR and CD4 nadir as fixed variables at baseline. Hepatitis B and C status, smoking status, BMI, family history of CVD, HIV viral load, CD4 count, anaemia, diabetes, hypertension, starting cART, and an AIDS diagnosis within the previous 12 months was included as time-updated covariates. Models were additionally adjusted for cumulative exposure to indinavir and mutually adjusted for use of other ARVs

Limitations

- D:A:D does not have data on proteinuria and limited information on race from some participating cohorts
  - Results consistent with CKD-EPI and to findings from others[1]
- Not yet enough power / follow-up to look at unboosted ATV or lesser used ARVs (tipranavir/darunavir)
- Considerably longer follow-up needed to determine if risk continues to increase with longer (>6 years) exposure
- Analyses with CKD as endpoint confounded by switching ARVs (esp. TDF) as eGFR declines

[1]Mocroft et al, AIDS 2010

Conclusions

- Study shows cumulative increasing risk of CKD with increasing exposure to TDF, ATV/r, LPV/r in persons with an initially normal eGFR

- Although a modest effect per year, risk is cumulative over time

	TDF	ATV/r	LPVr
1 year	1.12	1.27	1.16
2 years	1.25	1.61	1.35
5 years	1.74	3.27	2.11

- Consistent results
  - censoring for co-administered ARVs
  - for chronic renal impairment (confirmed eGFR < 70 mL/min/1.73m^2)*

- Individuals risk of CKD can be calculated using D:A:D CKD risk score[1] to help determine benefits / risk of incorporating these ARVs into ongoing treatment regimen

*data not shown. [1]Mocroft et al PLoS Med 2015

Acknowledgements

Steering Committee: Members indicated w/ *; ¢ chair;
Cohort PIs: W El-Sadr* (CPCRA), G Calvo* (BASS), F Dabis* (Aquitaine), O Kirk* (EuroSIDA), M Law* (AHOD), A d'Arminio Monforte* (ICONA), L Morfeldt* (HivBIVUS), C Pradier* (Nice), P Reiss* (ATHENA), R Weber* (SHCS), S De Wit* (Brussels)

Cohort coordinators and data managers: M Hillebreght, S Zaheri, L Gras, (ATHENA), M Bruyand, S Geffard, E Pernot, J Mourali (Aquitaine), H McManus, S Wright (AHOD), S Mateu, F Torres (BASS), M Delforge (Brussels), G Bartsch, G Thompsen (CPCRA), J Kjær, Dennis Kristensen (EuroSIDA), I Fanti (ICONA), E Fontas, K Dollet, C Caissotti (Nice), A Sundström, G Thulin (HivBIVUS), M Rickenbach (SHCS)

Statisticians: CA Sabin*, AN Phillips*, DA Kamara, CJ Smith, A Mocroft

D:A:D coordinating office: L Ryom, CI Hatleberg, RS Brandt, D Raben, C Matthews, A Bojesen, J Nielsen, JD Lundgren*¢
Member of the D:A:D Oversight Committee: B Powderly*, N Shortman*, C Moecklinghoff *, G Reilly*, X Franquet*
D:A:D working group experts: Kidney: L Ryom, A Mocroft, O Kirk *, P Reiss *, M Ross, CA Fux, P Morlat, O Moranne, AM Kesselring, DA Kamara, CJ Smith, JD Lundgren *¢ Mortality: CJ Smith, L Ryom, AN Phillips *, R Weber*, P Morlat, C Pradier *, P Reiss *, N Friis-Møller, J Kowalska, JD Lundgren*¢ Cancer: CA Sabin *, L Ryom, M Law *, A d'Arminio Monforte*, F Dabis*, M Bruyand, P Reiss *, CJ Smith, DA Kamara, M Bower, G Fätkenheuer, A Donald, A Grulich, JD Lundgren*¢
External endpoint reviewer: A Sjøl (CVD), P Meidahl (oncology), JS Iversen (nephrology)

Funding: 'Oversight Committee for The Evaluation of Metabolic Complications of HAART' with representatives from academia, patient community, FDA, EMA and a consortium of AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, ViiV Healthcare, Merck, Pfizer, F. Hoffmann-La Roche and Janssen Pharmaceuticals