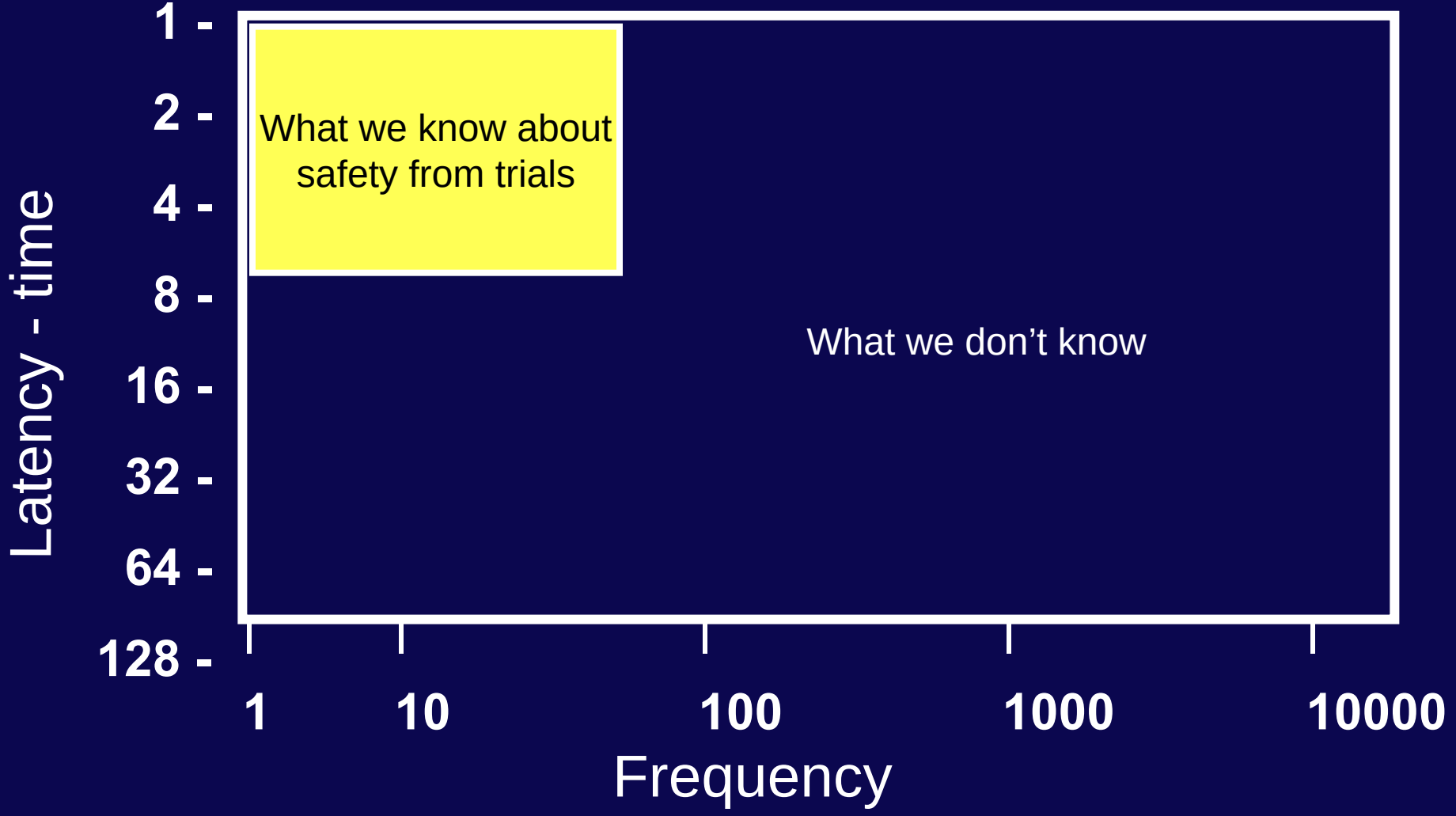
REGION Rigshospitalet

FACULTY OF HEALTH SCIENCES
UNIVERSITY OF COPENHAGEN

CHIP COPENHAGEN HIV PROGRAMME

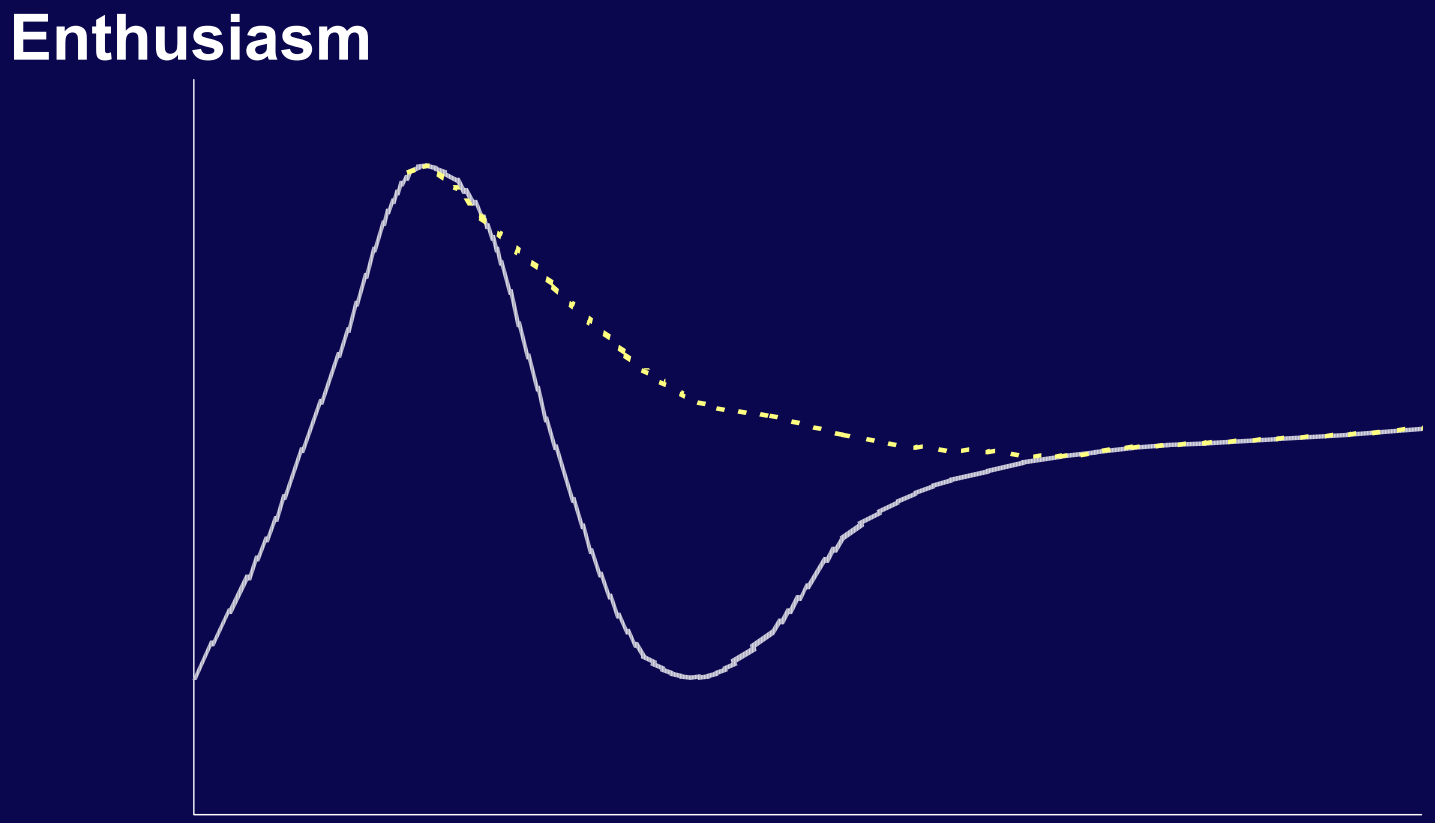
Definitions of AE related to ARVs: What are we talking about?

The case for ensuring pharmacovigilance

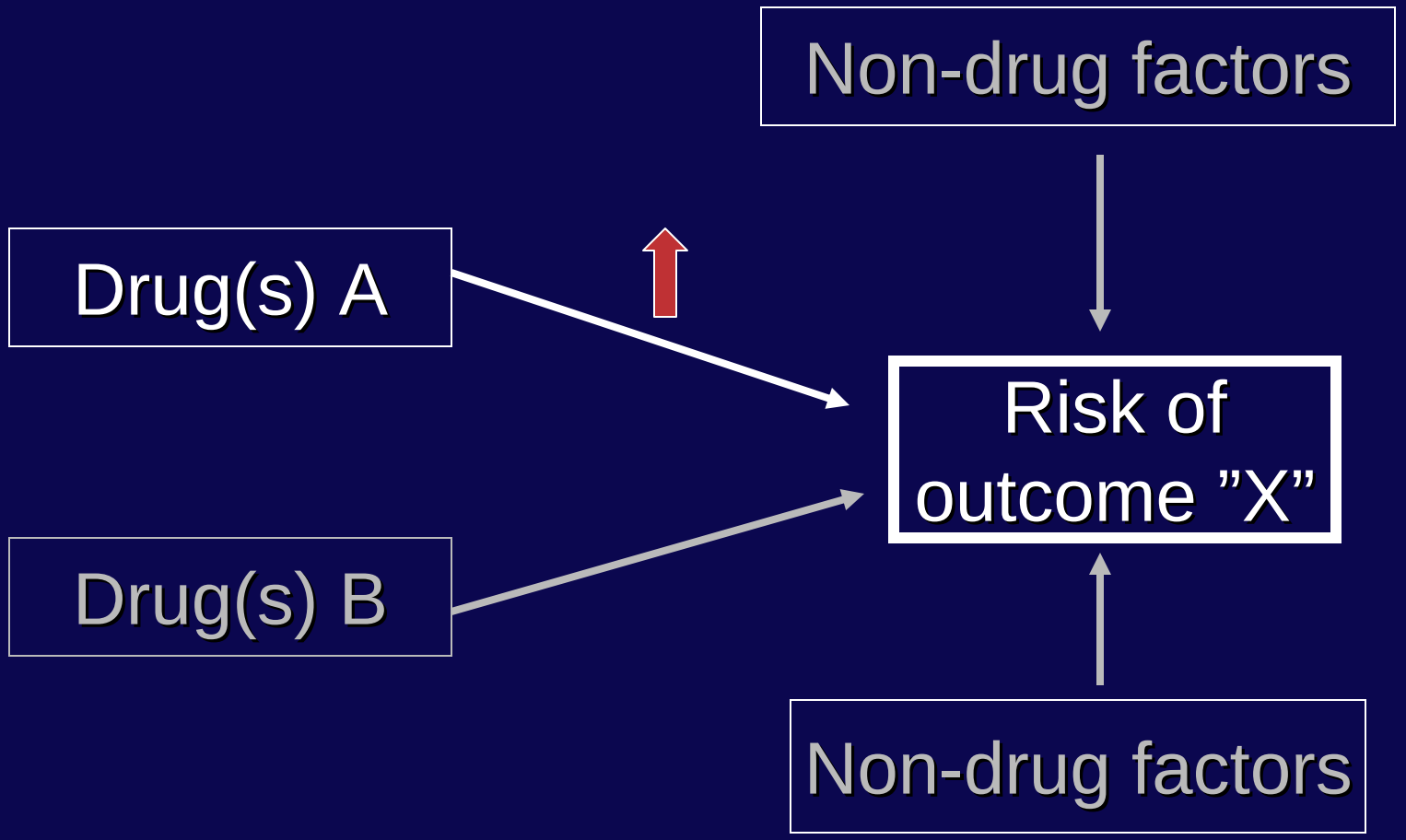


Evans and Waller, MCA 2002

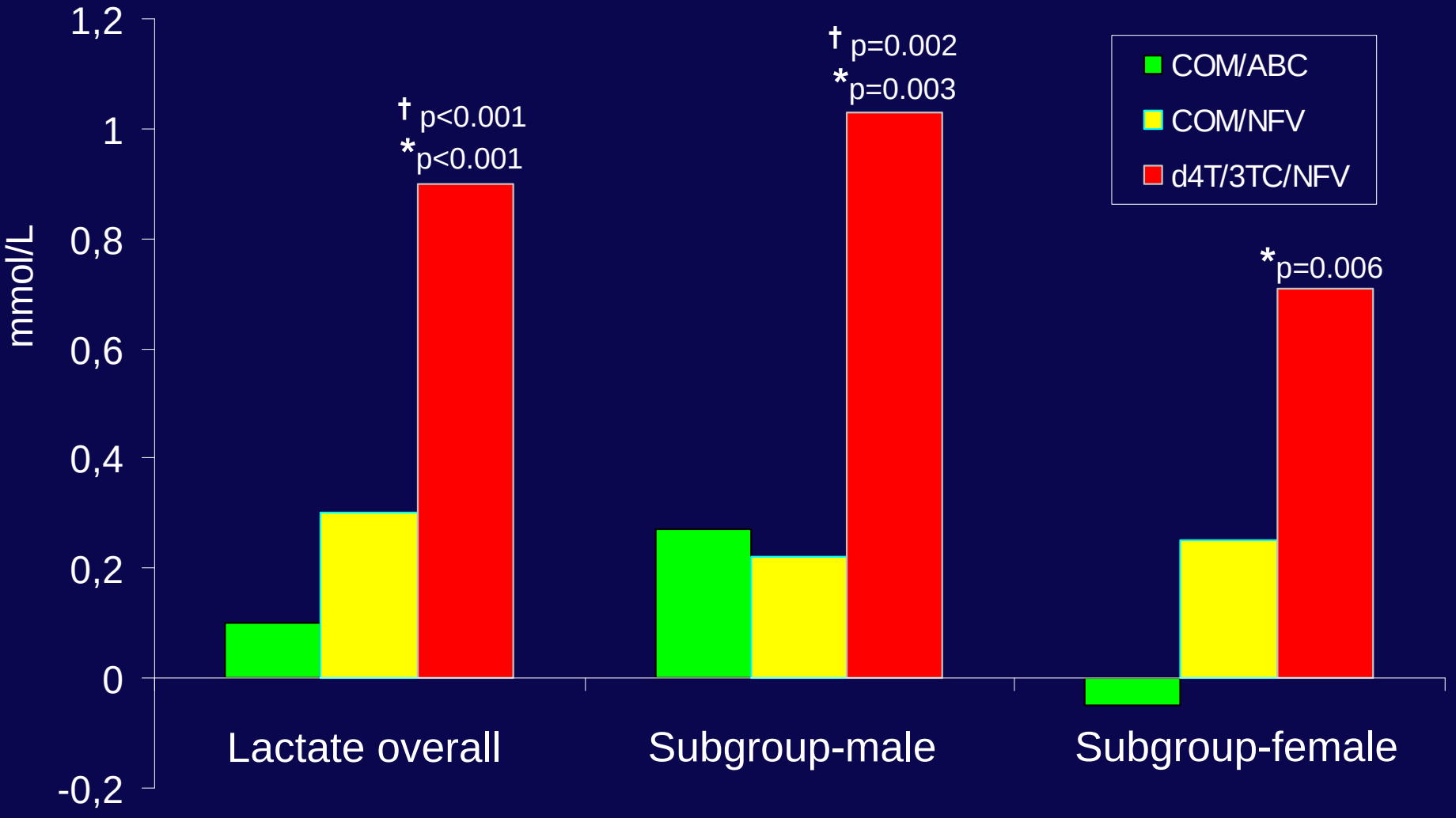
Enthusiasm for a treatment as a function of time since first entering clinical testing



Disentangling a drug effect



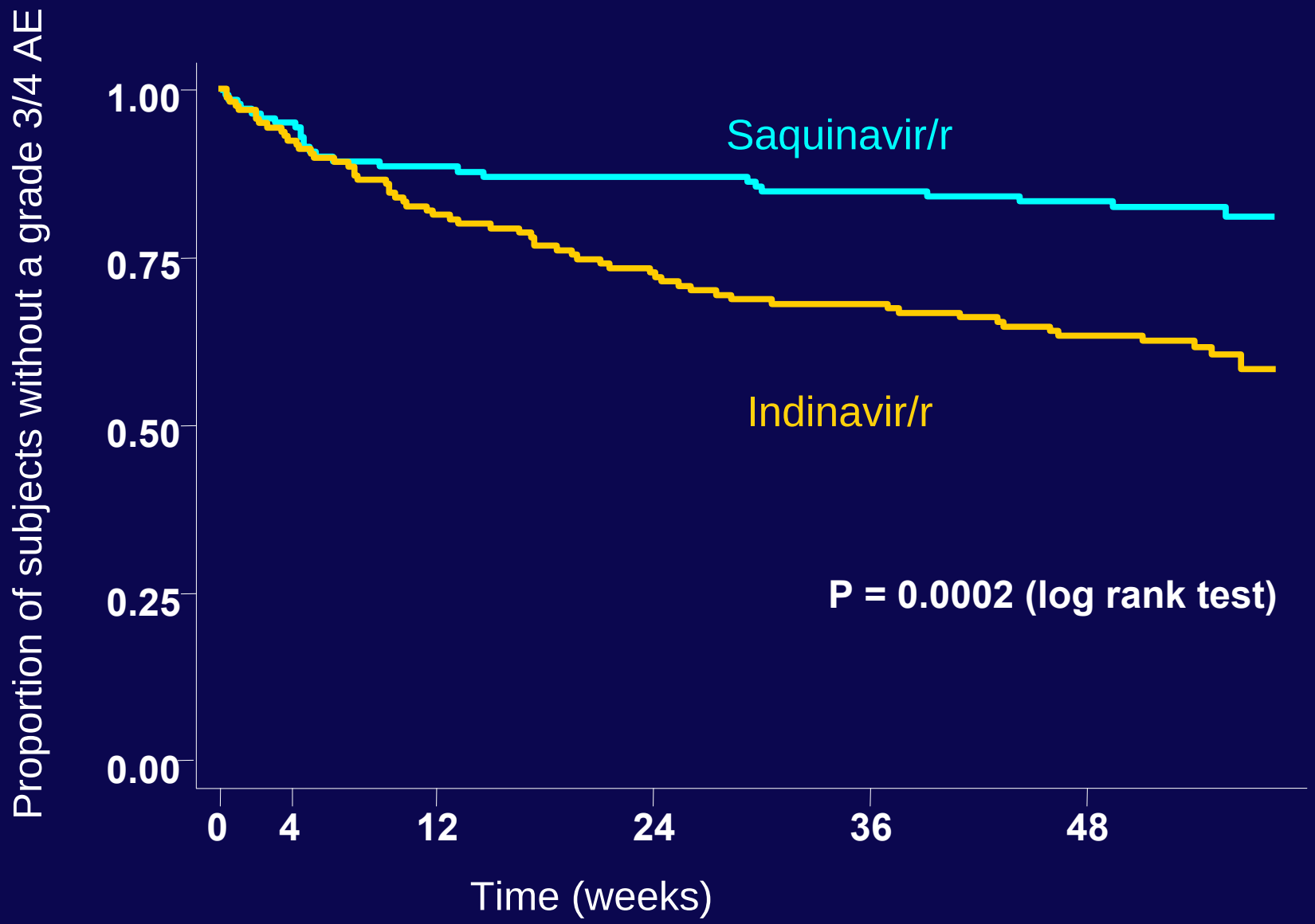
ART naïve patients: Mean lactate values at 48 weeks (Δ from BL)



* p-value as compared to ABC/COM
† p-value as compared to COM/NFV

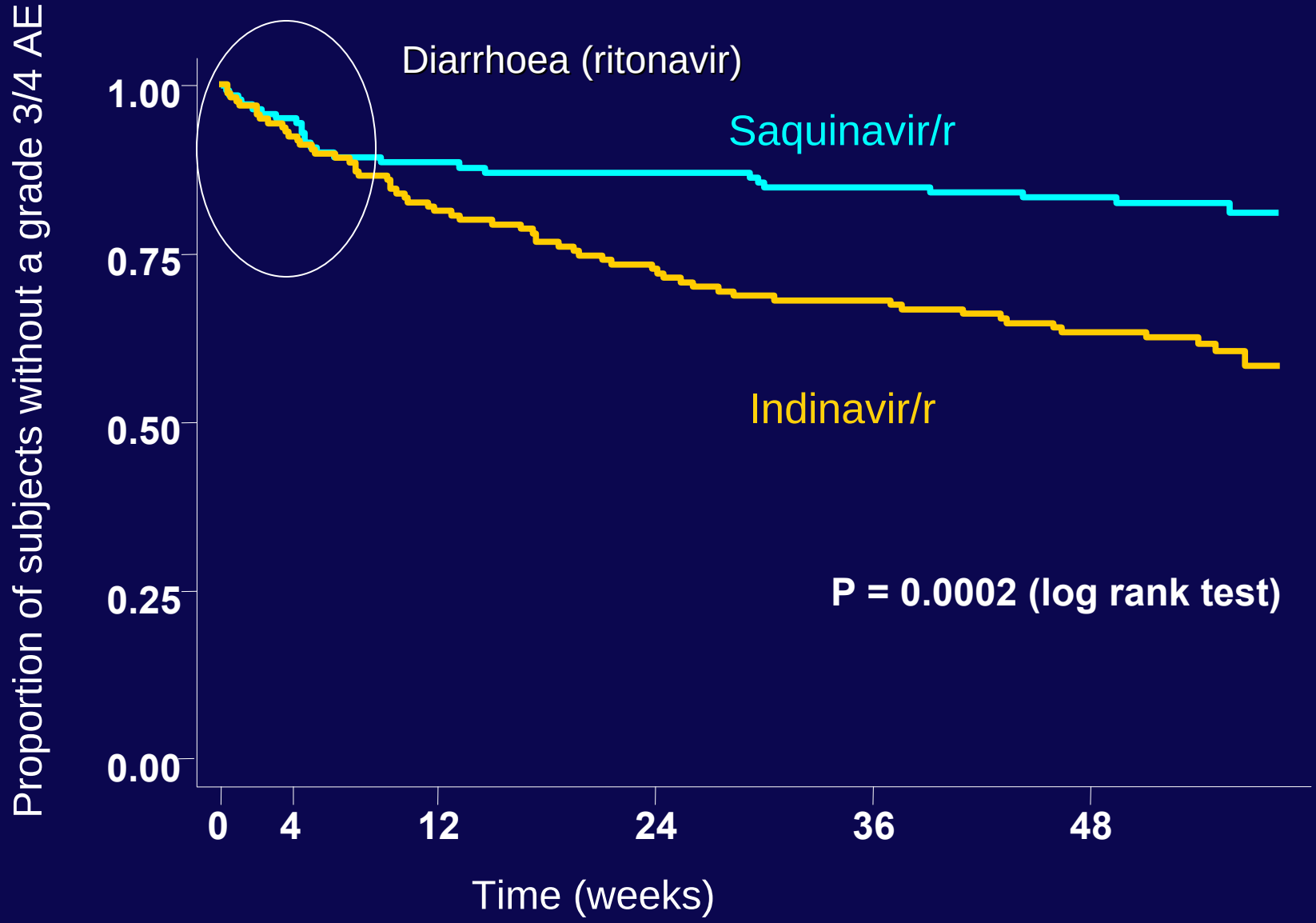
Kumar P, *et al*. 9th CROI 2002; Abs 33

Time to first severe drug-related AE



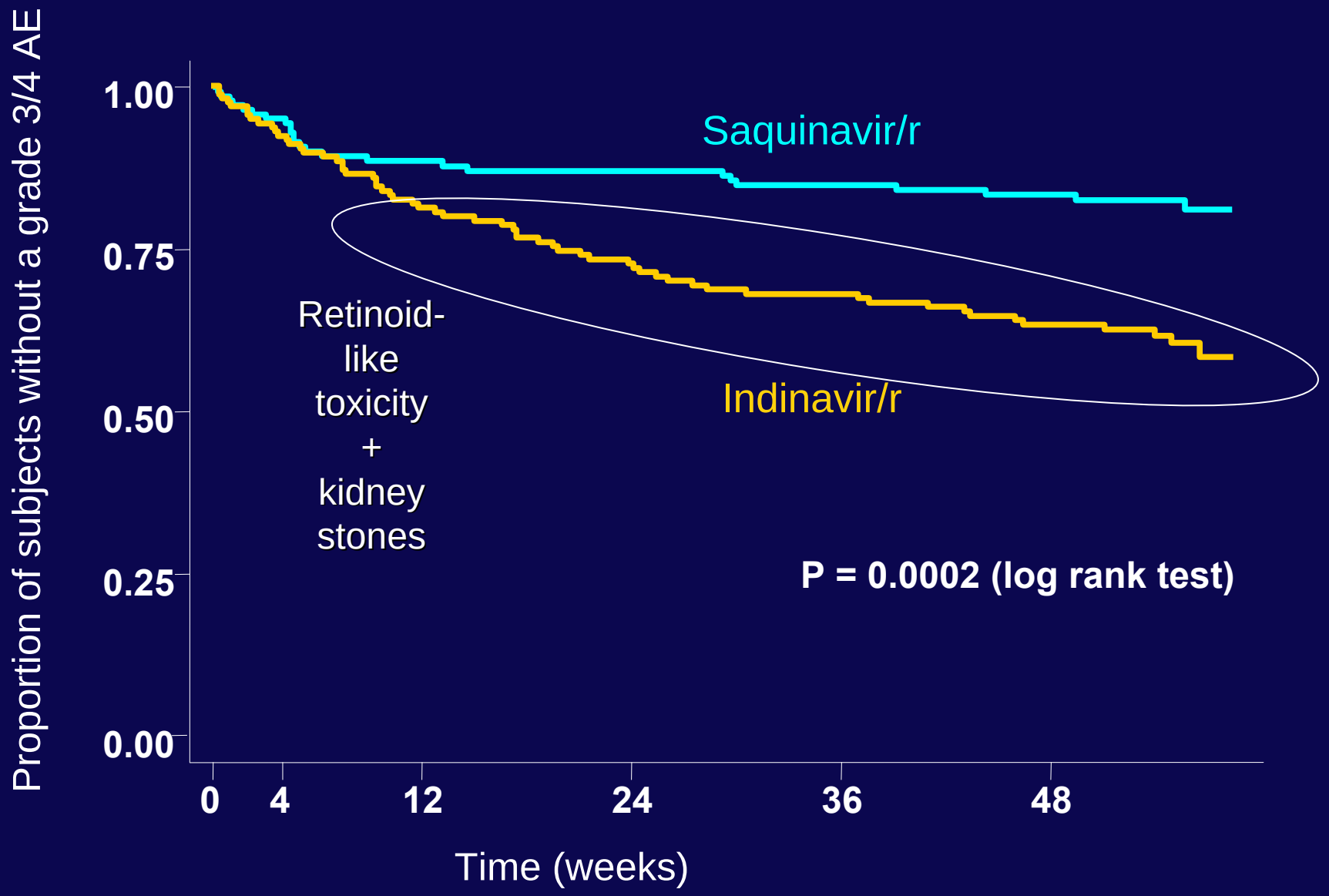
MaxCmin1: Dragsted *et al*, JID, 20

Time to first severe drug-related AE



MaxCmin1: Dragsted *et al*, JID, 20

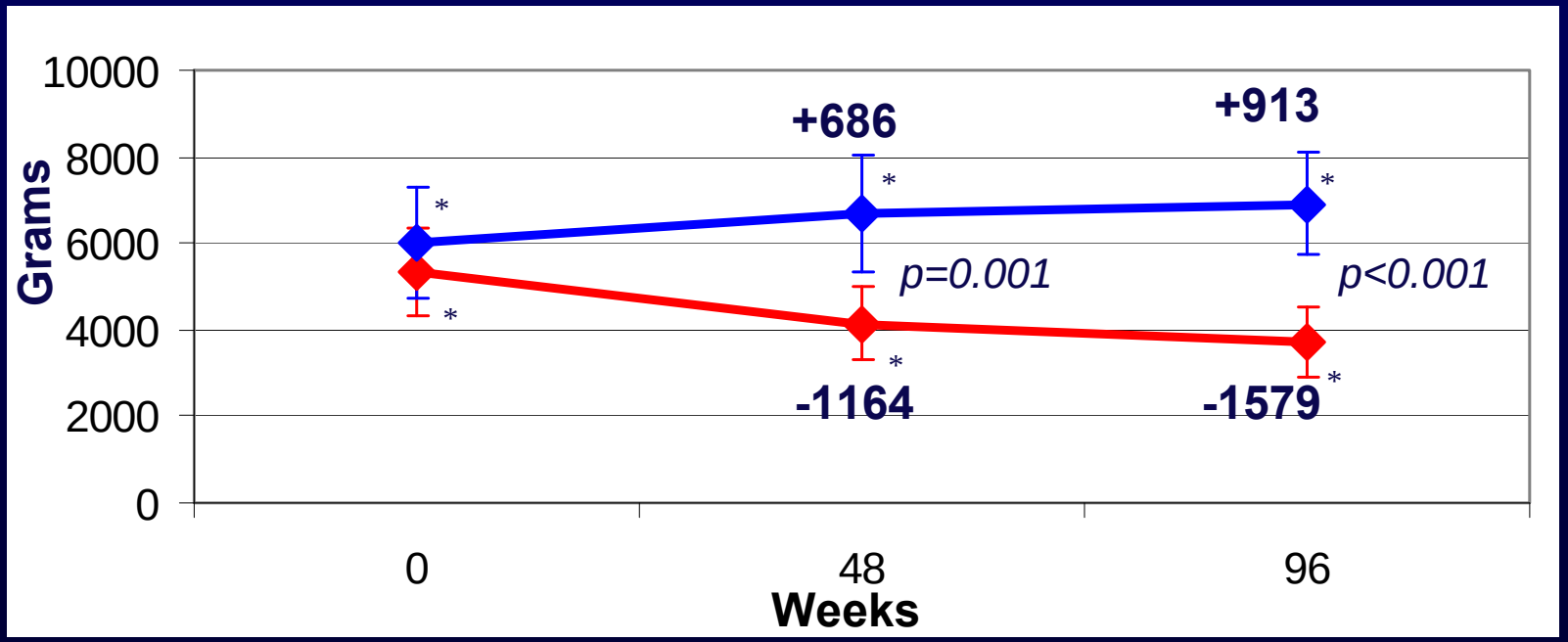
Time to first severe drug-related AE



MaxCmin1: Dragsted *et al*, JID, 2

Stavudine but not abacavir associated with depletion of limb fat

Changes in limb fat by dexa scan



Nº pts	57	57	57

*** 95% CI**

ITT= intent-to-treat analysis

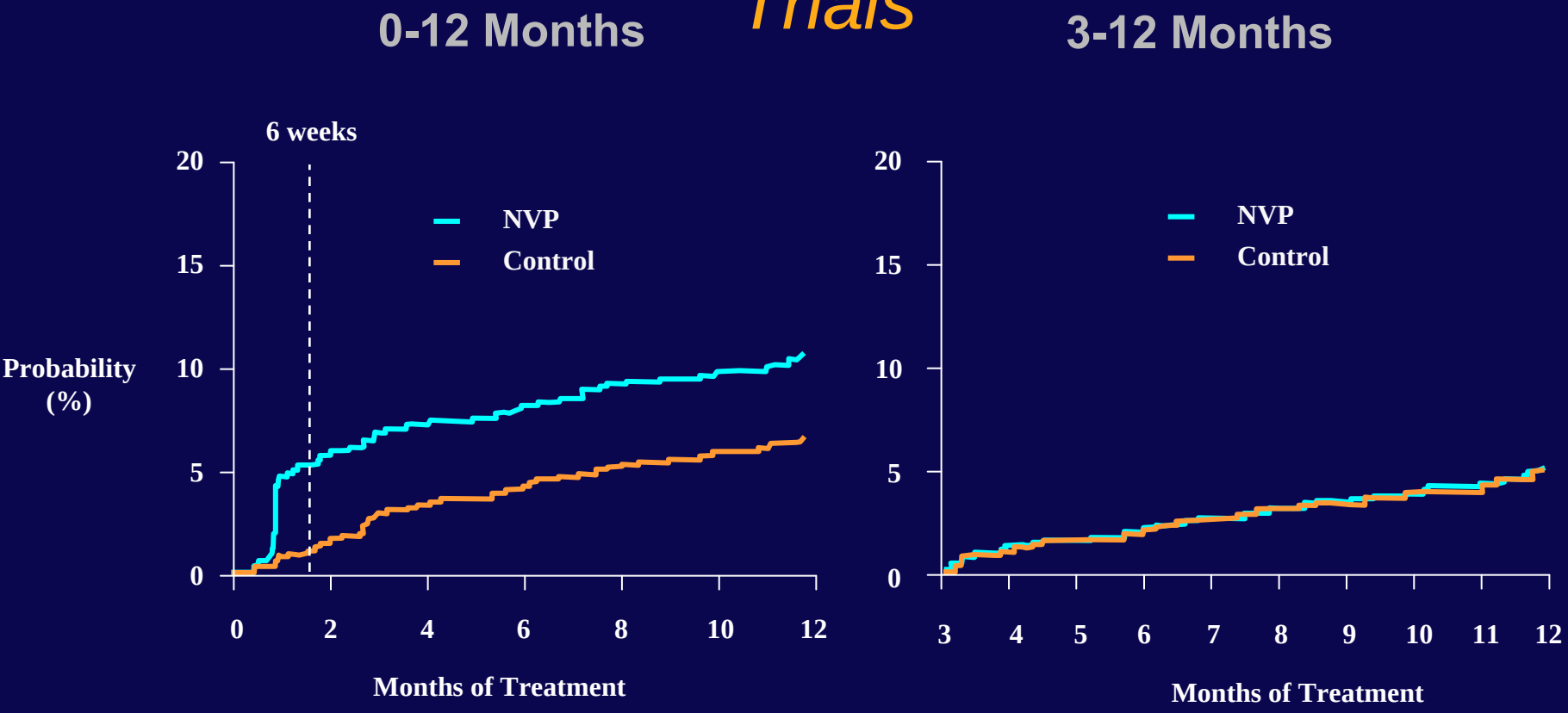
FIRST: Shlay *et al*. JAIDS 2005;38:147

Abacavir hypersensitivity reaction (HSR) and HLA haplotype

- Presence of HSR and HLA-B*5701 status:
  - B*5701 pos: 14/18 (78%)
  - B*5701 neg: 4/167 (2%)
- Reduction of prevalence of HSR by denying patients with HLA-B*5701, HLA-DR7, HLA-DQ3 abacavir:
  - 9% to 2.5%

Mallal *et al*, Lancet 2002

Time to Onset of *Asymptomatic* ALT or AST >5 x ULN on NVP in *Controlled Trials*



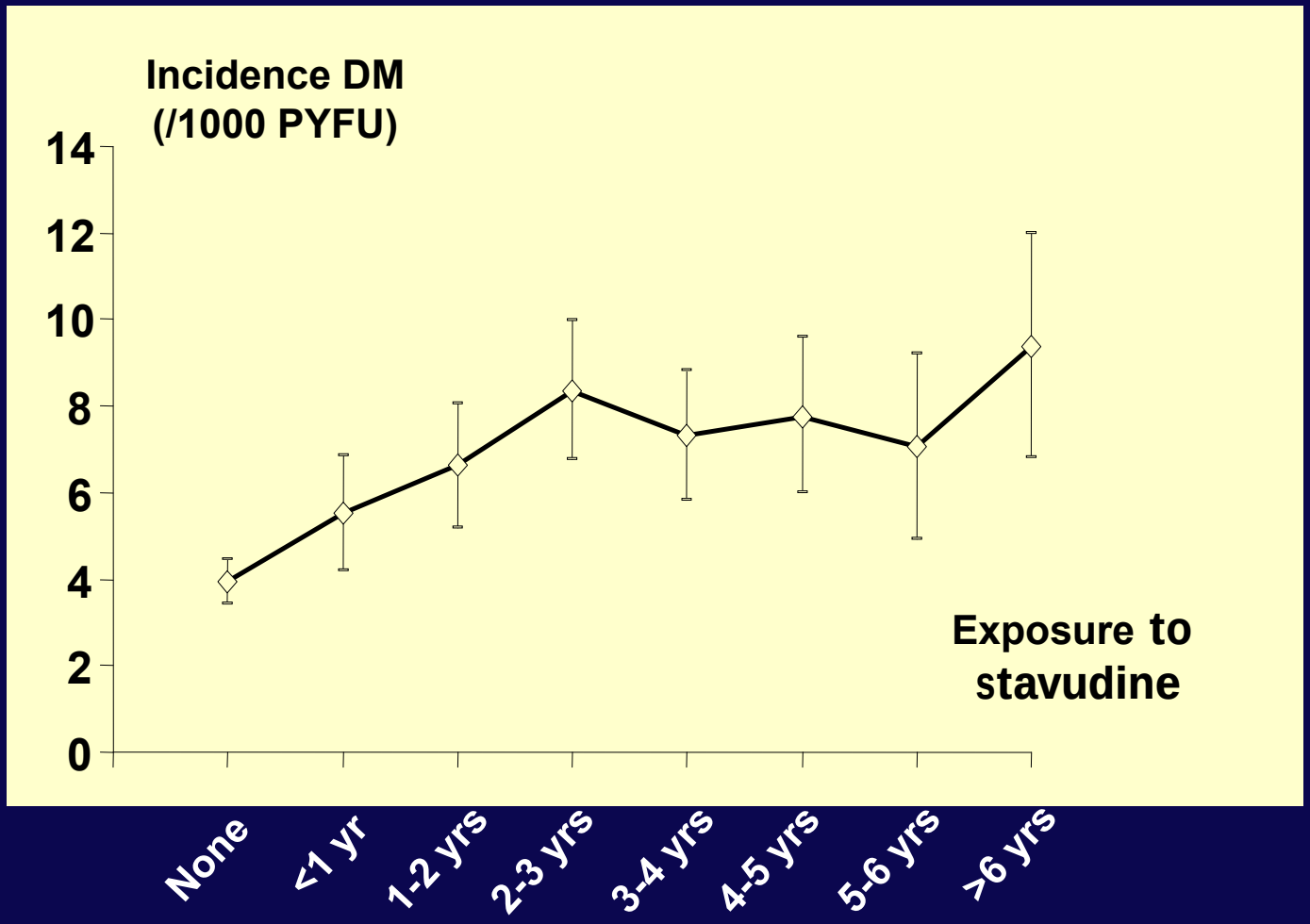
NVP (n = 1731) **Control (n = 1912)**

Stern JO *et al*. XIV IAS Conference, 2002

The ”conundrum” of using cART

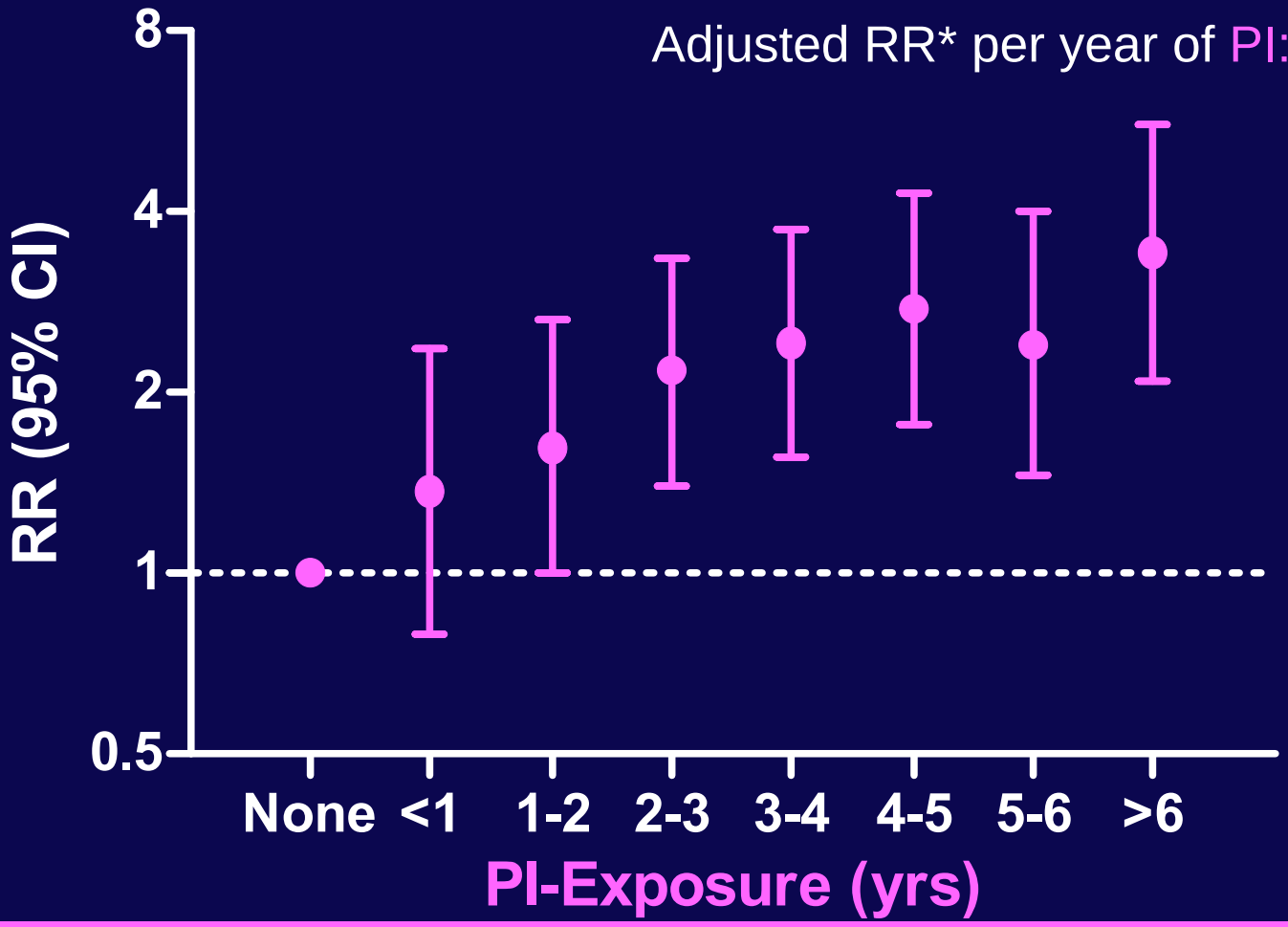
- Allow persons to get older
  - De-masking other HIV-associated disease processes
    - eg. HBV, HCV
  - Allow the normal aging process to manifest itself clinically
    - dementia, cancers, CVD, hypertension, diabetes, body shape changes, etc
  - Exacerbate AEs of cART that interacts with the normal aging process

Incidence of DM and exposure to stavudine



D:A:D study: deWit *et al*. Diabetes Care 200

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

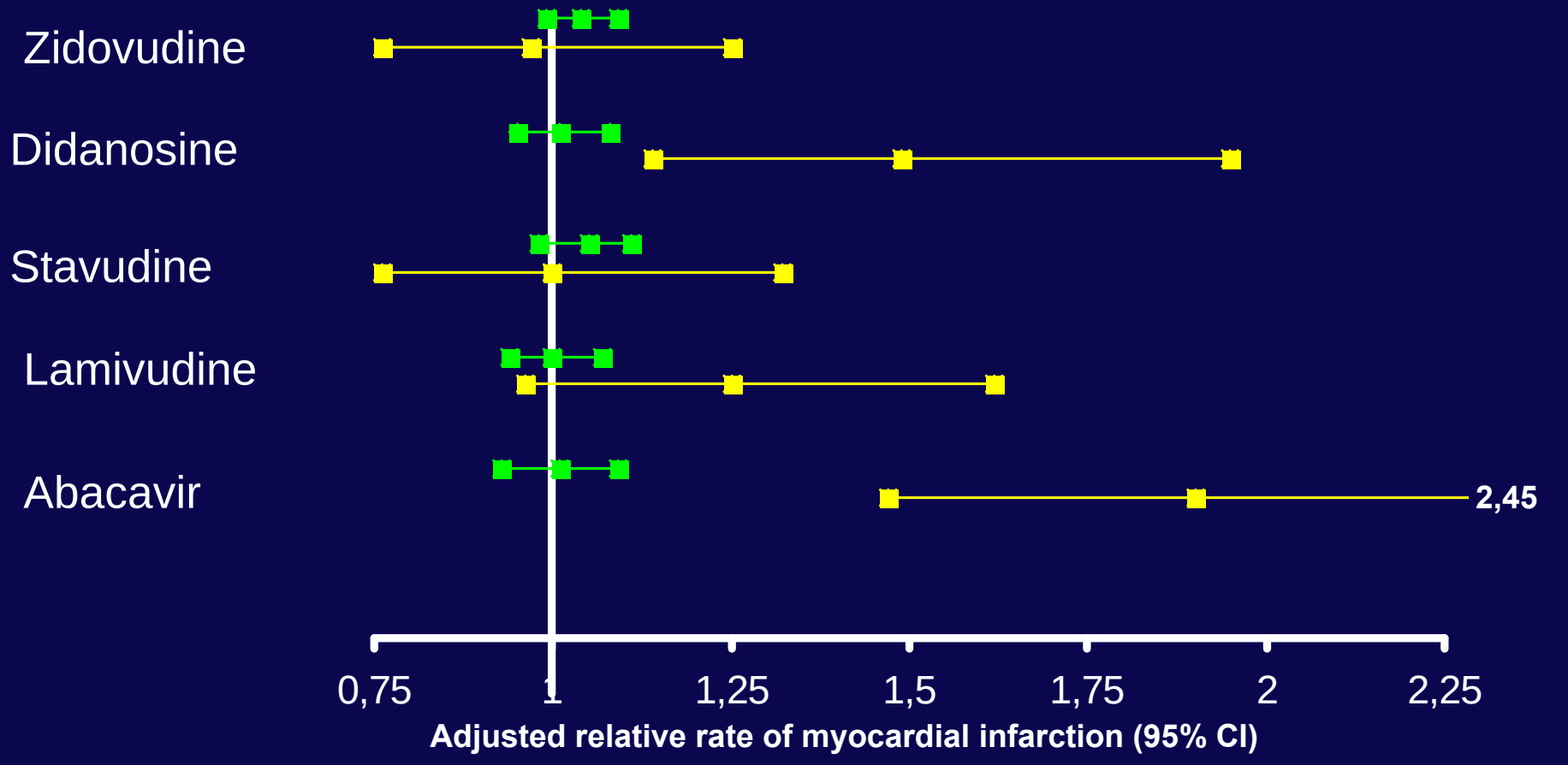


★: Adjusted for sex, age, cohort, calendar year, prior CVD, family history of CVD, smoking, body-mass index, NNRTI exposure

D:A:D study: Friis-Møller *et al*, NEJM 200

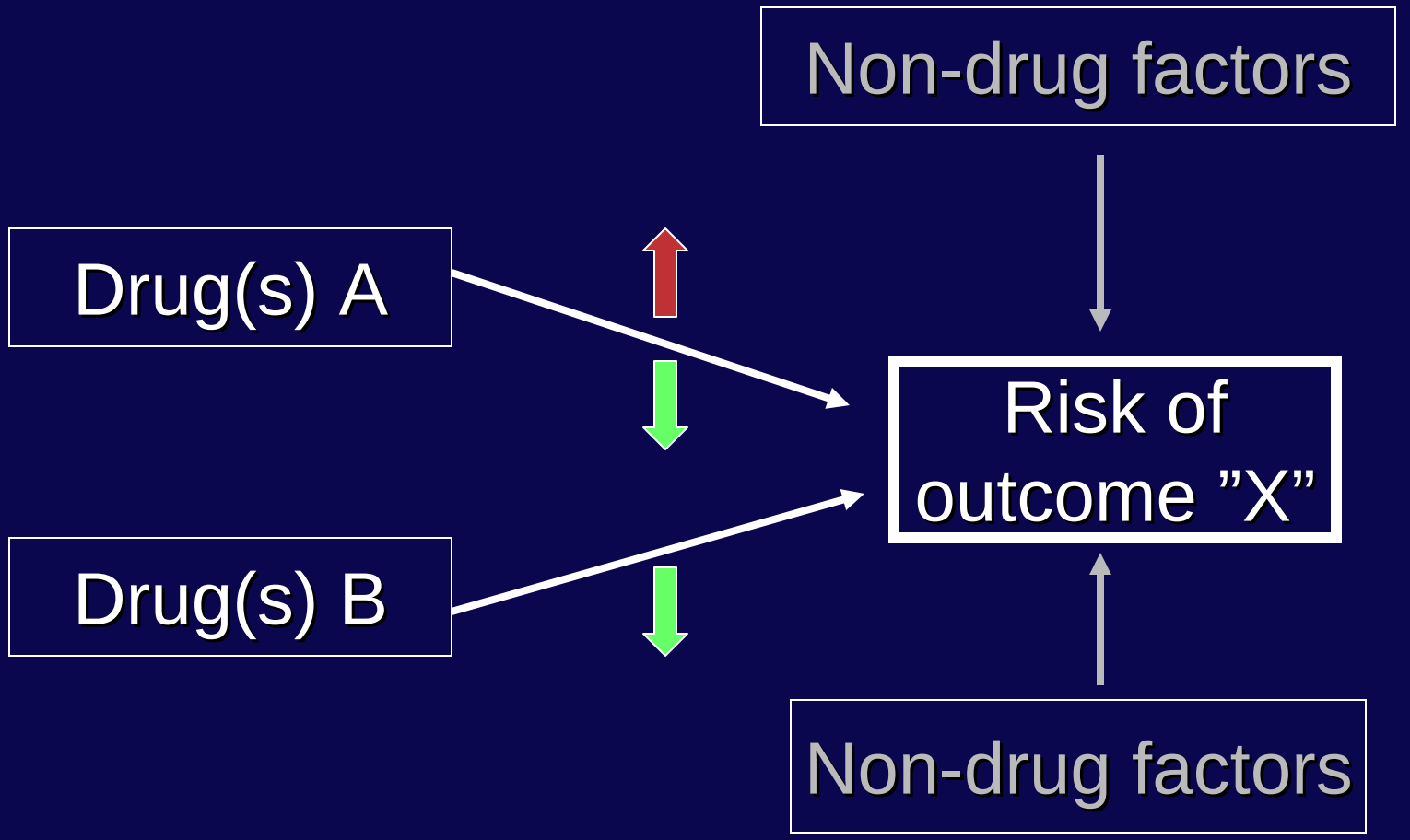
NRTIs and risk of myocardial infarction

cumulative and current/recent use

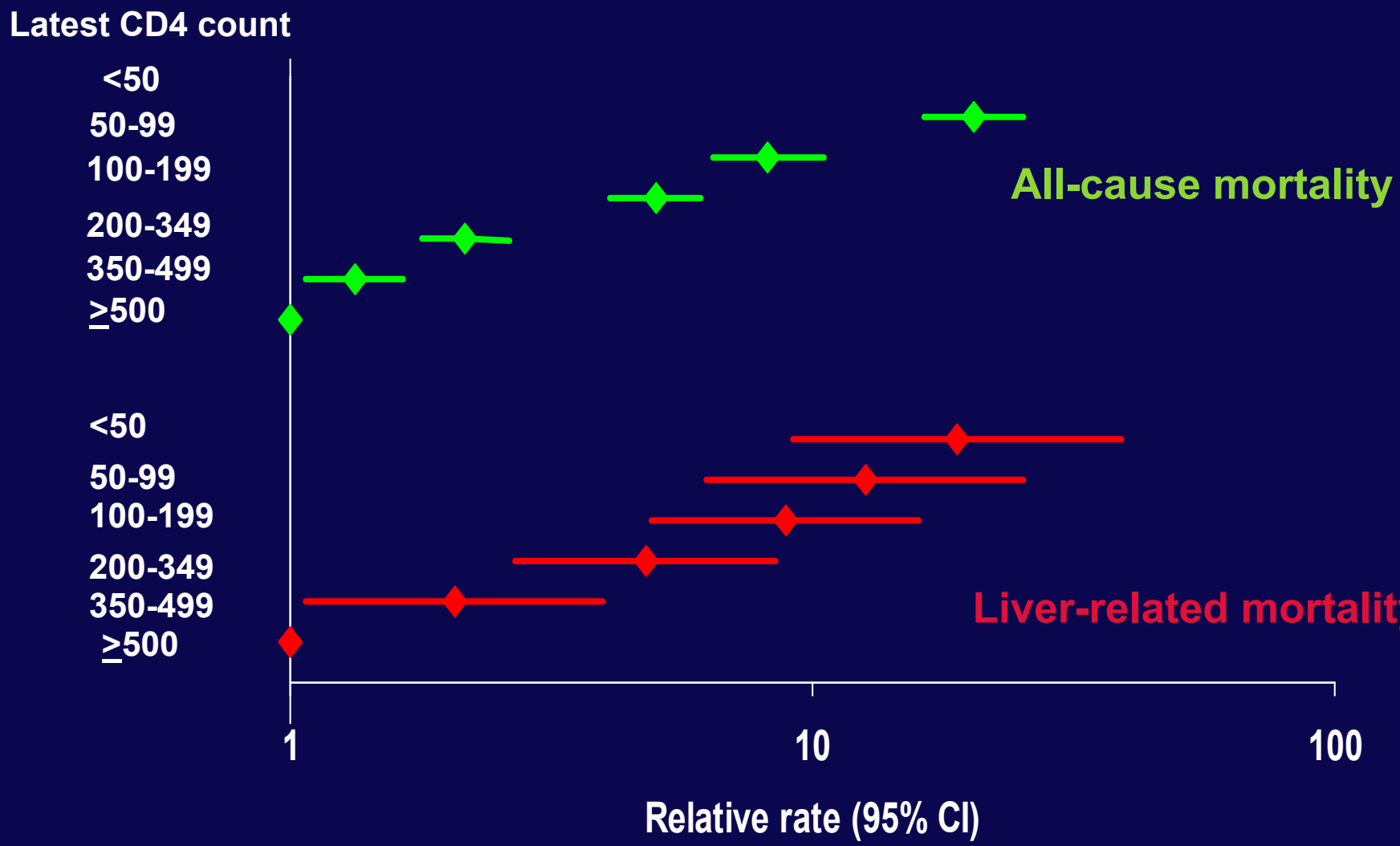


D:A:D: Sabin *et al*, 15th CROI 200

Disentangling a drug effect



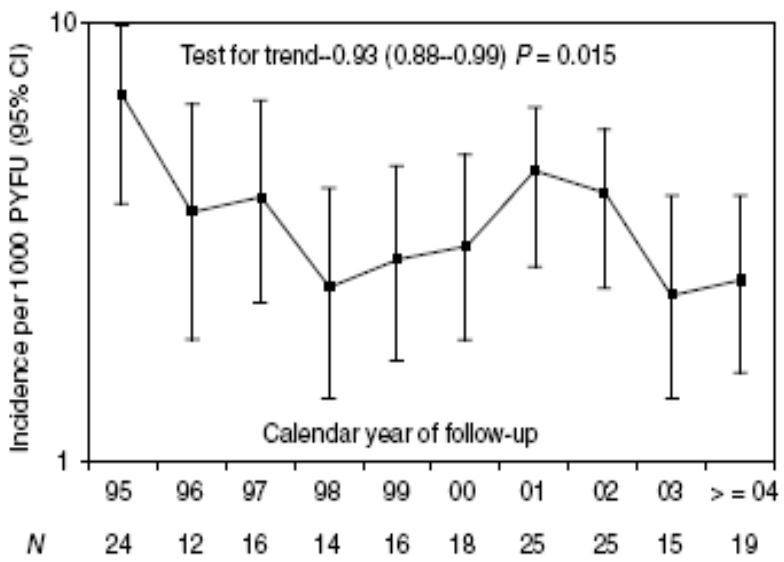
Deaths in D:A:D
Multivariable relationships with death rate
Latest CD4 count



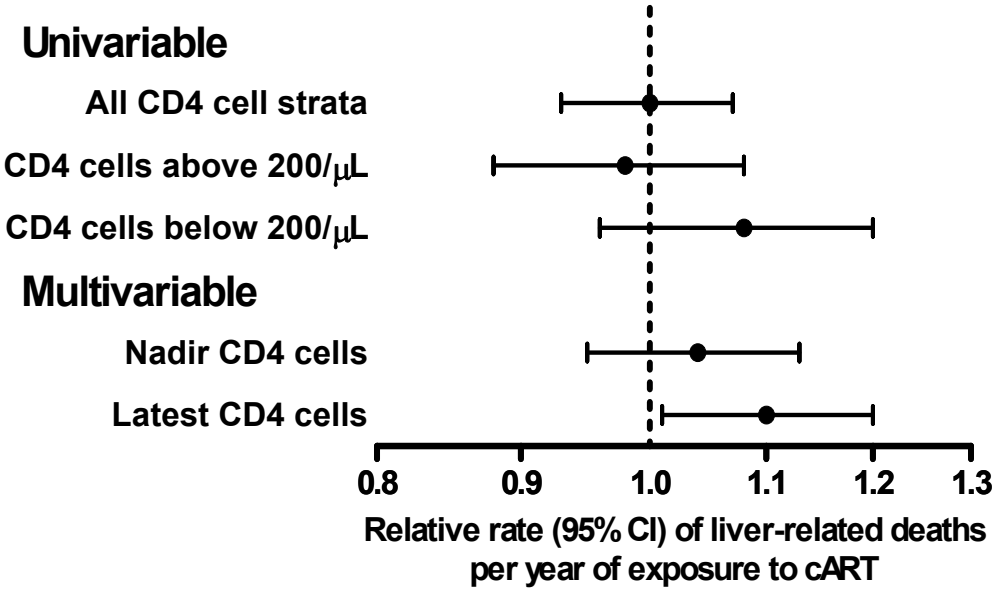
D:A:D study: Weber *et al*, Arch Intern Med 2006

Relationship between combination antiretroviral therapy and liver-related deaths: benefits and potential harm

Calendar time trends*



Risk per year of exposure to ART in recent years**

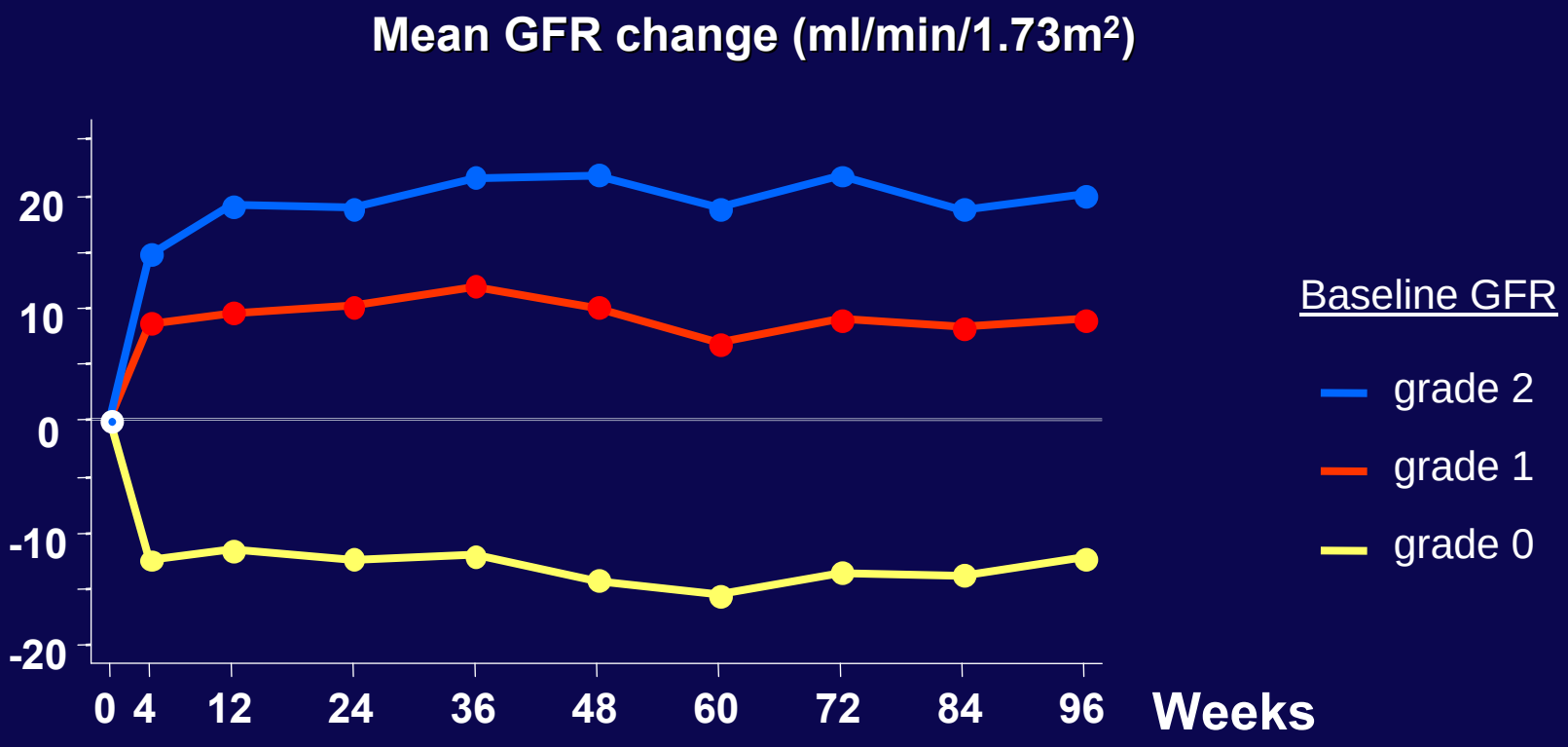


** EuroSIDA study: Mocroft *et al*, AIDS 2005

* D:A:D study: Weber *et al*, 13th CROI, 2006

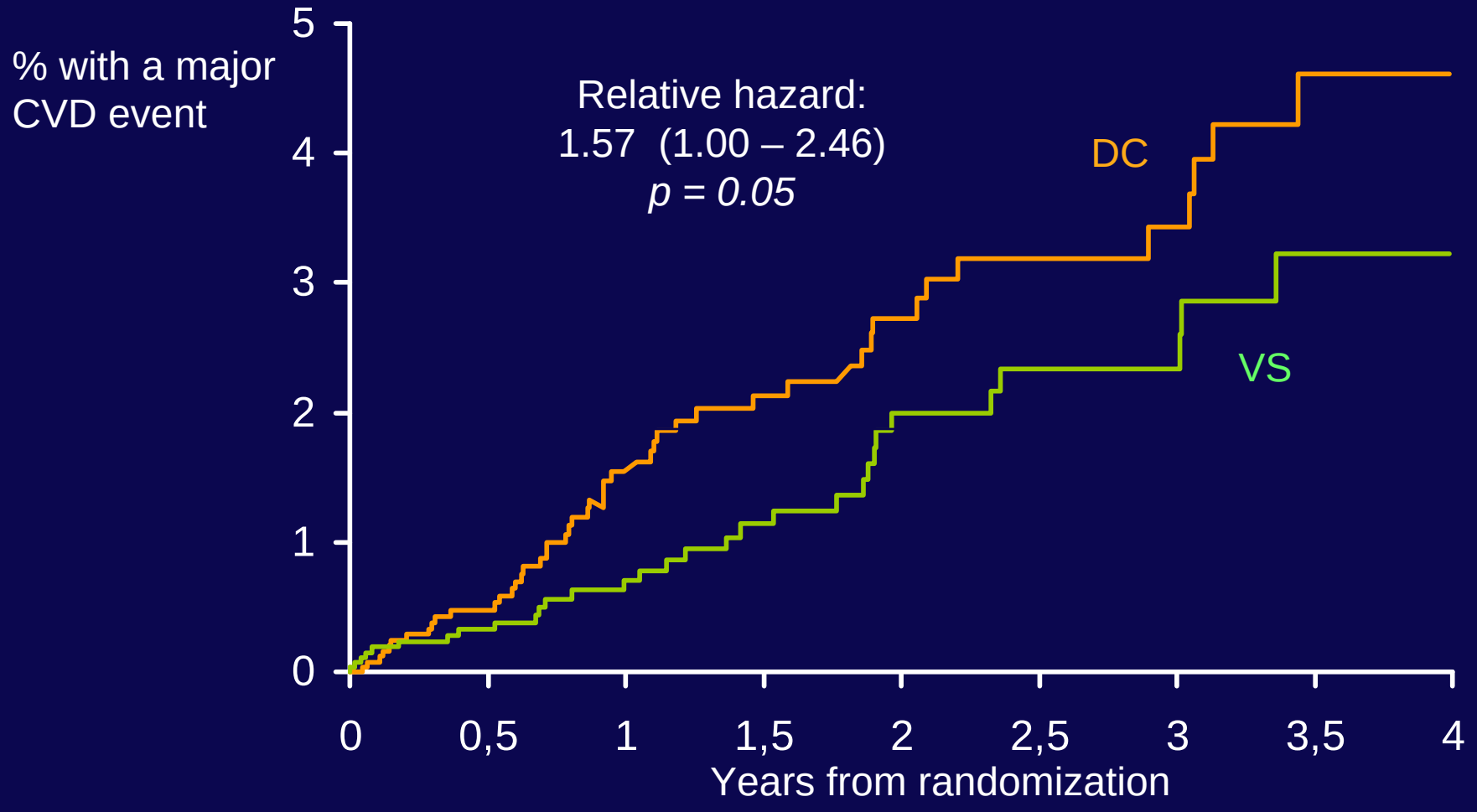
Glomerular filtration rate (GFR) over time by baseline GFR:

Impaired baseline GFR improved



DART: Reid *et al*. XVI IAC (2006). Abst. THAB0105

Risk of major CVD events in SMART: intermittent (DC) vs continous (VS) ART

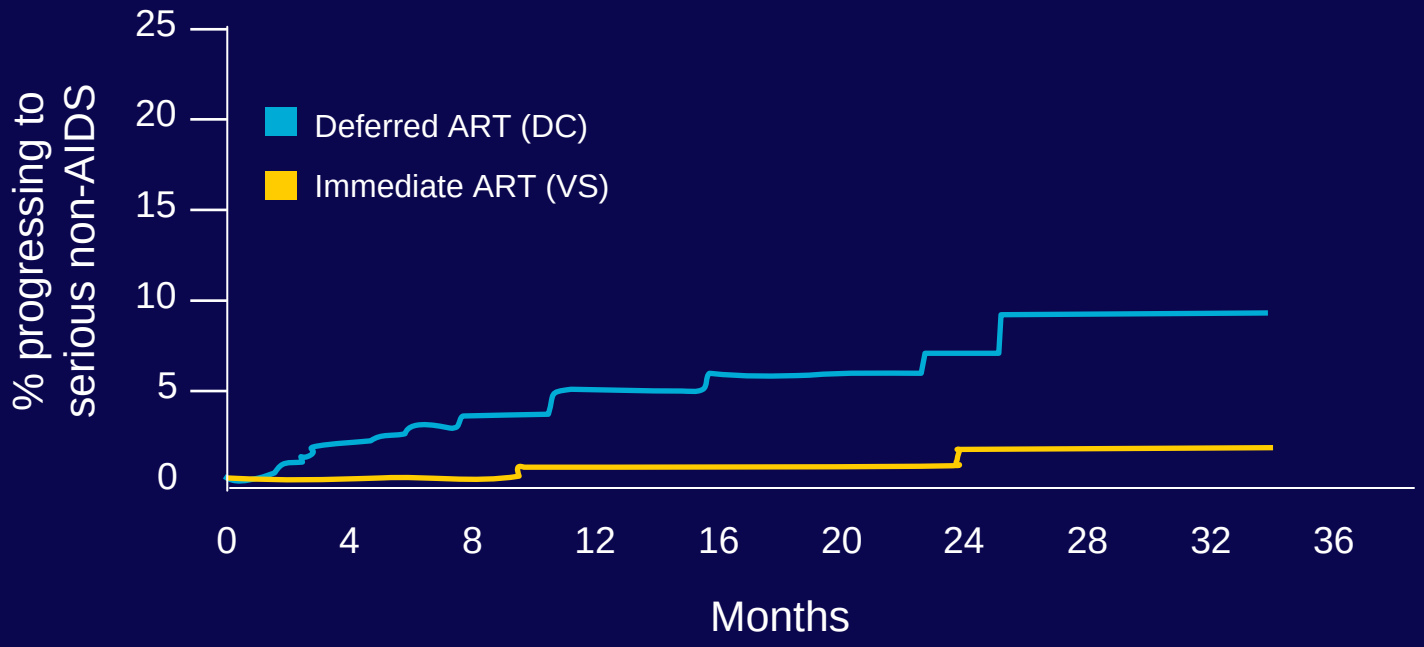


DC	2752	1306	713	379	10
VS	2720	1292	696	377	10

SMART/CVD-lipid: Phillips *et al*, AVT 2008

Subgroup in SMART either naïve or not currently on ART: early versus deferred

Serious Non-AIDS



No. at risk

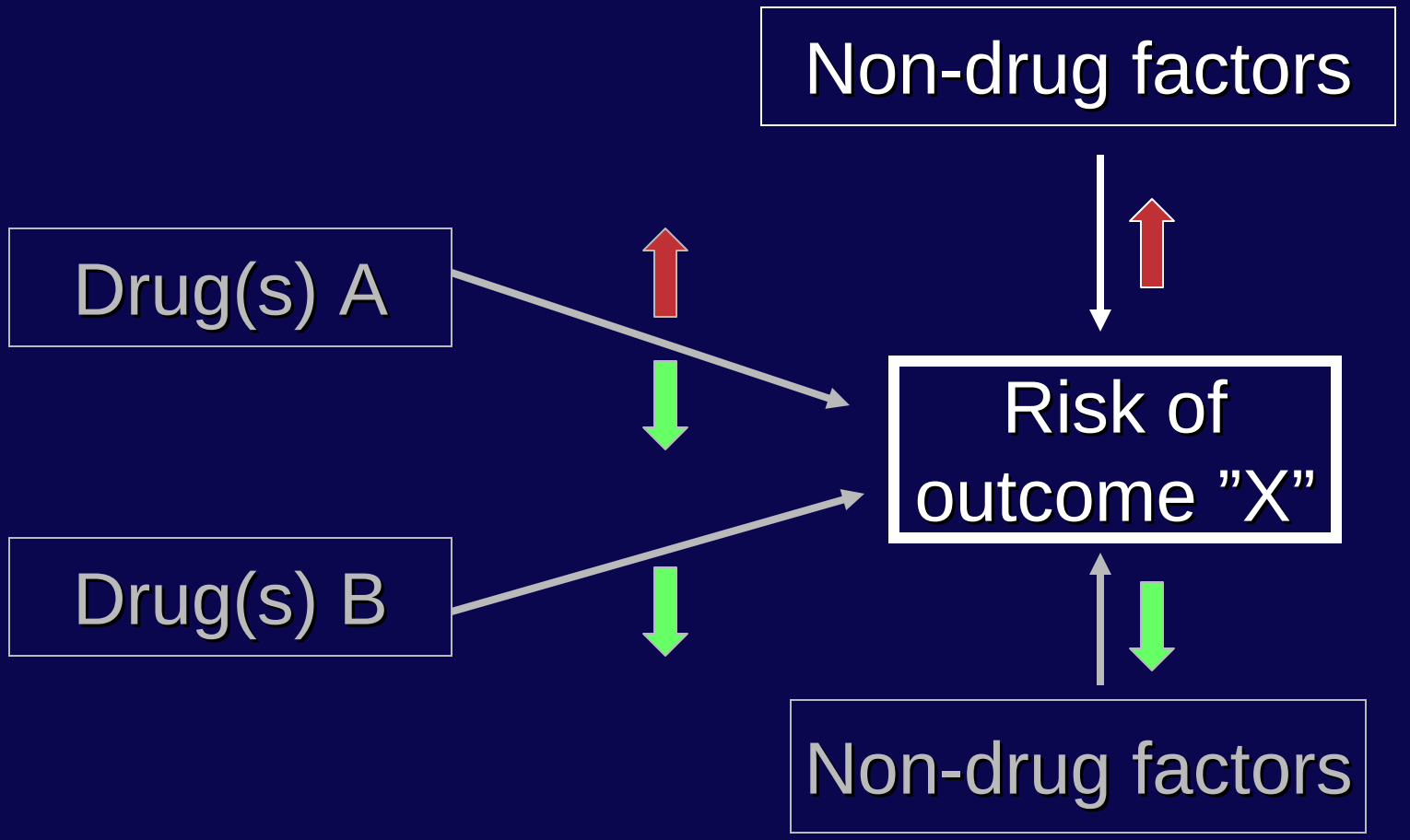
Def. ART	228	189	159	128	96	73	59	36	27	24
Imm. ART	249	210	180	145	125	106	80	58	44	36

SMART Study Group. J Inf Dis (in press)

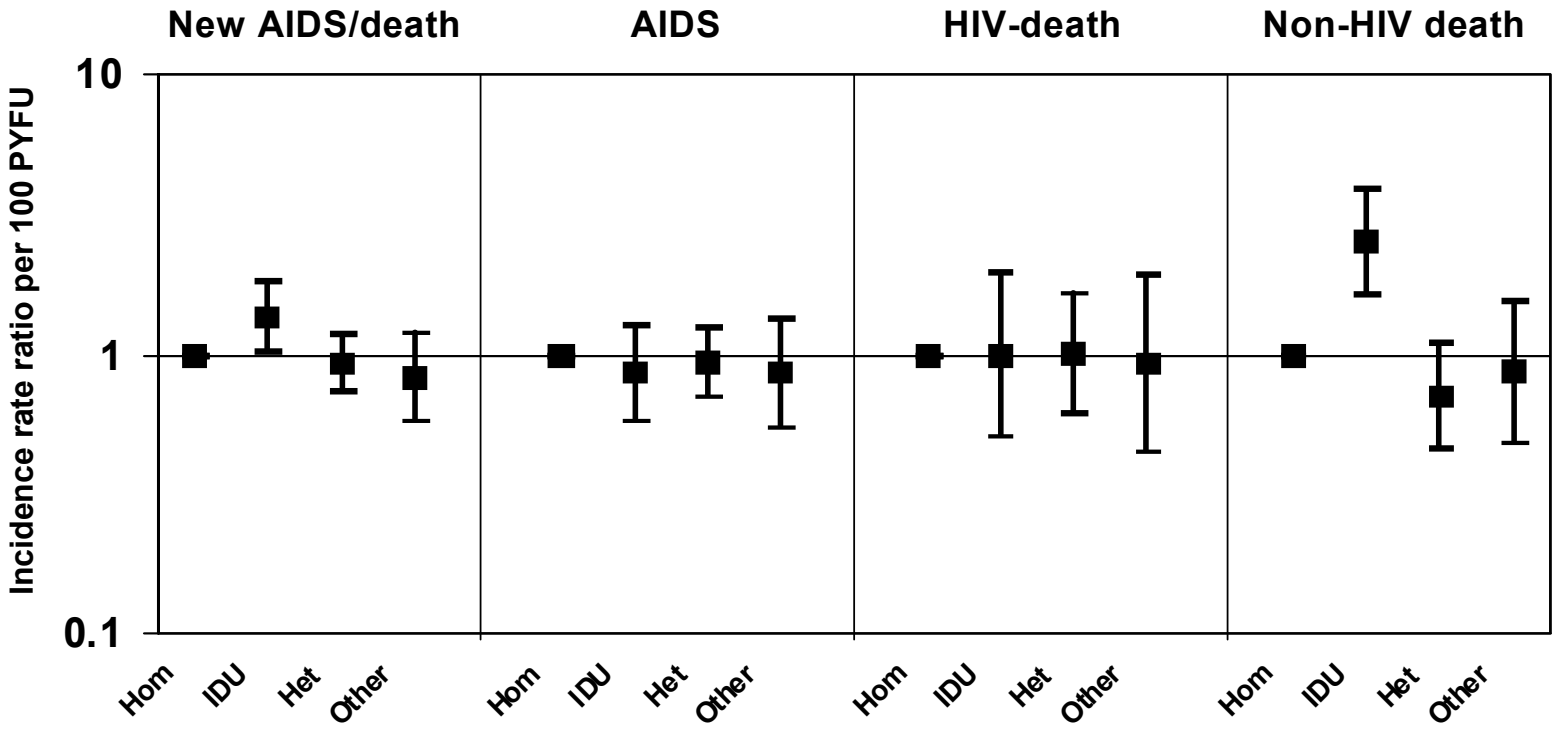
Serious non-AIDS events:
complication of using ART but also from untreated HIV

- Decompensated liver disease
- End-stage renal disease
- Cardiovascular disease
- Non-AIDS defining cancers

Disentangling a drug effect



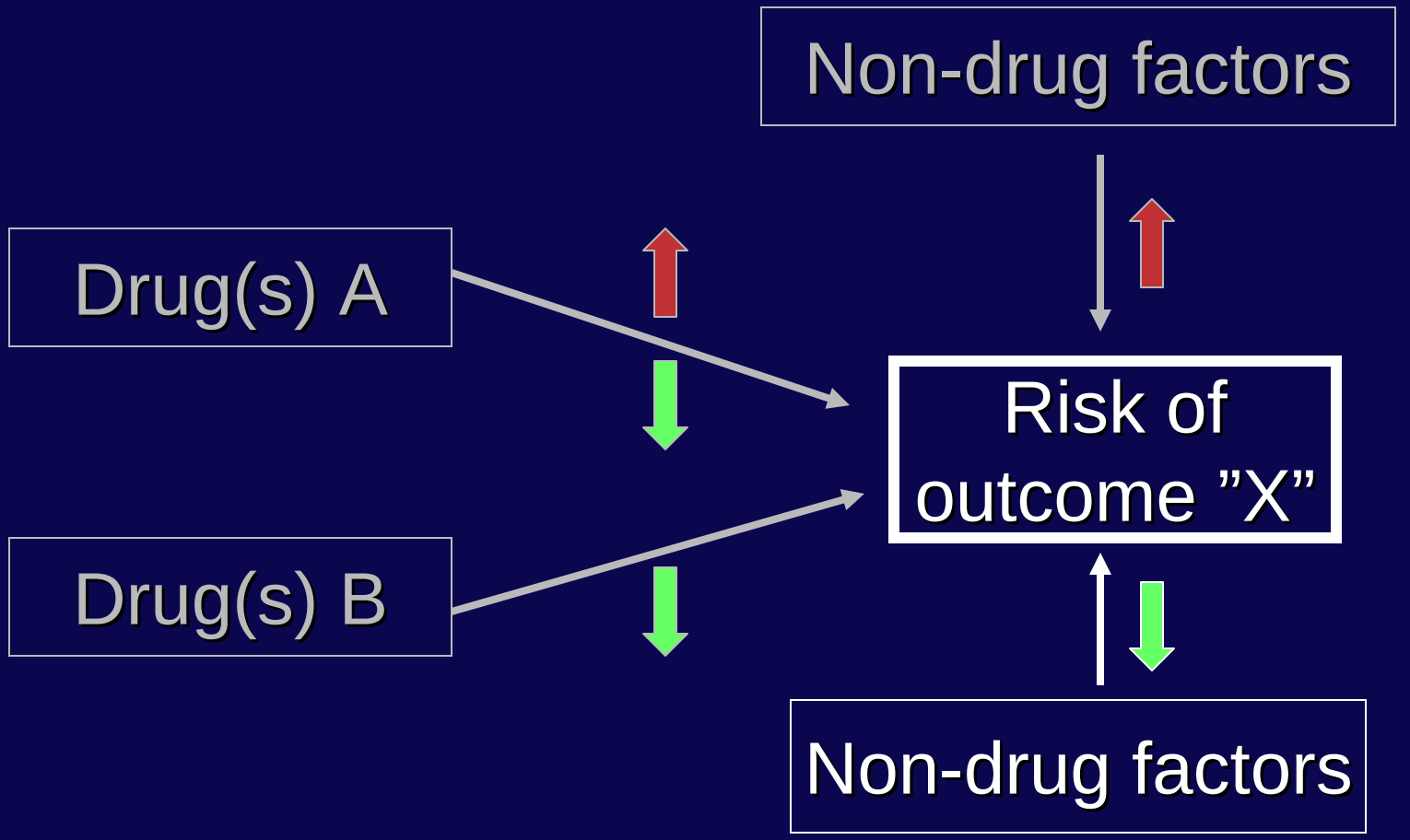
Adjusted incidence rate ratios of new AIDS/death, AIDS, HIV or non-HIV death after starting HAART



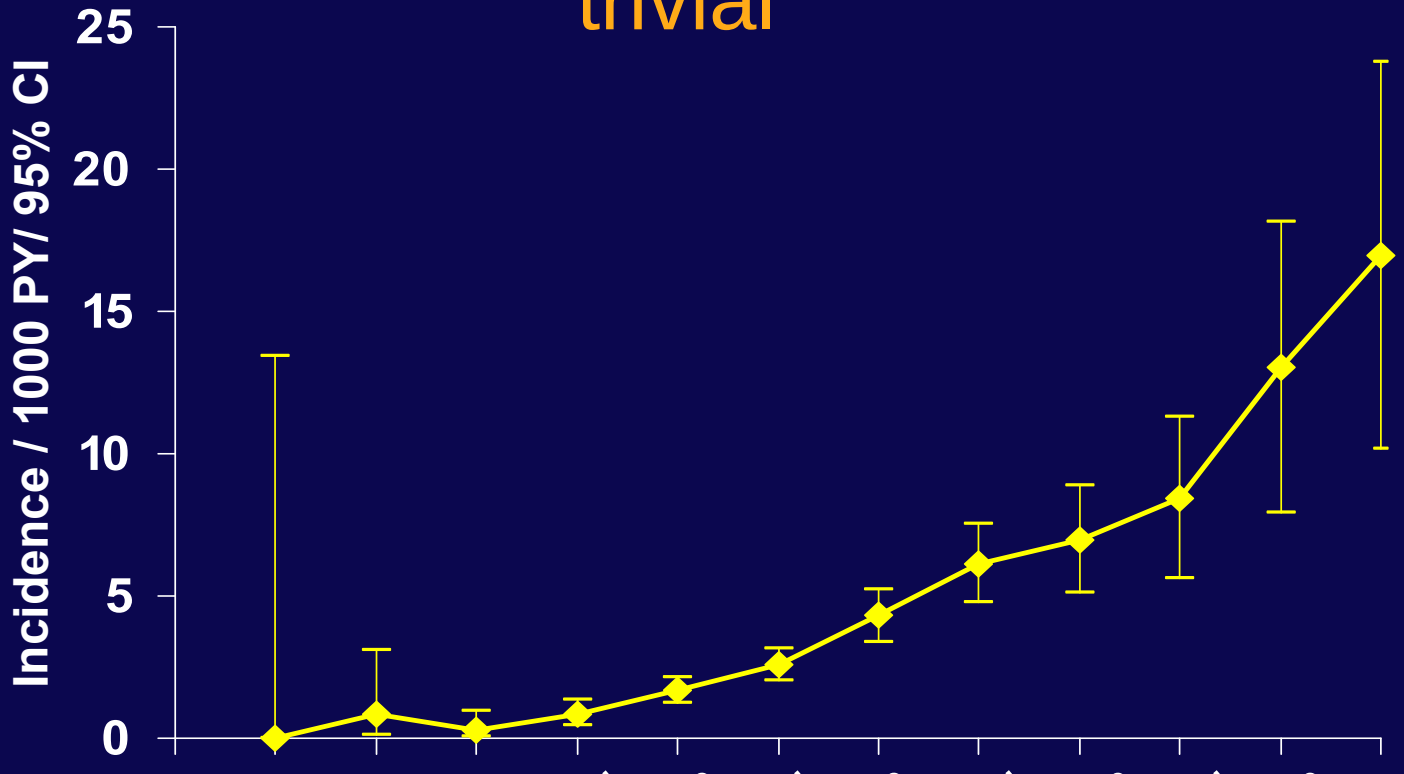
Adjusted for Age, AIDS, prior ARV treatment, HAART regimen started, Hepatitis C status, date started HAART and both CD4 and viral load as time-updated variables

EuroSIDA: Mocroft *et al*, AIDS 2005

Disentangling a drug effect



Young age makes adverse influence on risk of myocardial infarction from using PI trivial



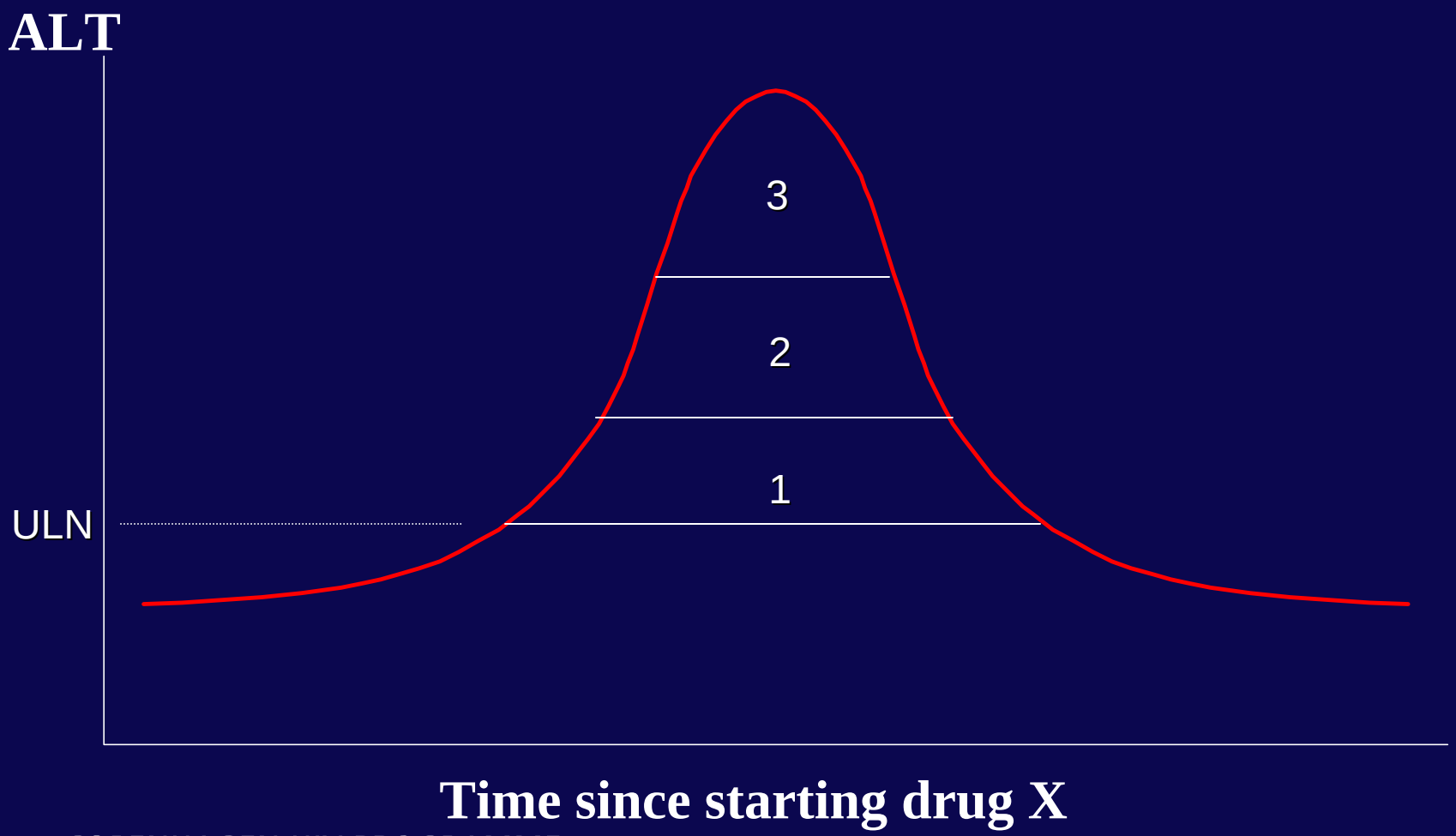
Age group	<20	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	>70	
Events	0	2	2	15	55	80	80	75	53	34	25	24	445
PYFU	275	2322	7408	18012	32551	30991	18600	12209	7583	4024	1916	1413	137310

✶: Adjusted for sex, age, cohort, calendar year, prior CVD, family history of

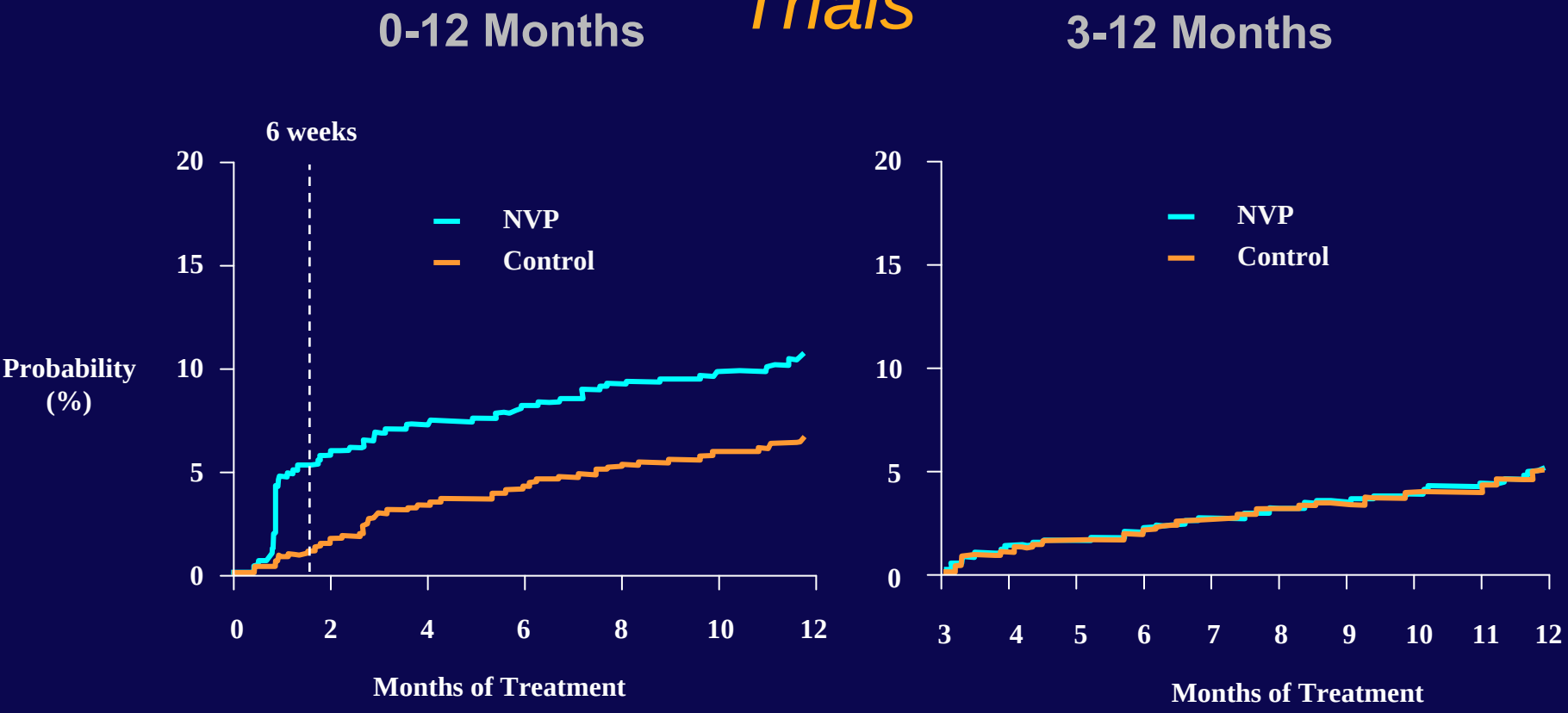
D:A:D study: Friis-Møller *et al*, NEJM, 2

Laboratory based AEs

Laboratory defined adverse effect endpoints: grading



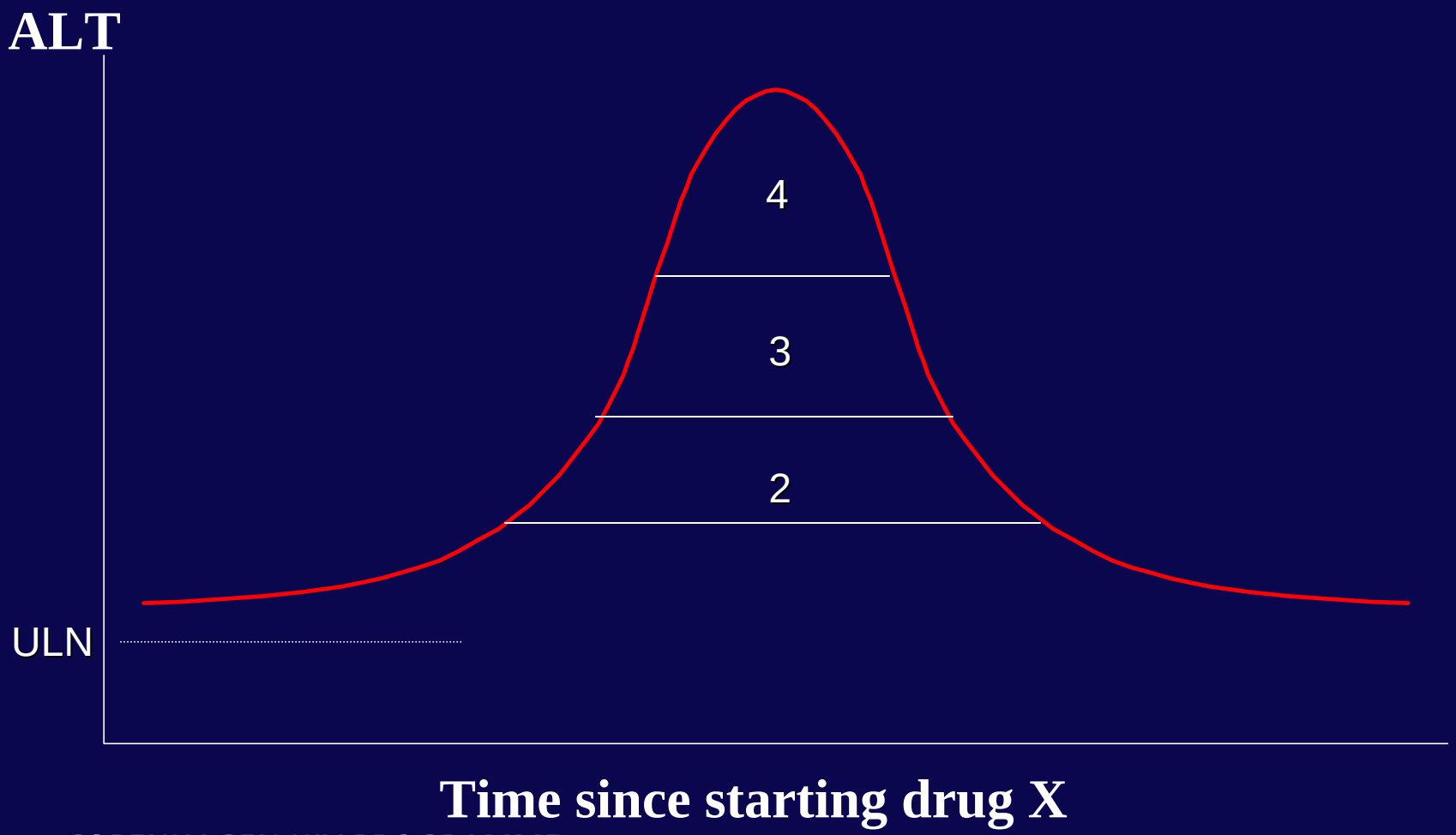
Time to Onset of *Asymptomatic* ALT or AST >5 x ULN on NVP in *Controlled Trials*



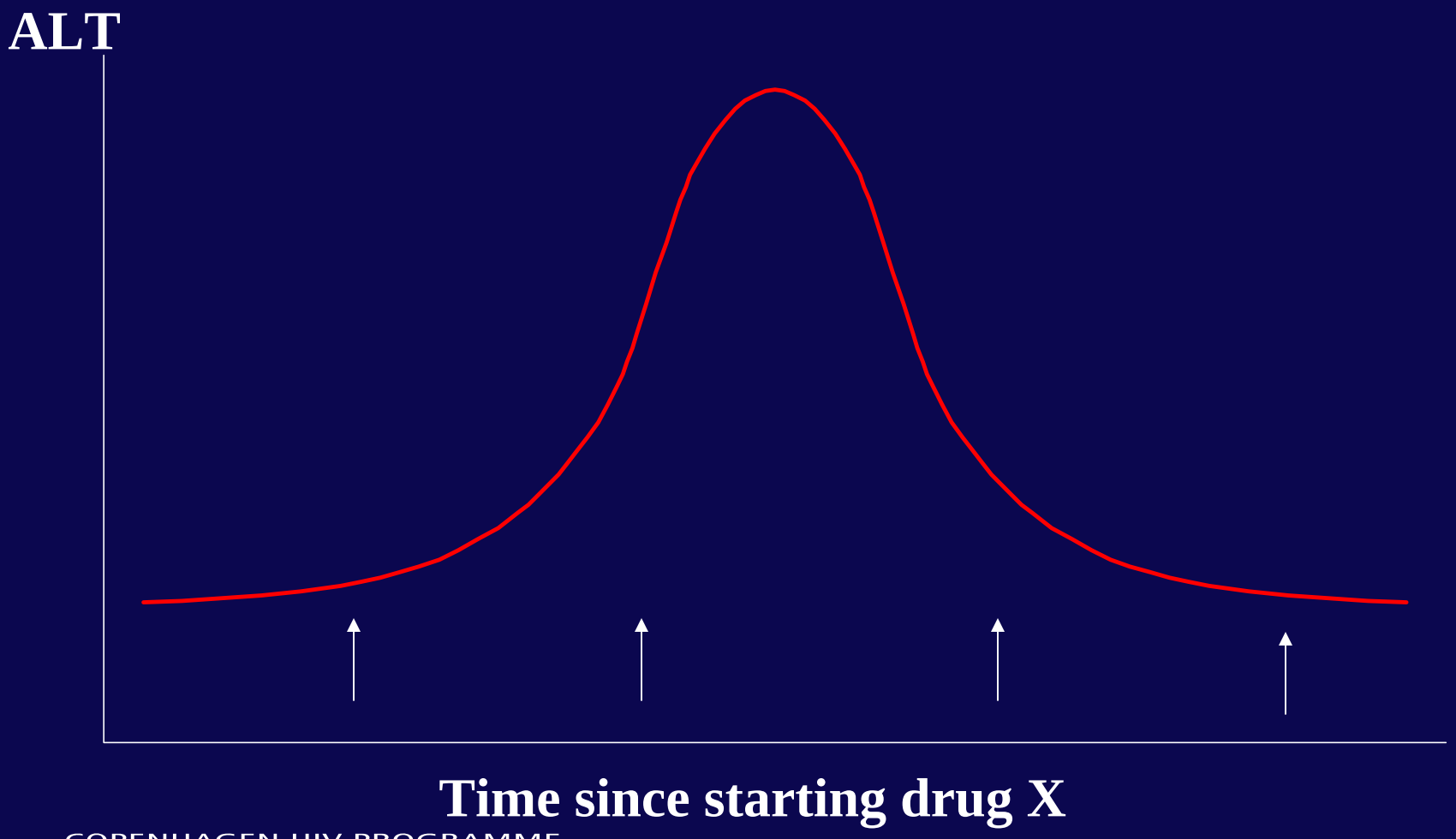
NVP (n = 1731) **Control (n = 1912)**

Stern JO *et al*. XIV IAS Conference, 2002

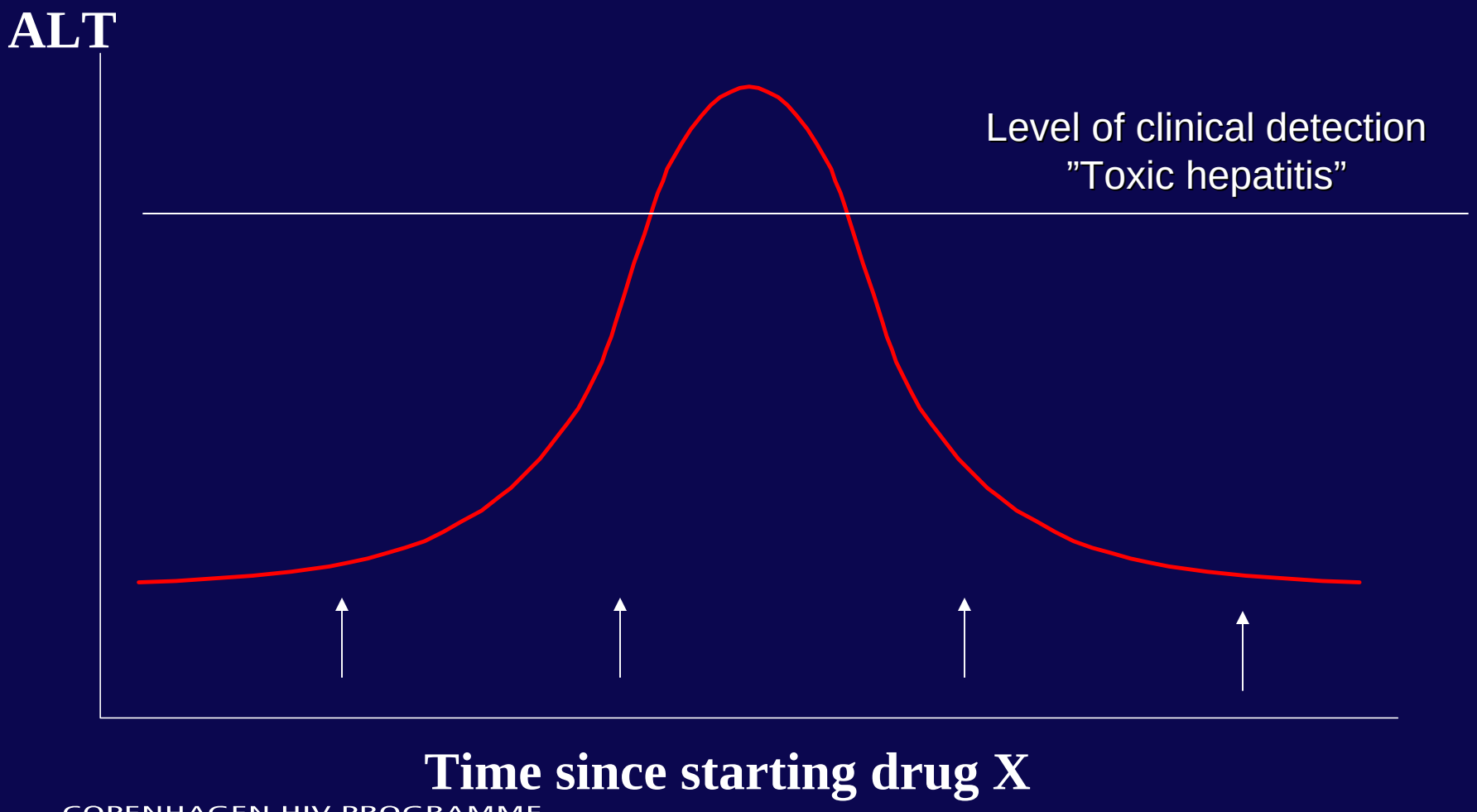
Laboratory defined adverse effect endpoints: already abnormal (e.g. viral hepatitis)



Laboratory defined adverse effect endpoints: timing of measurement



Laboratory defined adverse effect endpoints: clinical detectable consequences



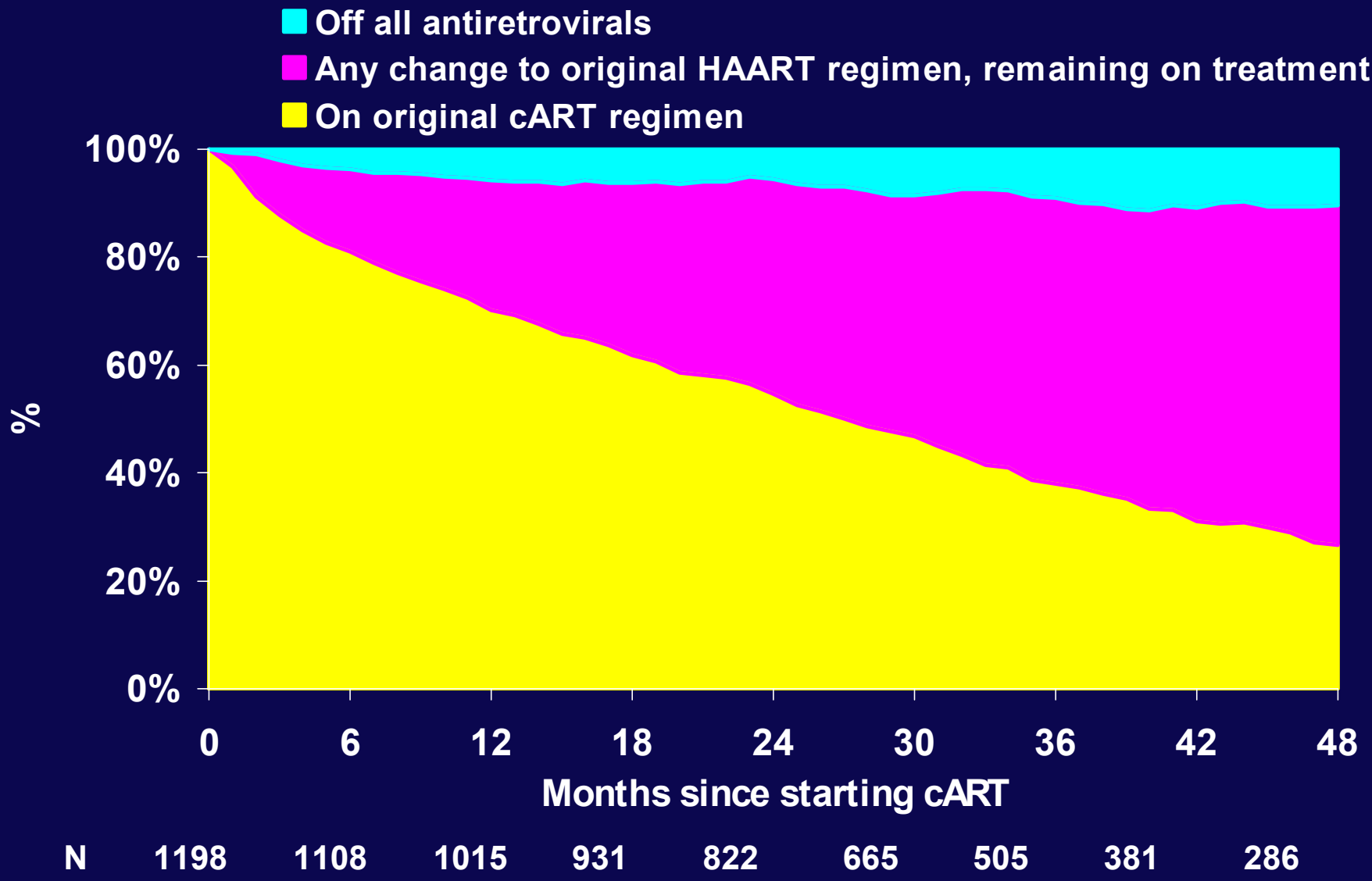
Critical issues in pharmacovigilance

- Prioritize collection of well defined events
  - Clear & simple case definition
  - Easy to ascertain & clinically important (to patient, his/her provider and treatment programme)
    - Severe clinical disease (fatal or non-fatal)
    - Reasons for treatment switch
    - (laboratory defined endpoints)
  - Keep track of emergence relate to starting drug (early vs late)
- Have procedures in place to capture emerging problems
  - Spontaneous reporting (UMC)
  - Causes of death

Serious non-AIDS events:
complication of using ART but also from untreated HIV

- Decompensated liver disease
  - Liver (pre)coma or transplantation
- End-stage renal disease
  - Permanent dialysis or kidney transplantation)
- Non-AIDS defining cancers
  - Pathology reports or clinical obvious
- Cardiovascular disease
  - Dundee classification (WHO Monica)

Changes to a first combination ART regimen



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EuroSIDA: Mocroft et al, AIDS Research Hum Retro, 2005

Quality versus quantity

Summary

- ARVs = millions of life-years gained
- All ARV induces AEs
- All AEs are not induced by ARVs
- PV system
  - Events: Clinical important, easy to define & ascertain
    - Keep it simple but consistent and harmonised
  - Keep things in perspective
    - Frequency
    - Benefits