Risk of myocardial infaction and exposure to specific antiretrovirals from the PI, NNRTI and NRTI drug classes:

The D:A:D Study

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On behalf of the D:A:D study group

CROI, 2009, late breaker presentation

D:A:D

Background

- Prior analyses* from the D:A:D study showed an increased risk of MI associated with:
  - cumulative exposure to PIs but not NNRTIs
  - current/recent exposure to abacavir (ABC) or didanosine (ddI)
- Drugs within PI and NNRTI classes associated with different metabolic profiles
- Previous NRTI analyses had insufficient follow-up to assess role of tenofovir

D:A:D

*: D:A:D Study Group, NEJM 2007; D:A:D Study Group, Lancet 2008

Background & aim

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Aim: Sufficient follow-up has now accrued to explore associations between a total of 13 drugs from these classes and MI risk

D:A:D

*: D:A:D Study Group, NEJM 2007; D:A:D Study Group, Lancet 2008

Drugs analyses and results presented

- The D:A:D Steering committee has decided to present data only when >30,000 person-years follow-up is available from individuals ever exposed to each drug
  - 4 PIs – indinavir (IDV), nelfinavir (NFV), lopinavir/r (LPR/r) and saquinavir (SQV)
  - 2 NNRTIs - efavirenz (EFV) and nevirapine (NVP)
  - 7 NRTIs – zidovudine (ZDV), stavudine (d4T), didanosine (ddI), zalcitabine (ddC), lamivudine (3TC), abacavir (ABC) and tenofovir (TDF)
- Other drugs with less follow-up time are included in analyses but not presented

Methods

- 33,308 patients from 11 cohorts were included
- Follow-up counted from D:A:D enrolment until the first MI event, 1st February 2008 or 6 months after the patient's last clinic visit (whichever occurred first)
- Poisson regression models assessed the association between MI risk and exposure to each drug
- Based on previous analyses, present analyses included
  - NRTIs: cumulative* and recent (current use or use within last 6 months) exposure
  - NNRTIs and PIs: cumulative* exposure only

***: if drug is discontinued, subsequent follow-up continues to be attributed to level of exposure at discontinuation**

Methods

- All models include adjustment for
  - demographics, cardiovascular risk factors not thought to be affected by ART and use of other ARV drugs (primary model)
- Further analyses included adjustment for
  - latest measures of lipids, metabolic parameters, CD_4 and HIV-RNA to identify possible mechanisms for any association
- Exposure to IDV and SQV was calculated regardless of concomitant use of ritonavir
  - sensitivity analyses explored separate associations for use with and without ritonavir

Characteristics of patients at time of MI/last follow-up

	With MI	Without MI
Number of patients	580	32728
Male sex; %	90.7	73.8
Age (years); median	49	44
BMI>26 kg/m^2; %	18.8	17.3
Current smoker; %	44.8	28.7
Ex-smoker; %	29.8	30.1
Prior CVD event; %	20.0	2.5
Family history of CHD; %	13.6	8.3
Diabetes; %	16.6	5.3
Any hypertension; %	43.5	19.2
Use of lipid-lowering medication; %	36.0	12.5
Any dyslipidaemia; %	74.8	44.3
Predicted 10-year CHD risk; %		
Moderate (10-20%)	30.3	14.5
High (>20%)	18.1	4.2

Characteristics of patients ever exposed to each of the drugs under study:

% of follow-up time

Class of drug	NRTIs							PI				NNRTIs	
Ever exposed to:	ZDV	ddI	ddC	d4T	3TC	ABC	TDF	IDV	NFV	LPV	SQV	NVP	EFV
% of FU contributed by:													
Men	74.4	75.4	77.0	75.1	74.6	75.7	75.1	77.5	71.5	77.0	78.1	74.0	75.7
>45 years (men)/ >55 years (women)	34.6	35.6	39.0	35.5	34.1	38.2	39.0	38.2	32.7	37.7	39.2	35.7	35.7
BMI>26 kg/m²	18.6	16.0	14.1	16.3	18.9	17.9	18.4	16.7	17.9	17.7	16.1	18.8	18.6
Current smoker	35.4	38.2	38.9	37.0	34.6	33.3	31.4	37.2	36.8	33.1	35.2	30.4	33.4
Ex-smoker	25.9	24.7	25.4	24.9	25.7	26.8	30.7	25.5	23.7	28.0	27.9	29.4	25.2
Family history of CHD	8.5	8.7	7.8	8.6	8.4	9.3	9.0	8.8	8.8	8.5	9.0	8.4	9.0
Previous CVD	2.2	2.4	3.0	2.4	2.2	2.8	2.5	2.8	2.4	2.4	2.5	2.5	2.4
Diabetes	5.2	6.0	7.3	6.0	5.1	6.3	6.0	6.3	5.4	5.5	6.1	5.3	6.1
Hypertension	16.0	16.5	16.5	16.6	15.9	17.6	19.1	17.8	16.1	17.1	17.5	16.4	16.9
Dyslipidaemia	49.8	54.7	59.0	55.0	49.2	53.4	50.1	55.8	51.8	58.0	58.6	49.4	51.5
Predicted 10-year CHD risk													
10-20%	13.0	14.6	15.5	14.2	12.7	14.8	15.1	15.3	13.2	15.1	14.9	11.9	14.1
>20%	6.2	6.7	7.6	6.8	6.0	7.0	6.2	7.8	6.4	6.9	6.9	6.0	6.5

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>20%	6.2	6.7	7.6	6.8	6.0	7.0	6.2	7.8	6.4	6.9	6.9	6.0	6.5

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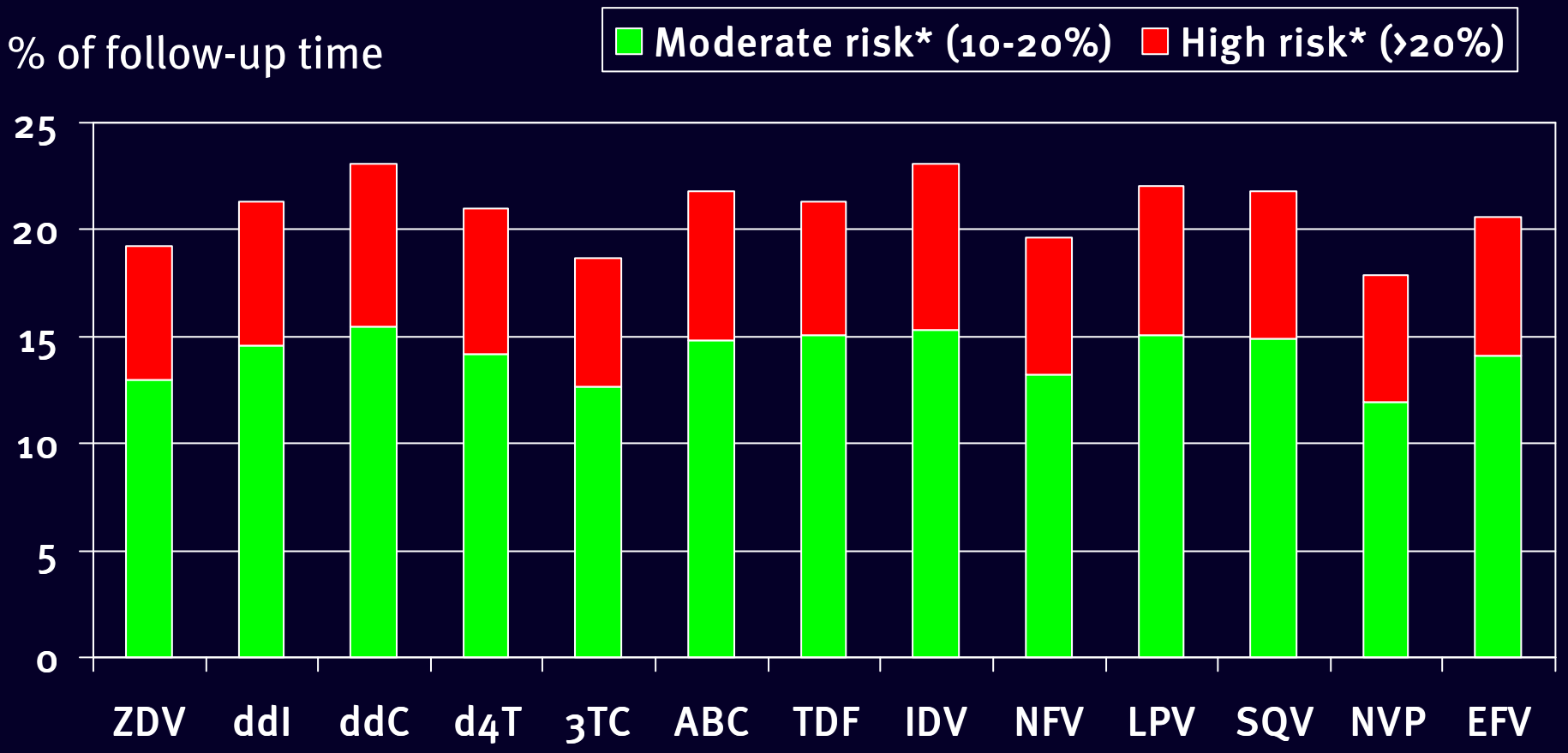
% of follow-up time at moderate and high CV risk after ever exposed to each of the drugs



*10 year predicted coronary heart disease risk (Framingham)

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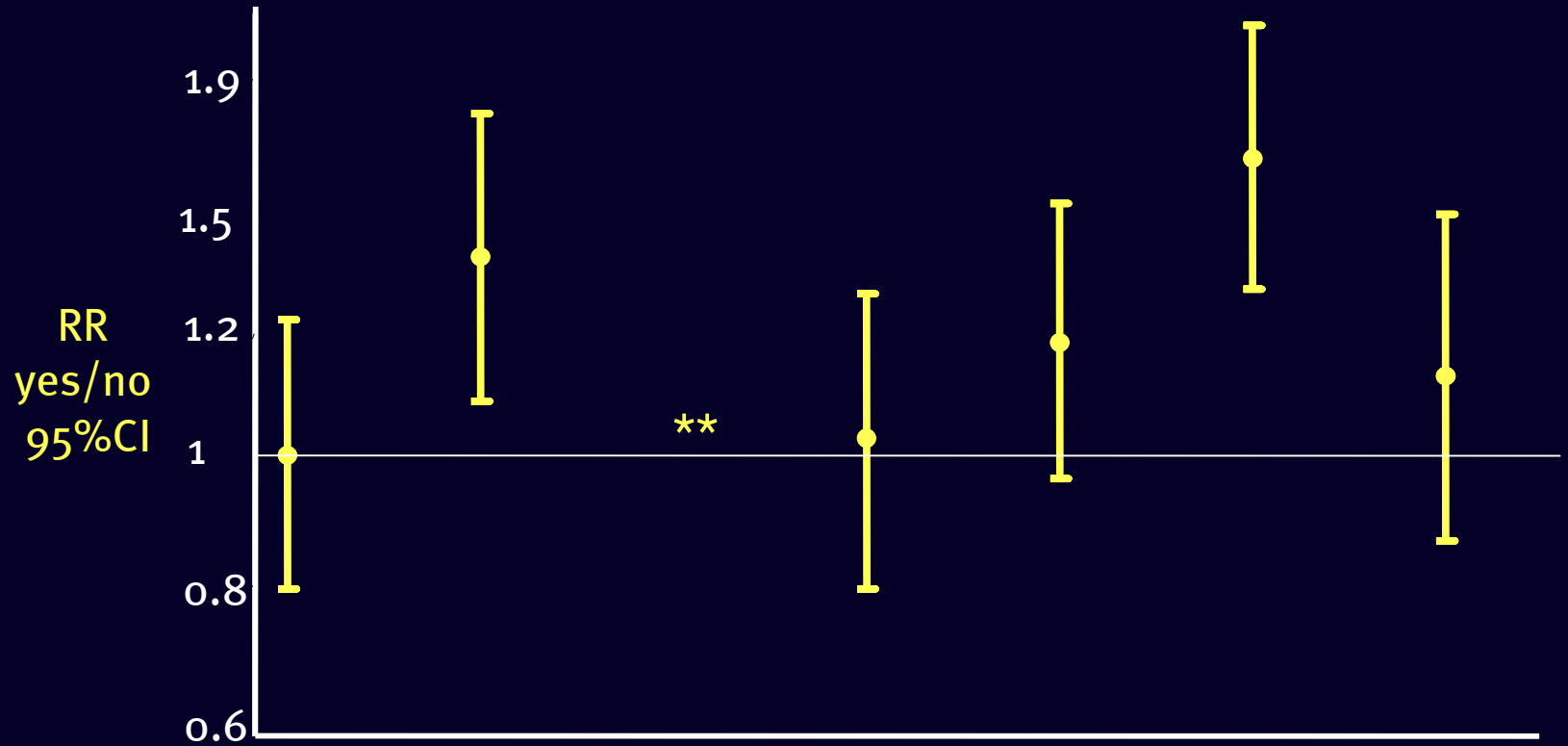
NRTIs and risk of MI: recent* exposure to each drug

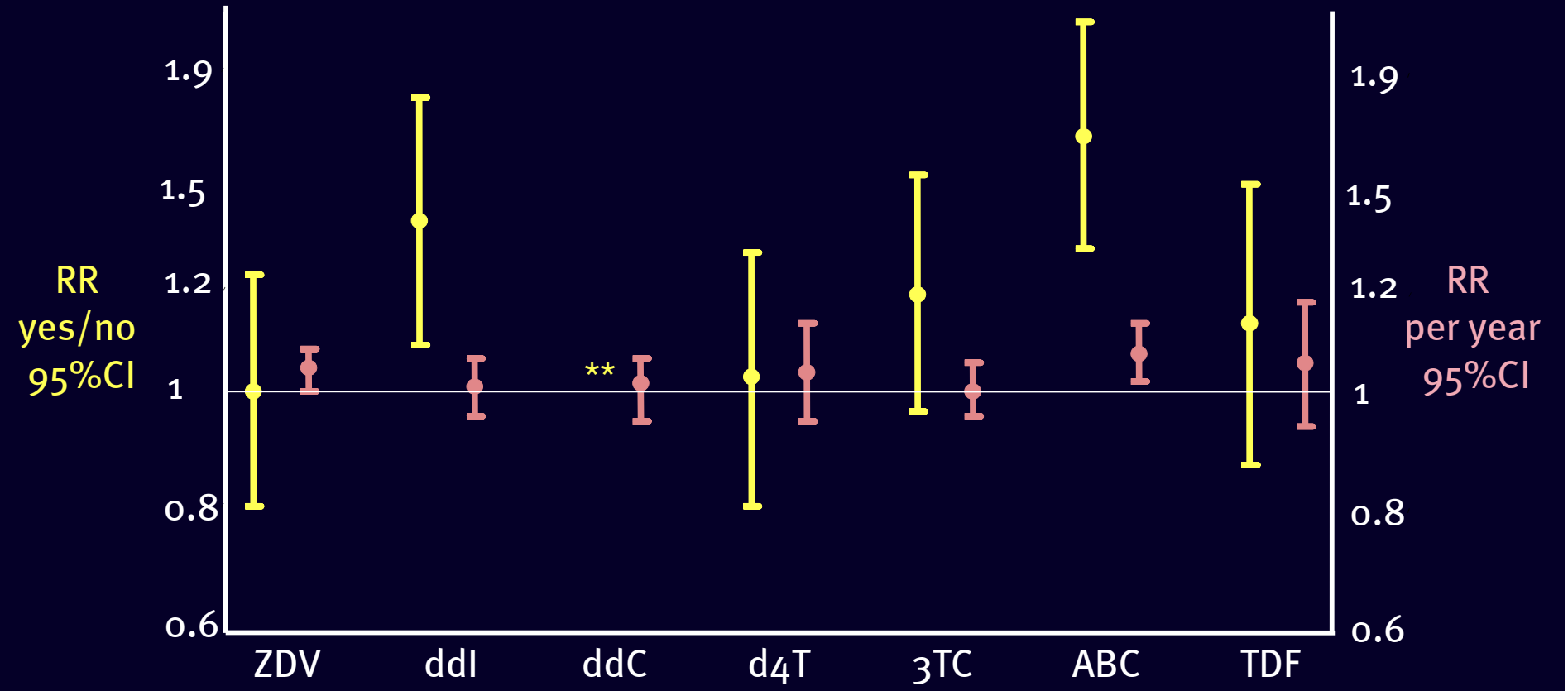


	ZDV	ddI	ddC	d4T	3TC	ABC	TDF
#PYFU:	138,109	74,407	29,676	95,320	152,009	53,300	39,157
#MI:	523	331	148	405	554	221	139

D:A:D

* recent use= current or within the last 6 months; **: not shown (low number of patient currently on ddC)

NRTIs and risk of MI: recent* and cumulative exposure



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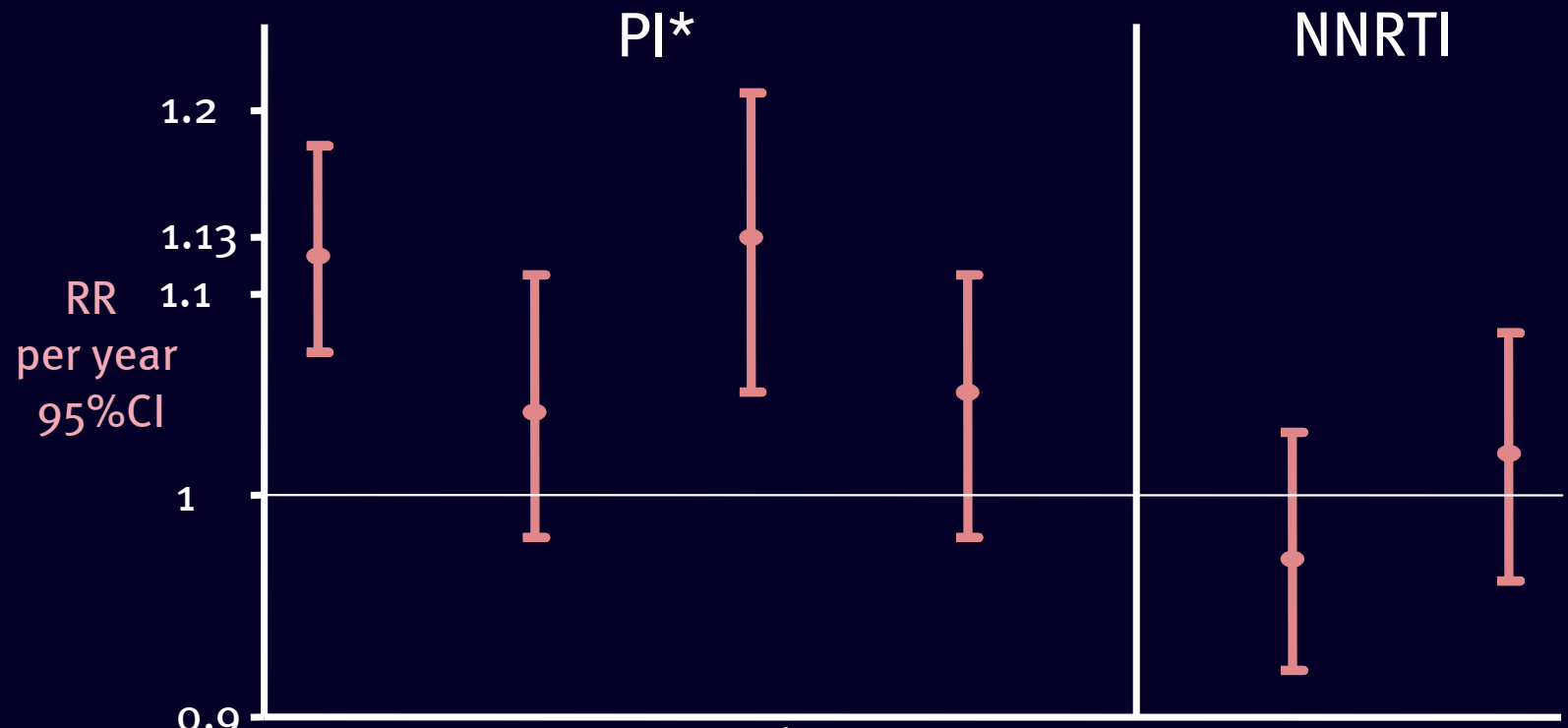
D:A:D

* recent use= current or within the last 6 months **: not shown (low number of patient currently on ddC)

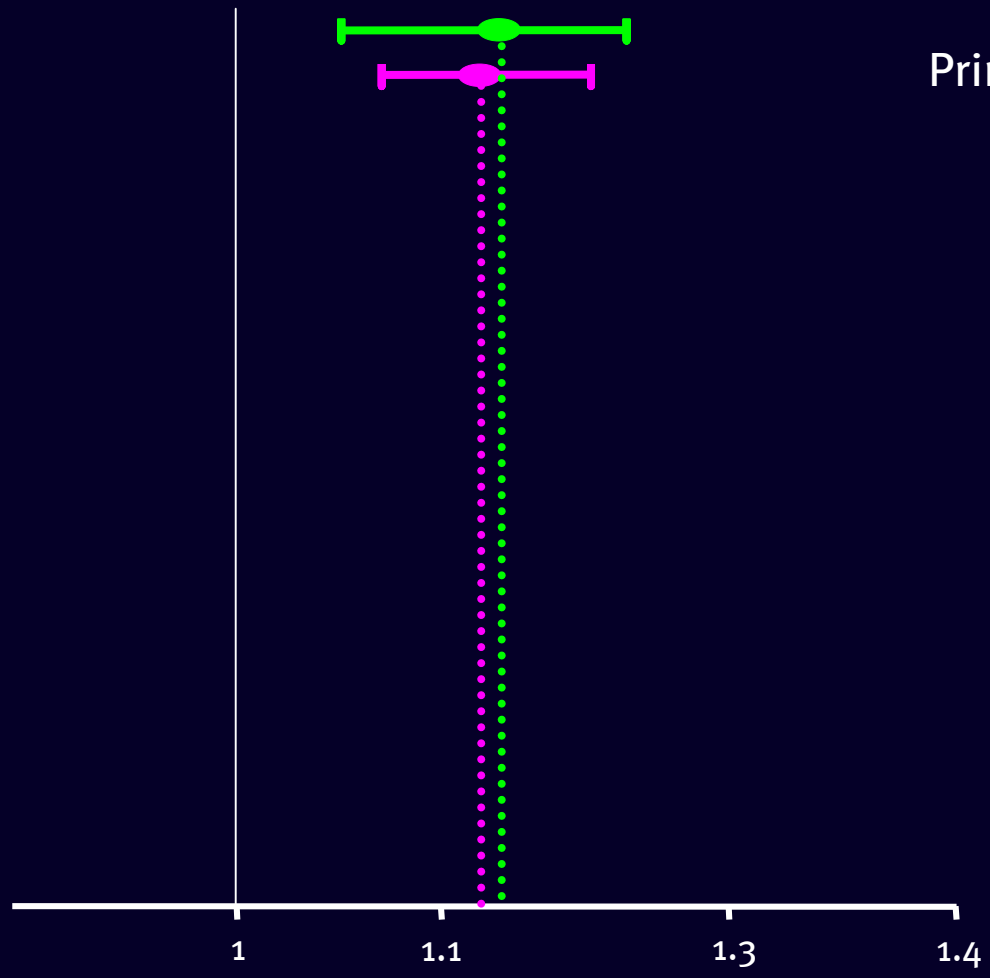
PIs/NNRTIs and risk of MI: cumulative exposure to each drug



	IDV	NFV	LPV/r	SAQ	NVP	EFV
#PYFU:	68,469	56,529	37,136	44,657	61,855	58,946
#MI:	298	197	150	221	228	221

*: Approximate test for heterogeneity: P=0.02

LPV/r and IDV: Effect of adjustment for latest metabolic factors on estimates of risk



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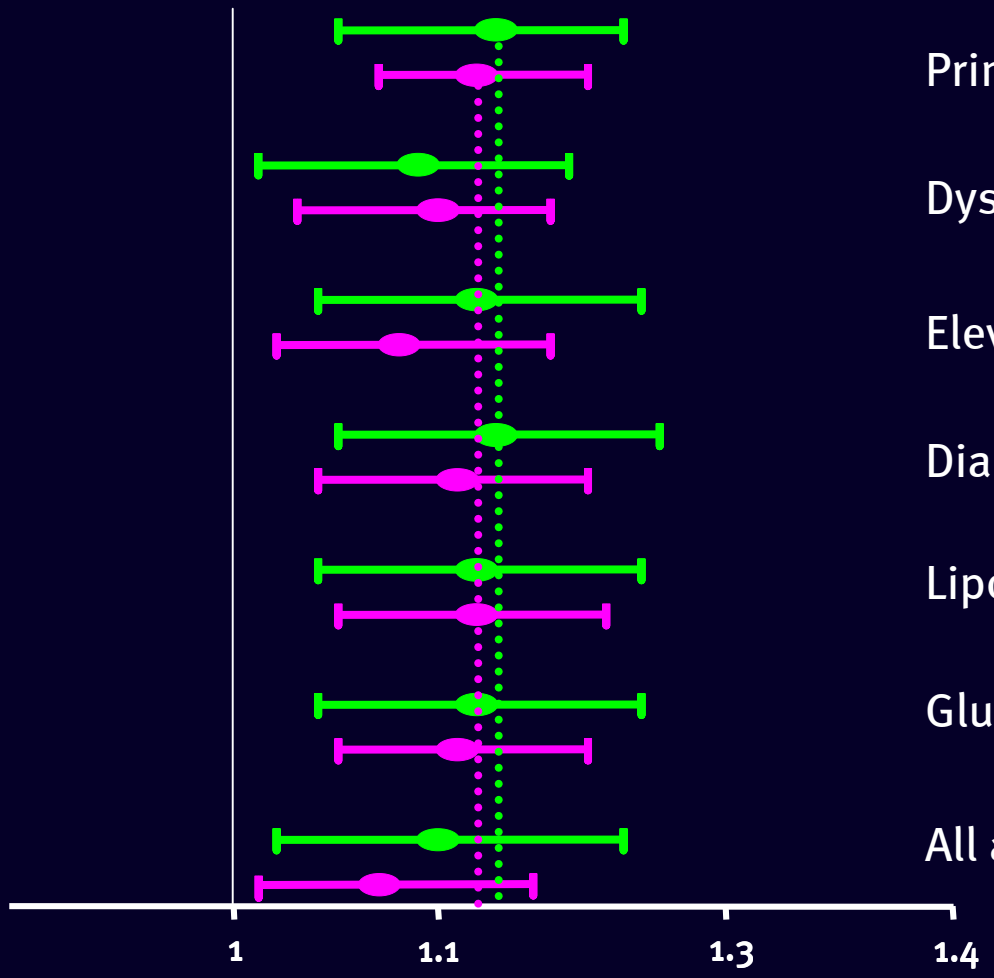
LPV/r and IDV: Effect of adjustment for latest metabolic factors on estimates of risk

Lopinavir/r
Indinavir



Primary model

Dyslipidaemia

Elevated blood pressure

Diabetes mellitus

Lipodystrophy

Glucose

All above +lipid-lowering and antihypertensive medication

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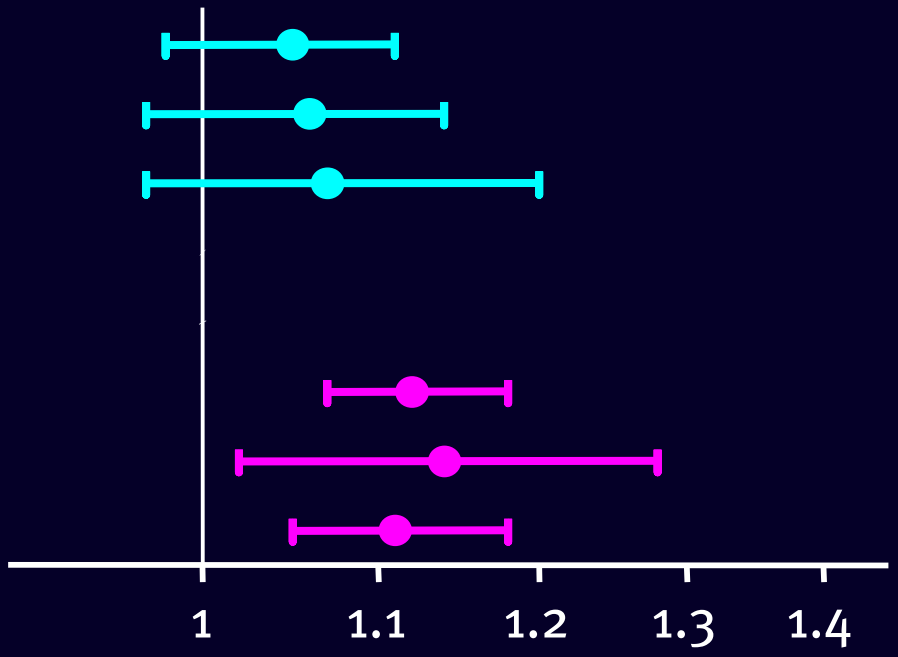
Impact of concomitant use of ritonavir on association between SQV and IDV on risk of MI

# PYFU:	
44,657	Saquinavir (overall)
24,727	Saquinavir+rtv
26,145	Saquinavir
68,469	Indinavir (overall)
22,186	Indinavir+rtv
57,961	Indinavir



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*: Primary model

Conclusion

- Abacavir, didanosine, indinavir and lopinavir/r associated with an increased risk of MI
- No significant associations between exposure to other NRTIs including tenofovir, either of the NNRTIs nor 2 other PIs (SQV/NFV) and the risk of MI
- For indinavir and lopinavir/r,
  - the risk increased with cumulative exposure,
  - partly explained by dyslipidaemia
- Concomitant use of ritonavir did not appear to modify the effects of saquinavir or indinavir

Discussion

- Findings stress the need to continue to examine the associations with *individual* drugs, as drugs from the same class may confer different risks of MI
- Given the observational design and the possibility of unmeasured confounding, cautious interpretation warranted
- Additional follow-up required to examine the risk of MI for more recently introduced PIs

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- **Community representative:** S Collins *
- **DAD coordinating office:** N Friis-Møller, S Worm, A Sawitz, JD Lundgren *¢
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  Additional members: S Storfer *, D Pizzuti *, I Weller *
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