Long-term safety monitoring of HIV patients in an observational setting

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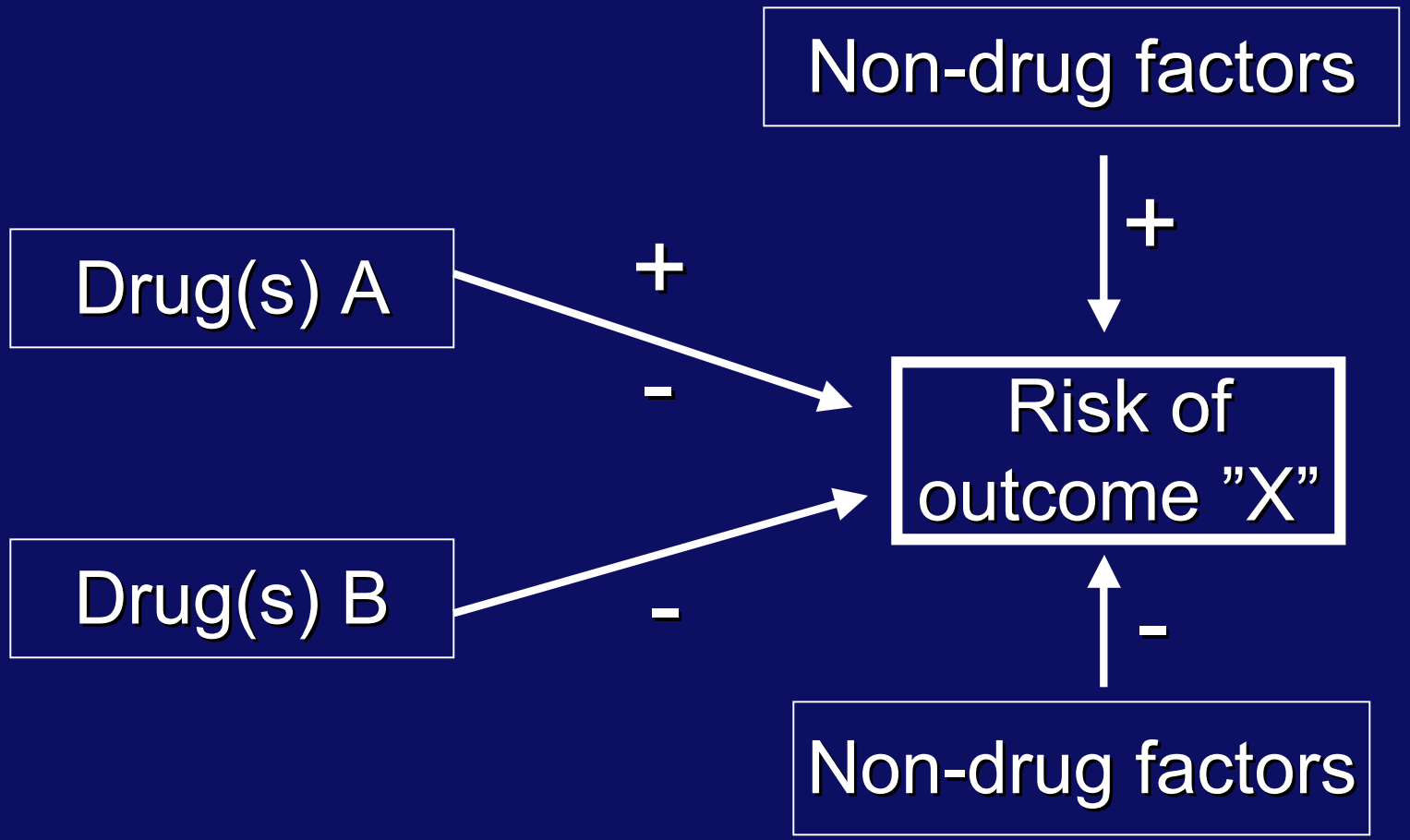
Setting

The outcome X is an adverse event caused by drug A although both drug A and B also reduced the risk (as compared with not using them). Other non-pharmacological factors also influence the risk of X.



Why use observational studies to assess long-term safety of ART ?

PRO

- Cohort studies are designed to follow patients long-term
- Randomised long-term comparison of individual drugs as part of a 3/4 –drug regimen with sufficient power to assess clinical outcomes not done in HIV in the last decade

CON

- Lack of randomisation allows for known and unknown confounders to affect the comparison of the outcome “X” from exposure to drug A vs B
- This problem compromises the ability to assess causal relationships between drug A and outcome X

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Disclaimer: I do both types of studies

Observational studies the best second choice

- Better source of evidence than evidence that is opinion-based and based on case studies
  - Allows for assessment of incidence of outcome X and risk factors affecting this
    - Place safety issues into perspective (potential risk:benefit ratio)
  - Ability to control for confounders
    - REDUCED risk of biased comparison of drugs
- Verifiable criteria can be set to assess whether probable causality of a safety signal has been established
  - Reproducible
  - More than doubling of risk of outcome X for drug A vs B
  - Biologically plausible

Co-morbidities as outcome X

e.g. cardiovascular disease, pancreatitis, liver failure, or lymphoma

- Adverse event/background risk ratio !
  - Characteristics of the cohort – incidence of co-morbidity “X” without exposure to drug A
    - Negatively associated with ability to identify signal that drug A increases the incidence of X
    - Low incidence cohorts are to be preferred
      - the study has to be adequately powered !!!!
- Identification of an ”independent” effect from drug A
    - Requires the collection of all important factors that otherwise influence the risk of developing the co-morbidity

Combining cohorts to optimise power: issues

- Quality of data collection and individual components
  - quality versus quantity
  - prospective versus retrospective
- Uniformity & harmonisation of data to be collected
- Merging databases
- Inter-cohort collaborations
  - Competitors for science/funding team up -
  - Each cohorts own profile versus the aim of the collaboration
    - Question can only be answered by larger sample size than what own cohort

Quality versus quantity

Consequences of the the association between quantity and quality

- Need for carefull design and focused data-collection
  - Open-ended questions STRONGLY discouraged
  - Allow for flexible data collection scheme
    - if new and interesting aspects emerges while study is ongoing then data on these aspects should be readible started to be collected
  - But: what you don't suspect (and hence don't study), will likely not picked up !
- Carefull attention should be made that those data you are really interested in gets appropriately QA's
  - Case definition of clinical variable – ascertainable and independent verifiable

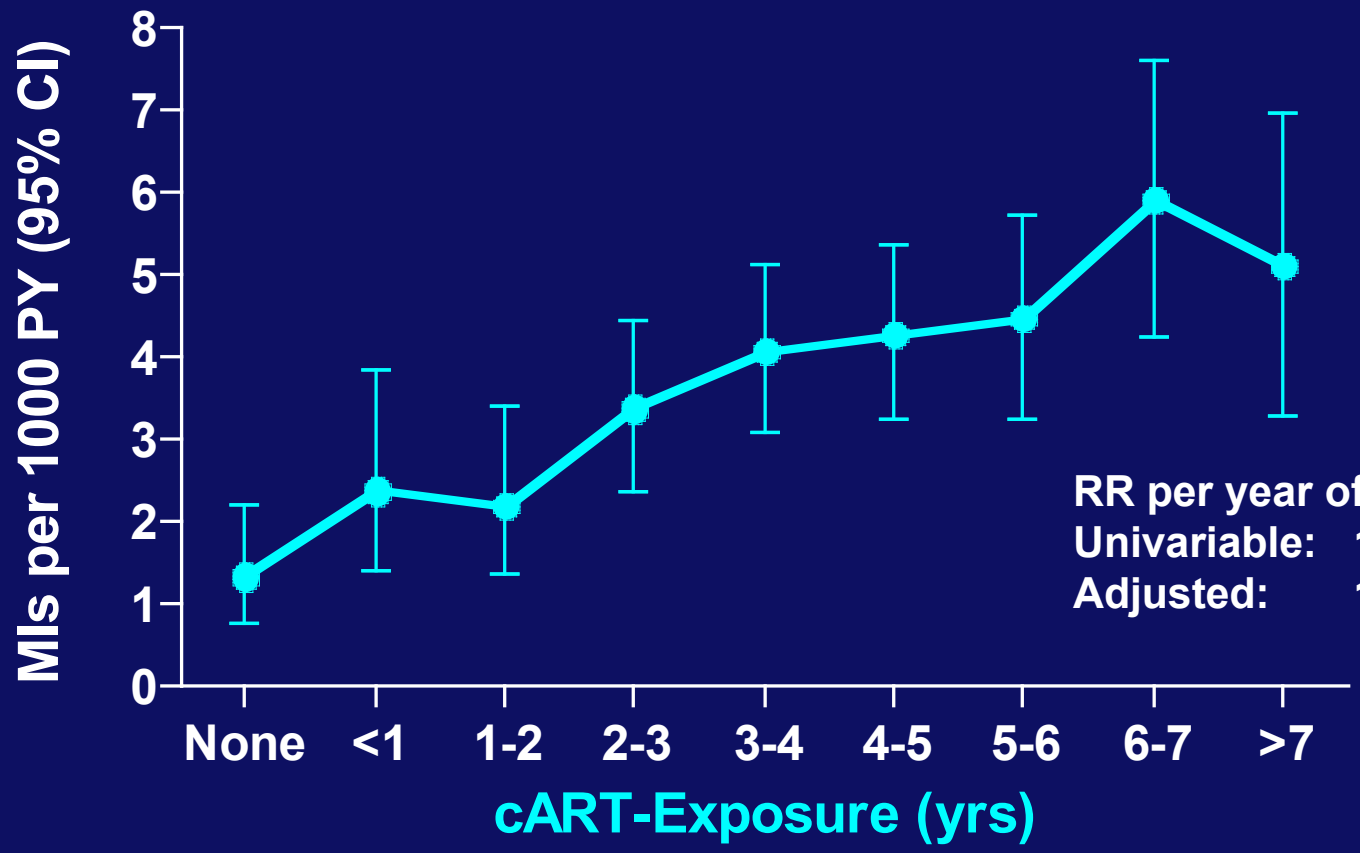
And low lost-to-follow-up rate
is a precondition !

Study done in regions with centralised and state-subsidised health care or otherwise within net-work setting with sufficient allocation of funds to ensure good follow-up

Treatment bias while study is ongoing

- Suspicion of increase in risk of outcome X from exposure to drug A in community will tend to ”dilute” differences in risk of outcome X for drug A vs drug B
  - Patients at high perceived risk of X will tend to be switched away from drug A
- Necessary initiatives to address this
  - Keep results blinded for as long as possible – and certainly until there is sufficient number of endpoint accrued to reliable compare drug A vs B
  - Focus data collection on ”causes of drug switch/discontinuation”
  - Don’t conclude until data are GDO

Incidence of Myocardial Infarction according to cART Exposure



RR per year of cART:
Univariable: 1.16 [1.11-1.21]
Adjusted: 1.16 [1.09-1.23]

	None	<1	1-2	2-3	3-4	4-5	5-6	6-7	>7	*Total*
Events	16	17	20	41	61	62	51	47	30	*345*
PYFU	11815	7105	9027	12098	14892	14394	11351	7935	5853	*94469*

D:A:D study: Friis-Møller *et al*, CROI 20

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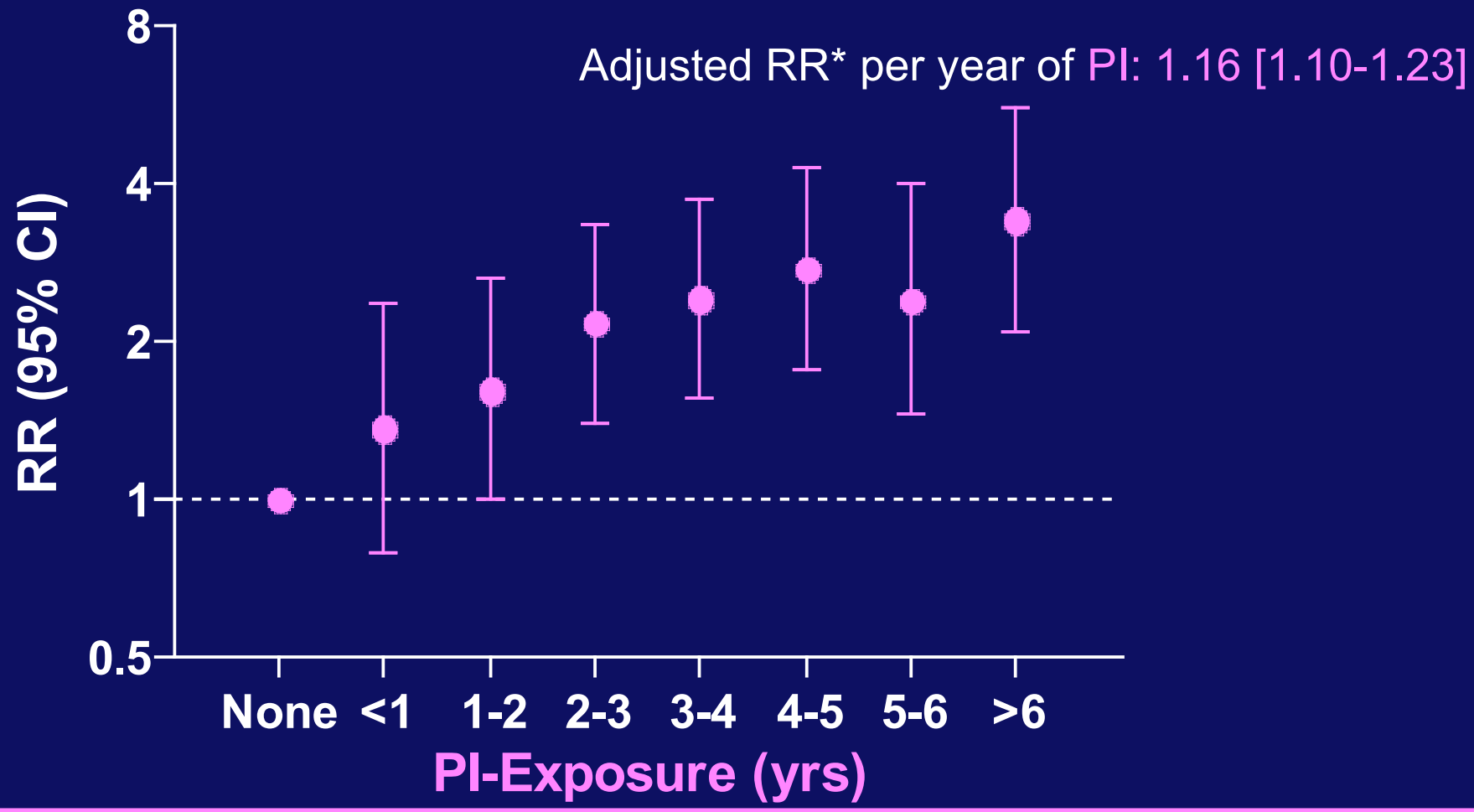
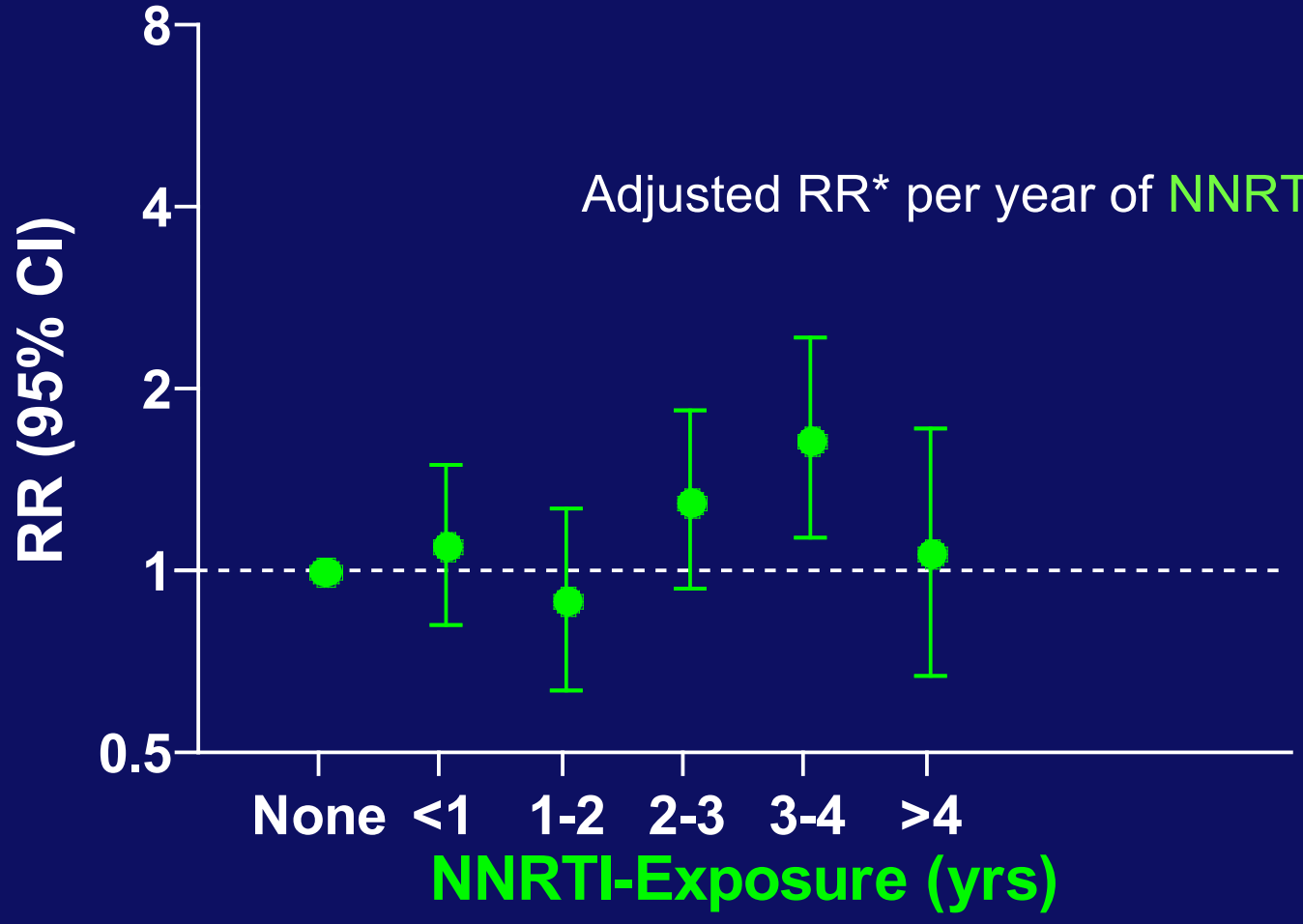
Relative Rate of MI according to PI Exposure – Adjusted for NNRTI



★: Adjusted for sex, age, cohort, calendar year, prior CVD, family history of CVD, smoking, body-mass index, NNRTI exposure

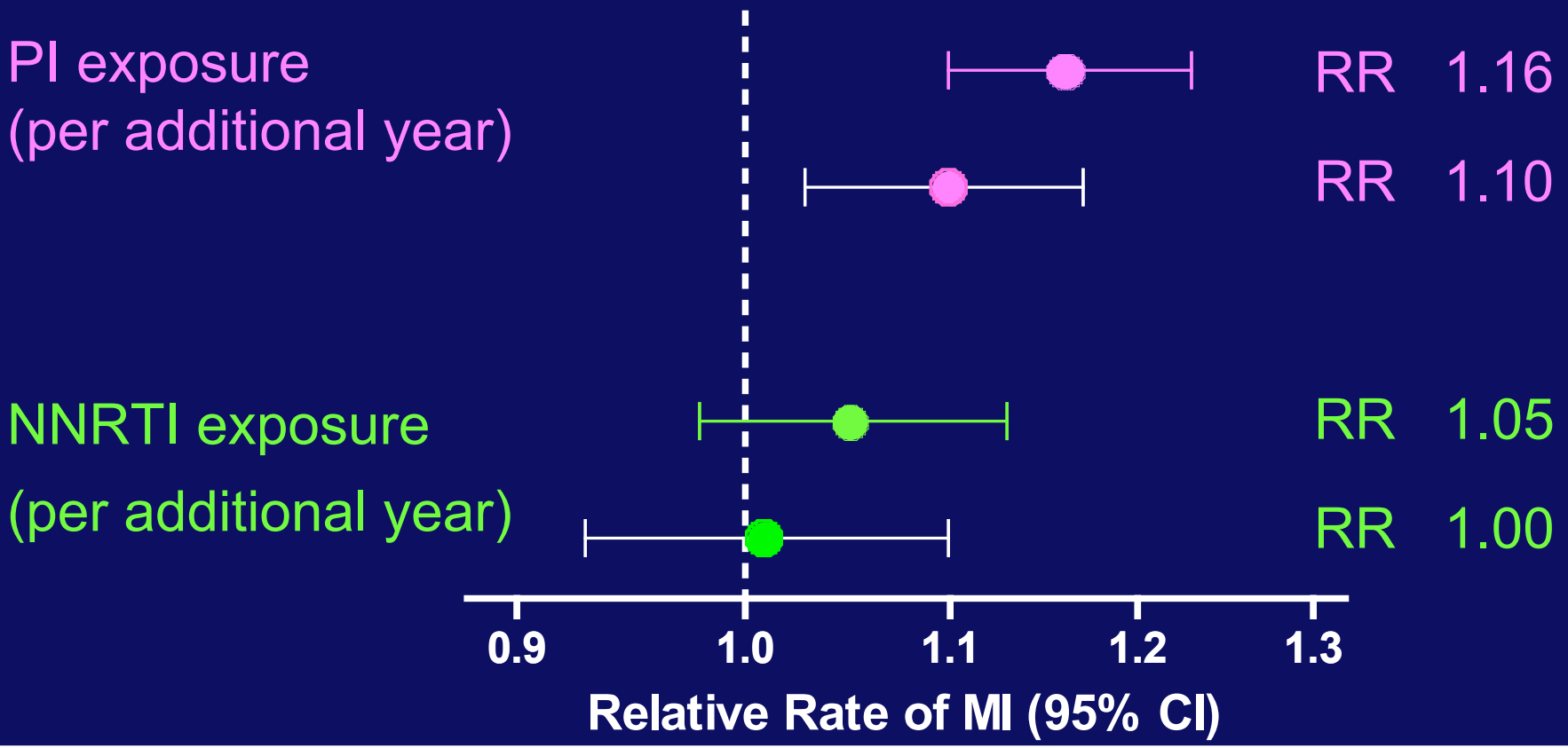
Relative Rate of MI according to **NNRTI** Exposure – Adjusted for **PI**



Adjusted RR* per year of NNRTI: 1.05 [0.98-1.13]

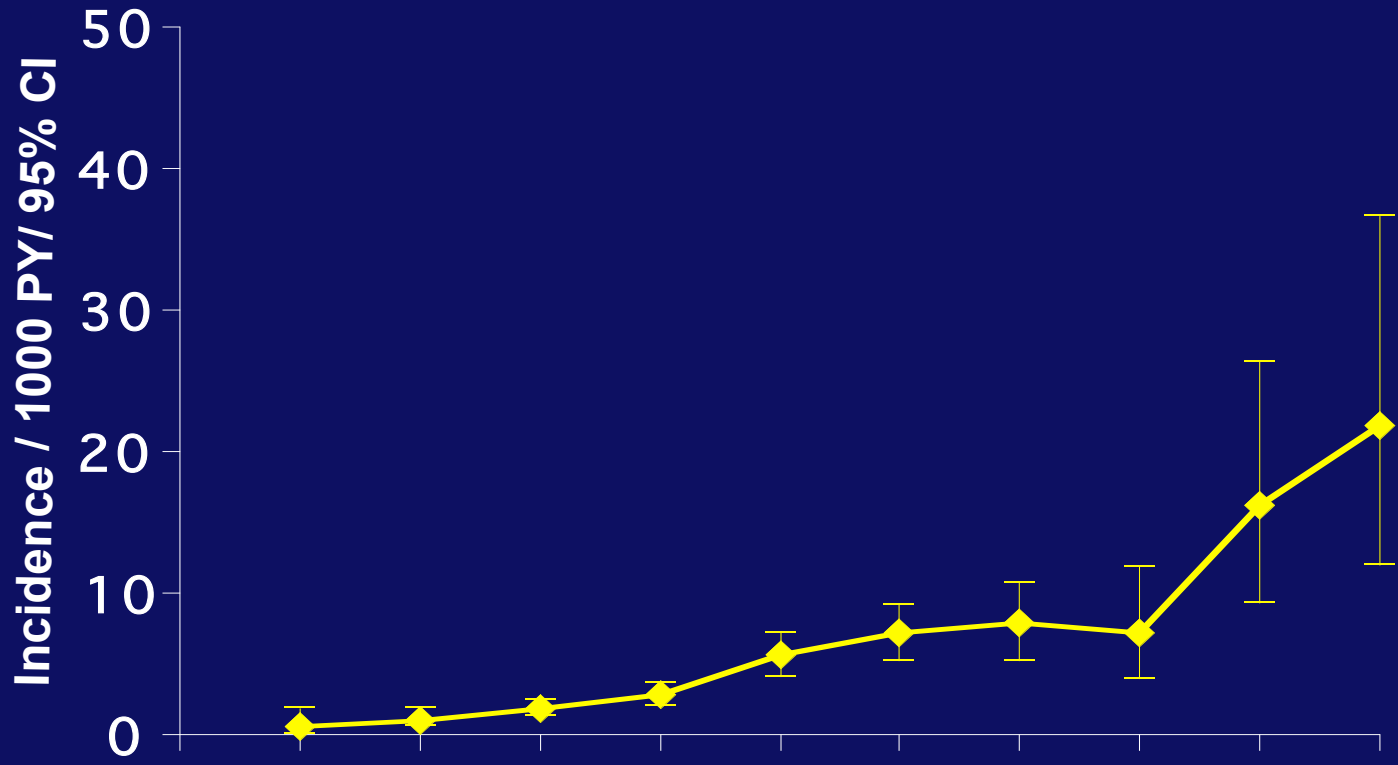
★: Adjusted for sex, age, cohort, calendar year, prior CVD, family history of CVD, smoking, body-mass index, PI exposure

Effect of Exposure to **PI** and **NNRTI** – before and after Adjusting for Lipids



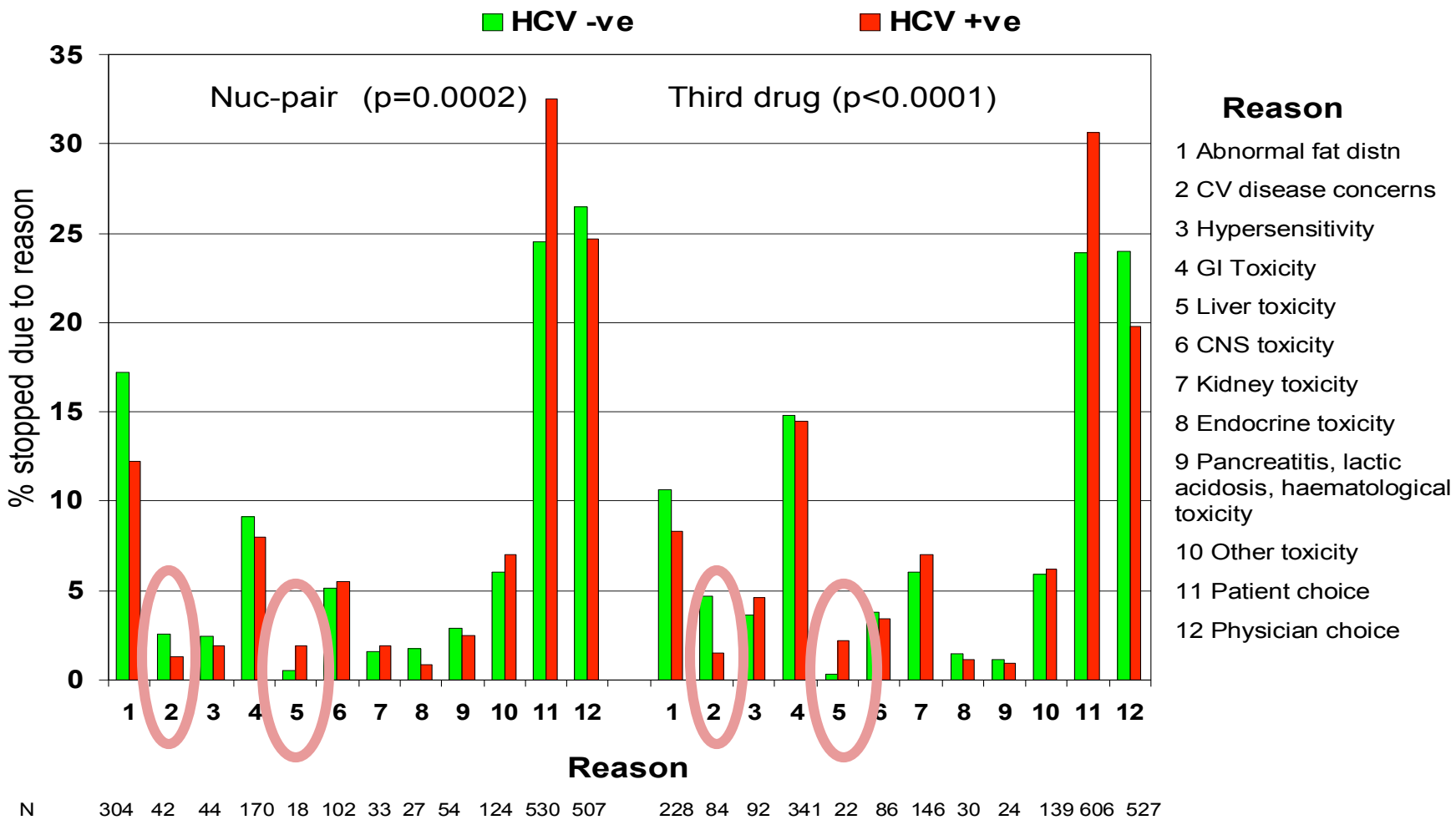
✶: Adjusted for sex, age, cohort, calendar year, prior CVD, family history of CVD, smoking, body-mass index, the other drug class

Incidence of MI according to age in D:A:D



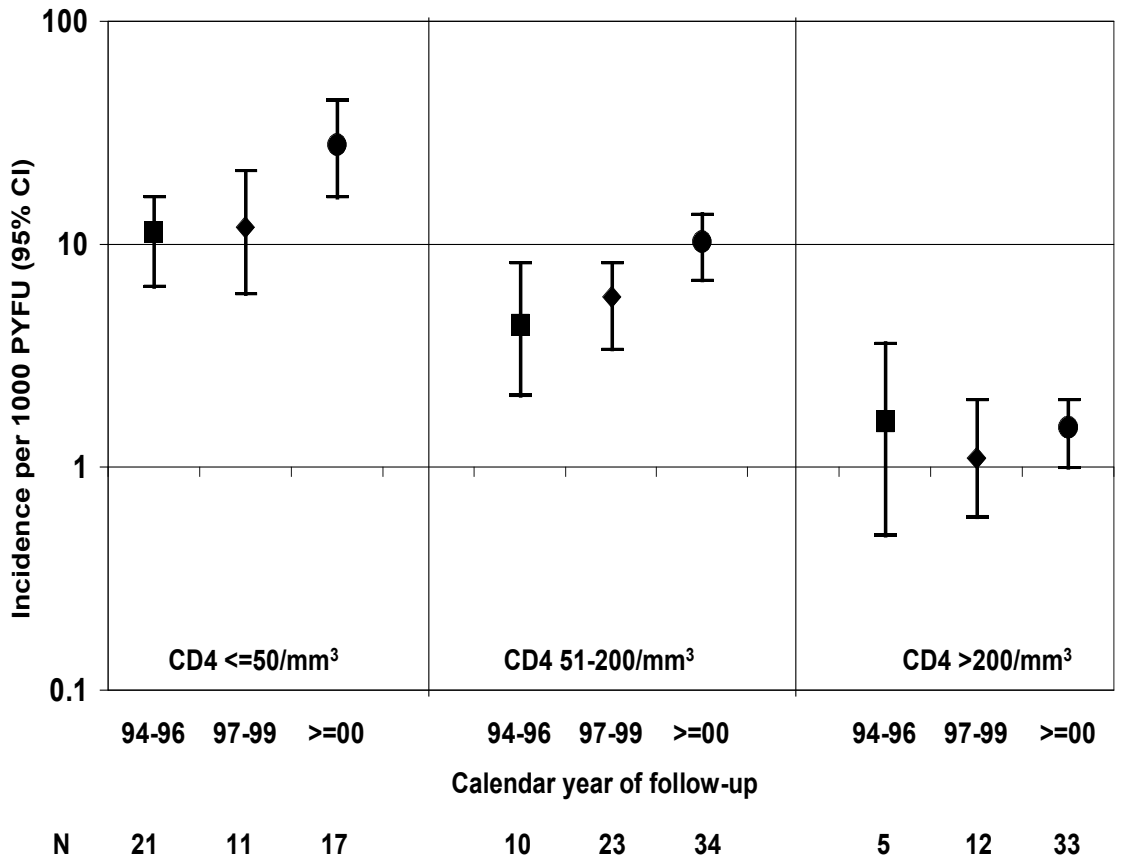
Age group	25-30	30-35	35-40	40-45	45-50	50-55	55-60	60-65	65-70	>70
Events	2	11	36	48	55	48	31	15	16	14
PYFU	3834	10801	20075	16900	9741	6687	3899	2093	989	641

Reasons for discontinuation due to TOX



EuroSIDA: Mocroft et al, AVT 2005

Trends in liver related deaths in EuroSIDA according to current CD4 count: 1994-2004



Risk per 50% higher CD4:

-35% (95%CI -40 – - 30%

<0.0001)

Risk per 1 more recent year

16% (8–26%, p<0.0001)

current <200/mm^3

22% (12%–33%, p<0.0001)

current CD4 >200/mm^3

16% (2%–33%, p=0.027)

HBsAg+

286% (84%–444%, p<0.0001),

anti-HCV

516% (288%–924%, p<0.0001)

N=10,714 (#LRD's 166 (1.5%)); 48,612 PY (rate of LRD: 3.4 per 1000 PYFU (2.9–3.9))

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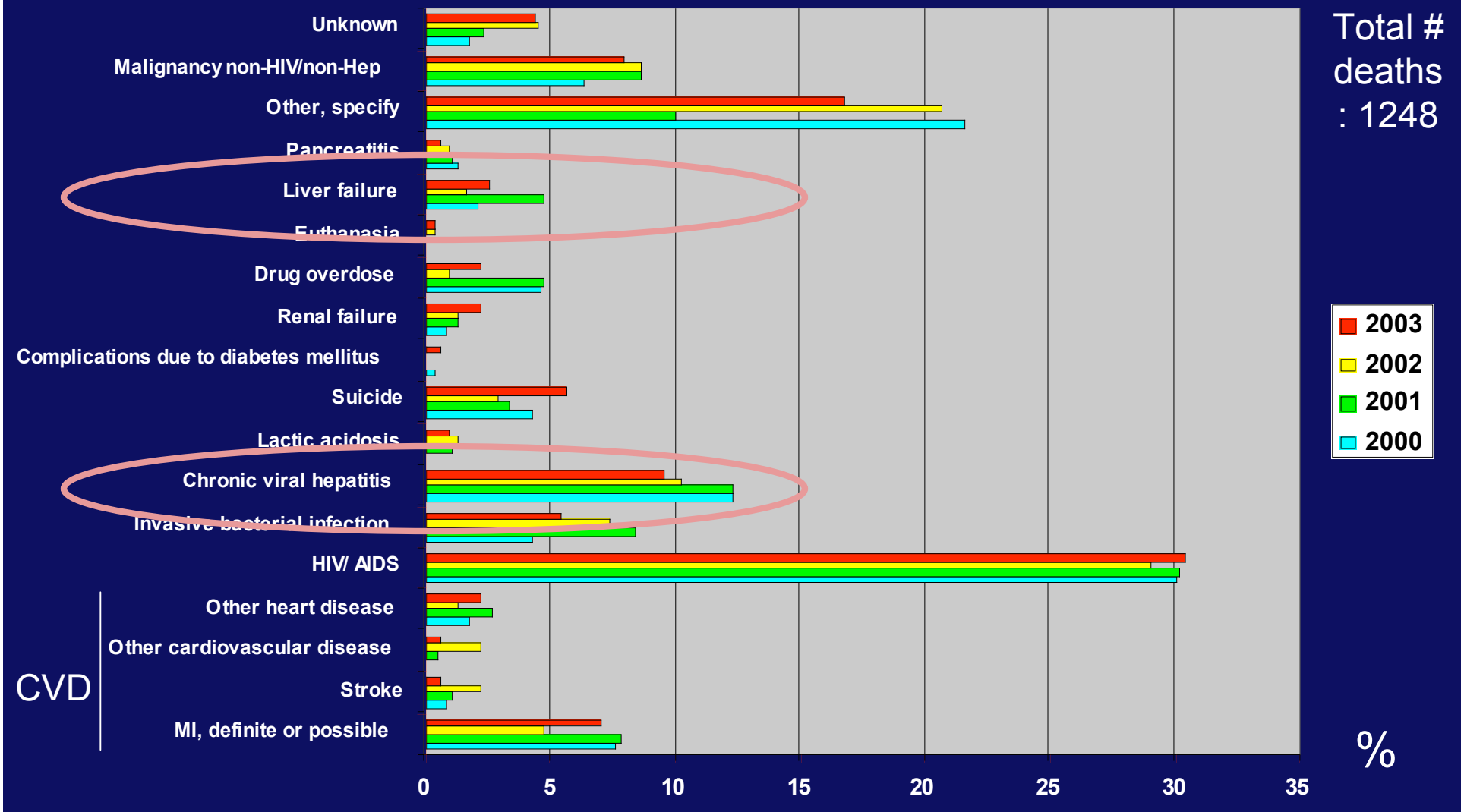
Mocroft *et al*, AIDS 2005

Causes of death in D:A:D 2000-2004 percentage / year



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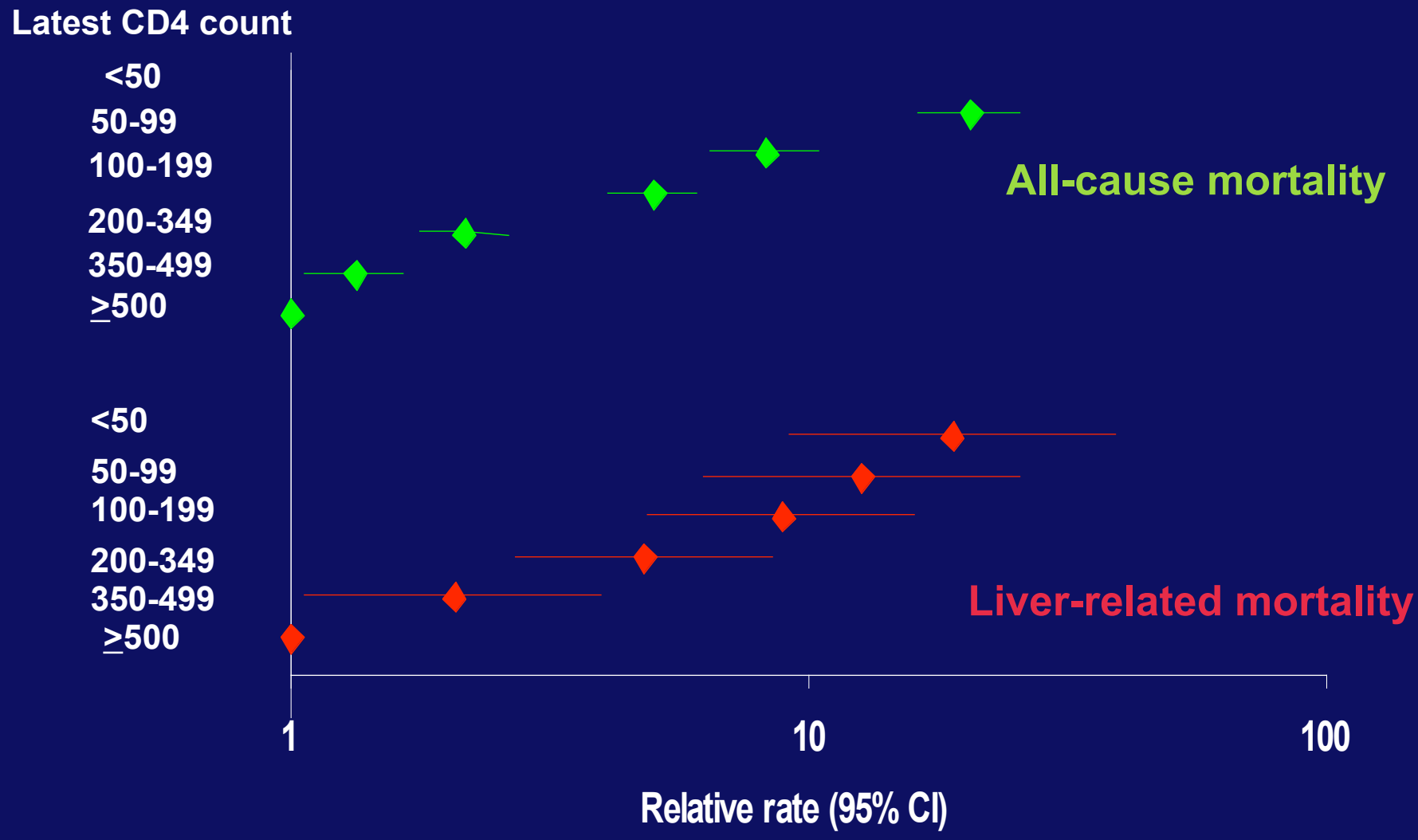
Weber et al, CROI, 2005

Deaths in D:A:D
Multivariable relationships with death rate
Latest CD4 count



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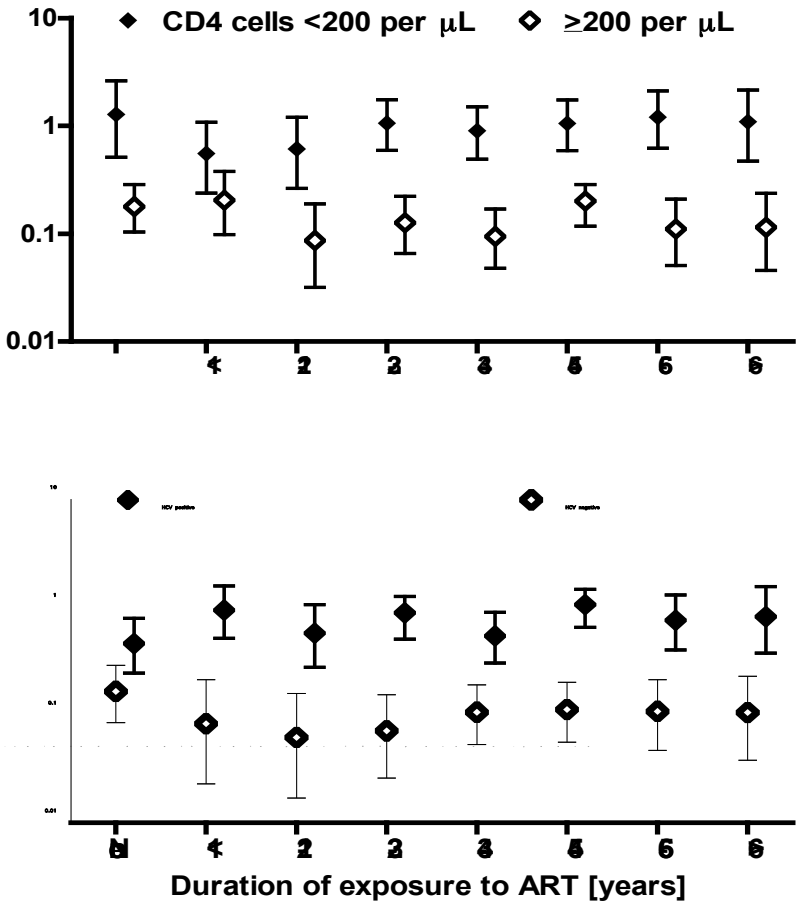
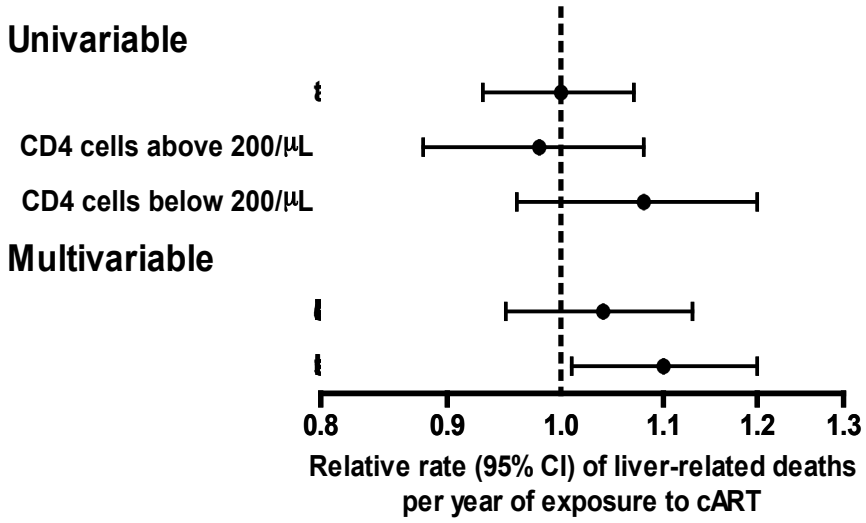
Weber *et al*, Arch Intern Med (in press)

Relationship between combination antiretroviral therapy per year of exposure and liver-related deaths





D:A:D study: Weber *et al*, Arch Intern Med (in pres

Summary

- Observational studies can provide important information on long-term safety of AVT
  - Requires carefully designed, prospective data collection
  - A priori selected endpoints
  - Large sample size
- Exposure to protease inhibitors – but not non-nucleoside reverse transcriptase inhibitors – is associated with excess risk of CVD
  - Still insufficient power to assess individual drugs
- Risk of liver-related death is stable with longer exposure to ART
  - Should be reduced as ART increases CD4 counts that are associated with reduced risk of liver-related deaths
  - Still insufficient power to assess drug classes and individual drugs
- How longer-term exposure to ART affects risk of pancreatitis, renal function and malignancies under active investigation