Rigshospitalet

FACULTY OF HEALTH SCIENCES
UNIVERSITY OF COPENHAGEN

Centre for Health + Infectious Disease Research

WHO Collaborating Centre on HIV and Viral Hepatitis

Cohorts; past, present and future

BHIVA, 15th November 2013

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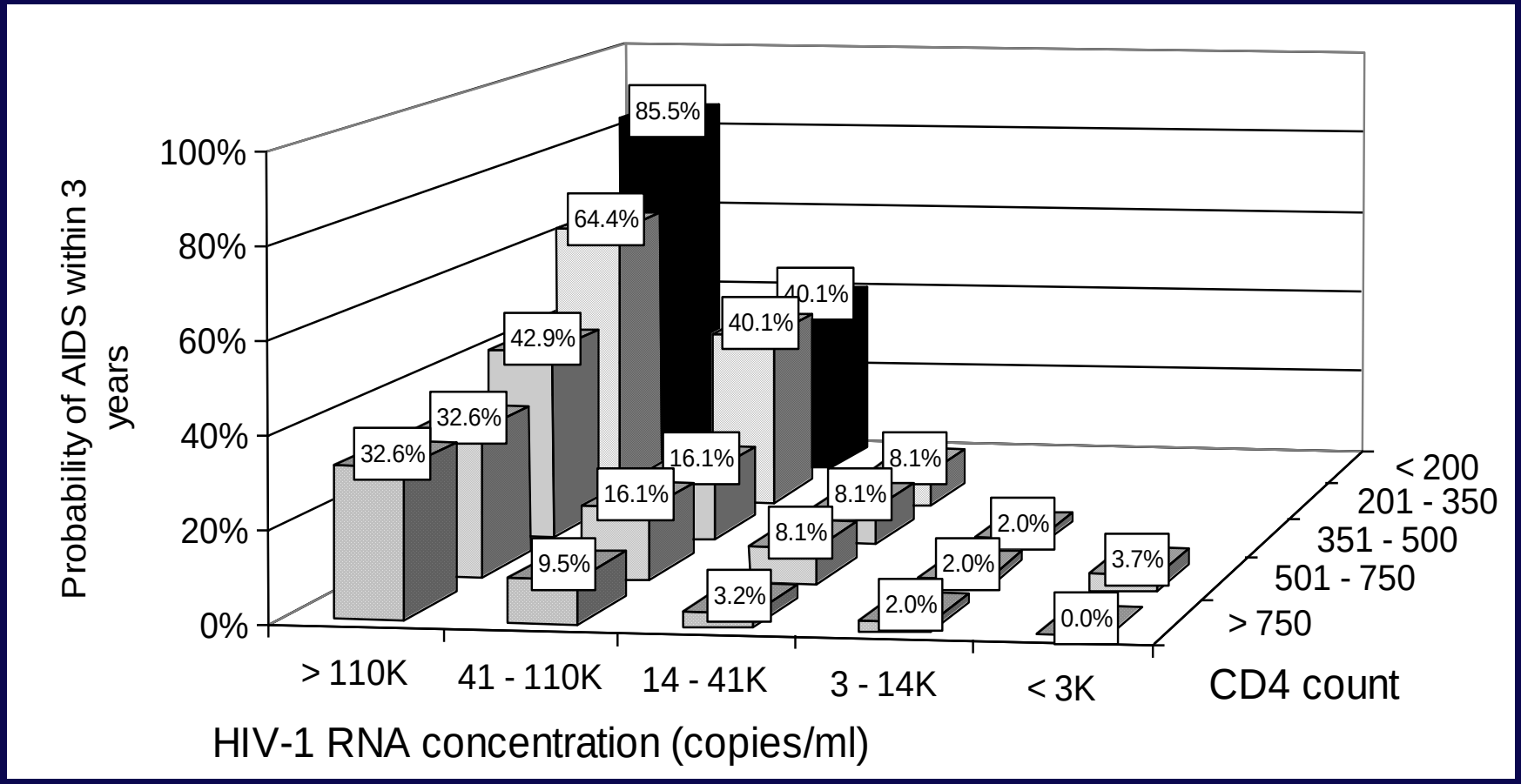
Department of Infectious Diseases, Rigshospitalet,
University of Copenhagen
Denmark

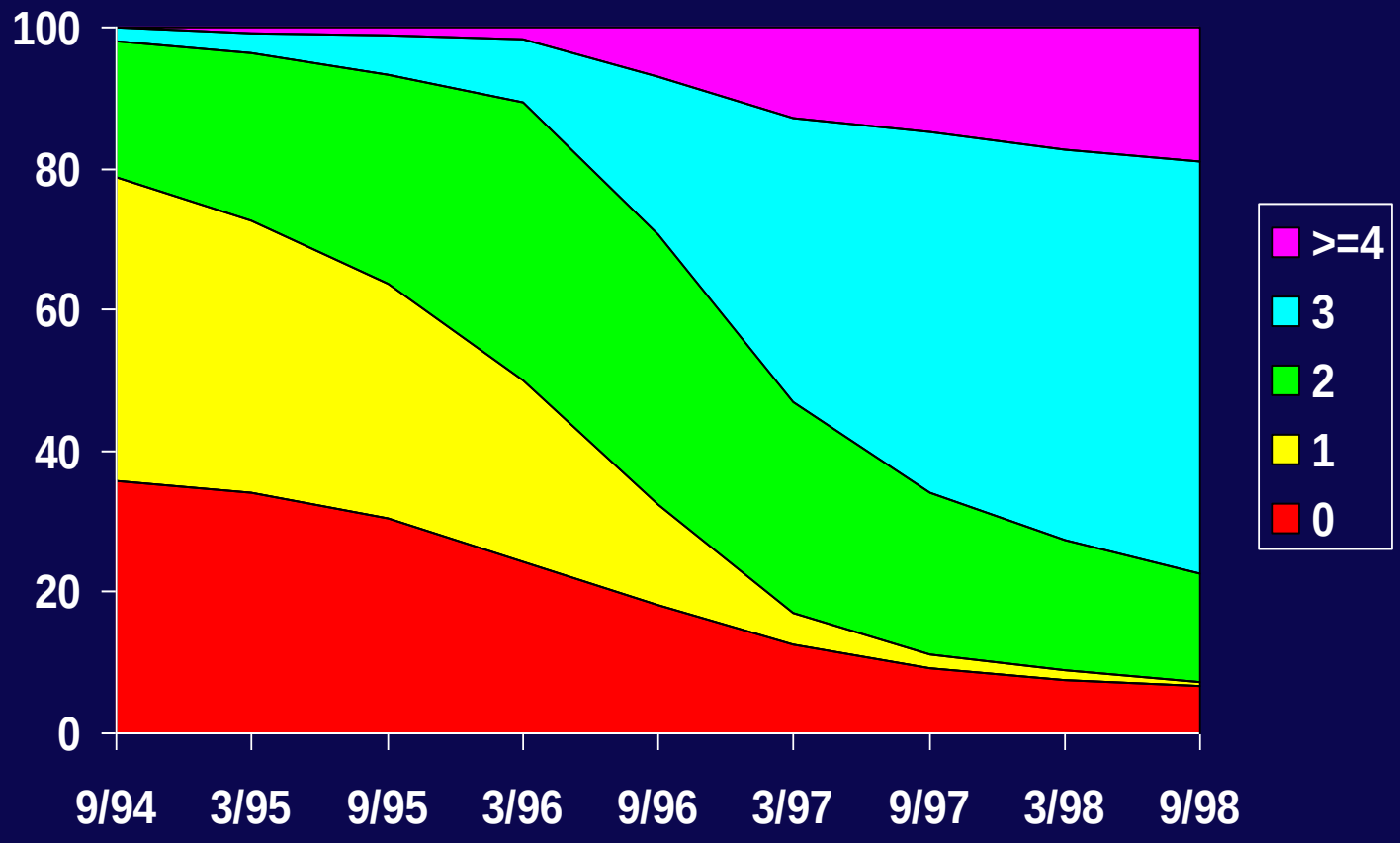
Prognosis without ART: interplay between quantity of CD4 and HIV-RNA



3-year probability of AIDS in 1604 men enrolled in the Multicenter AIDS Cohort Study (MACS) 1984-1985

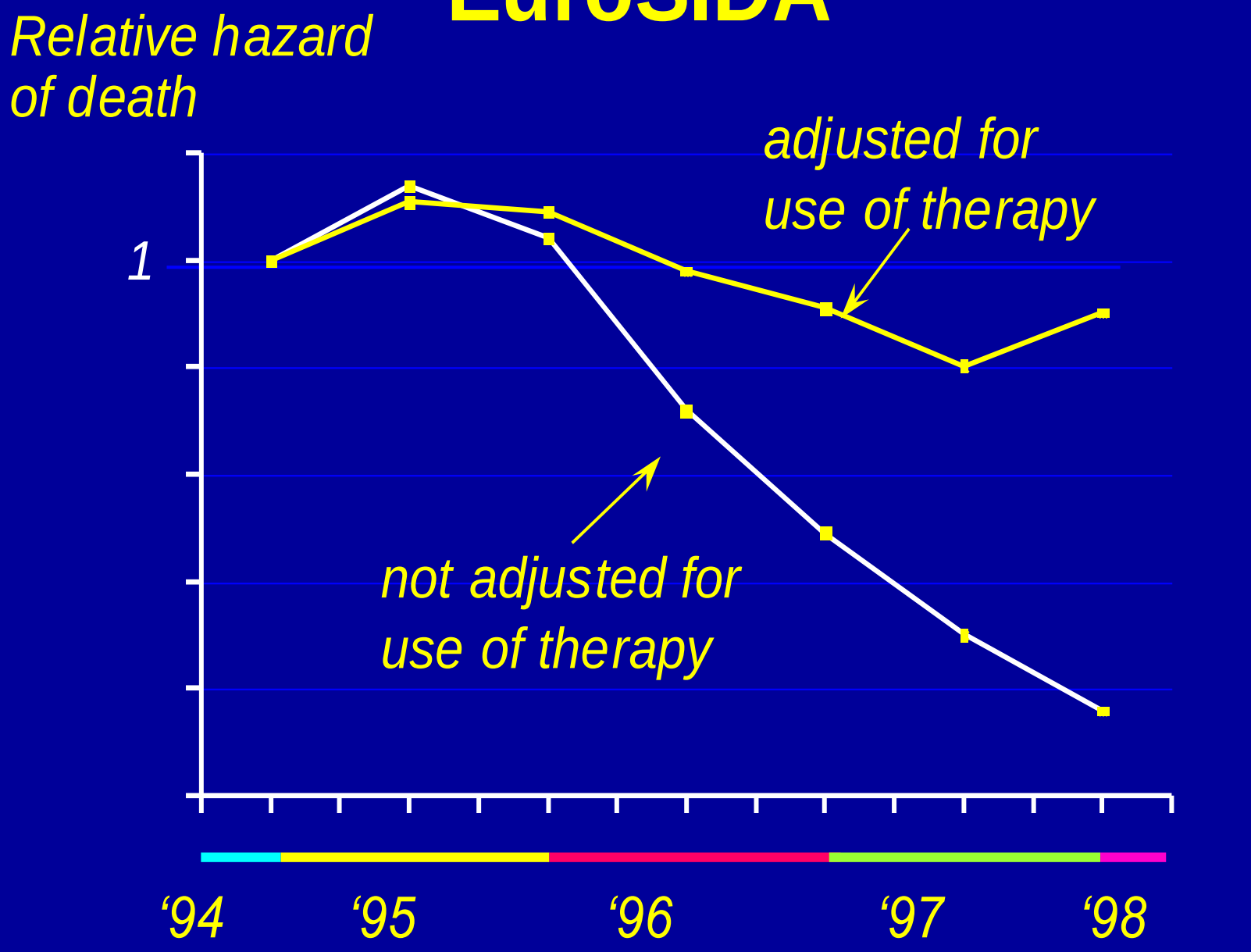
Mellors JW, et al. *Ann Int Med* 1997

Number of drugs in ART across Europe: 1994-1998



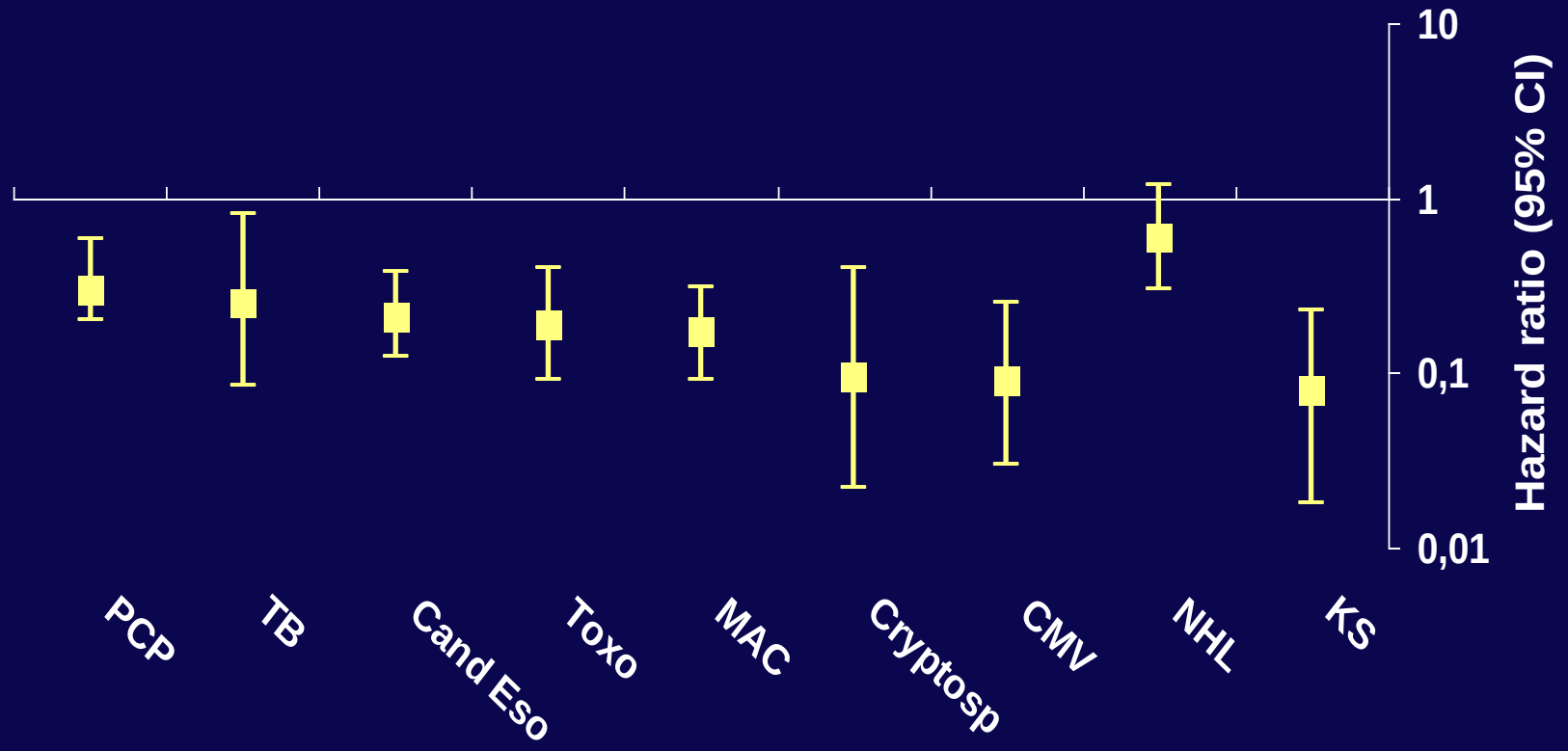
EuroSIDA: Mocroft *et al*, Lancet 1998

EuroSIDA



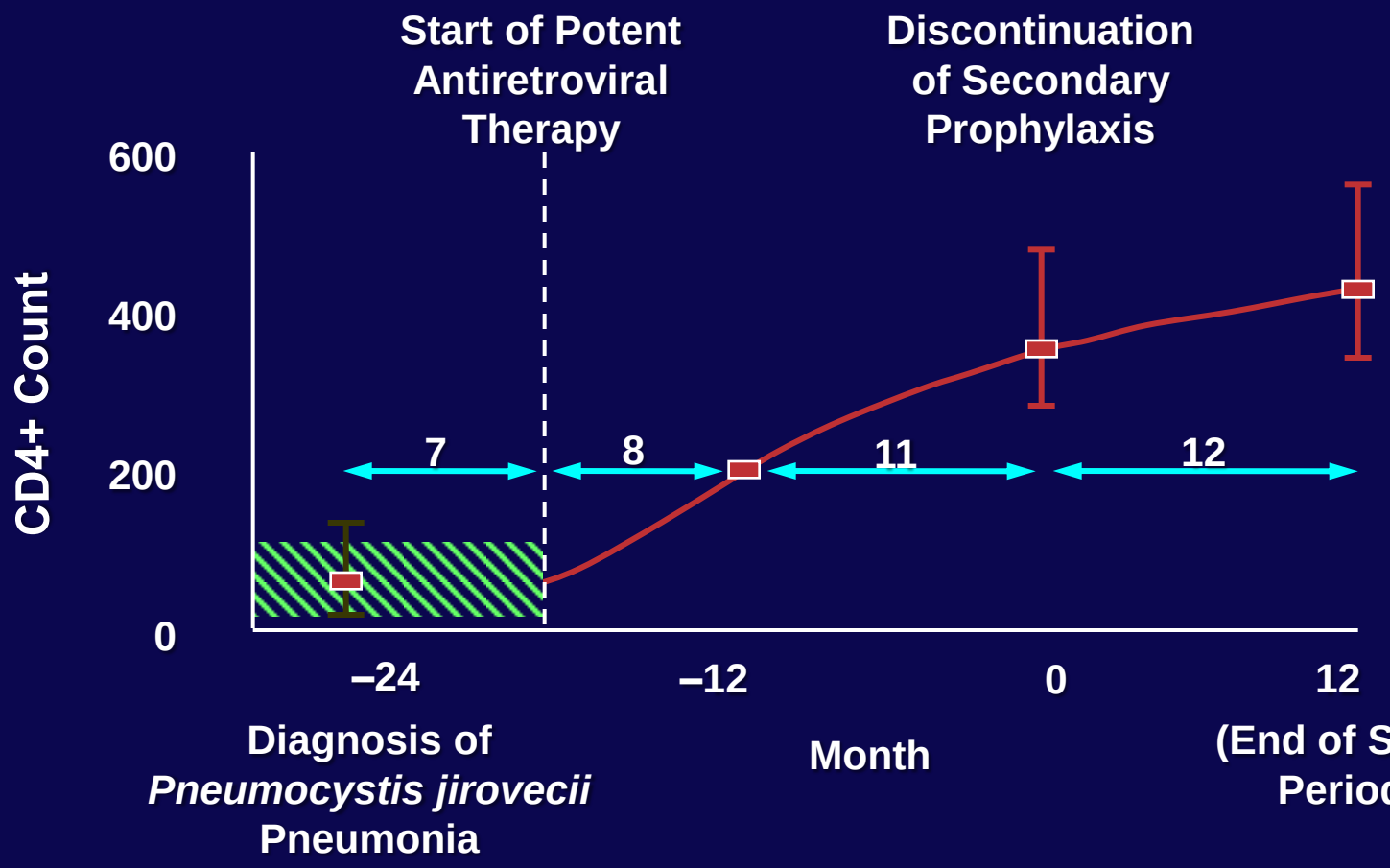
Mocroft et al. Lancet 1998

Relative risk of different AIDS-defining events in July/1997-June/1998 versus 1992-4



Swiss HIV Cohort Study: Ledergerber *et al*, BMJ 1999

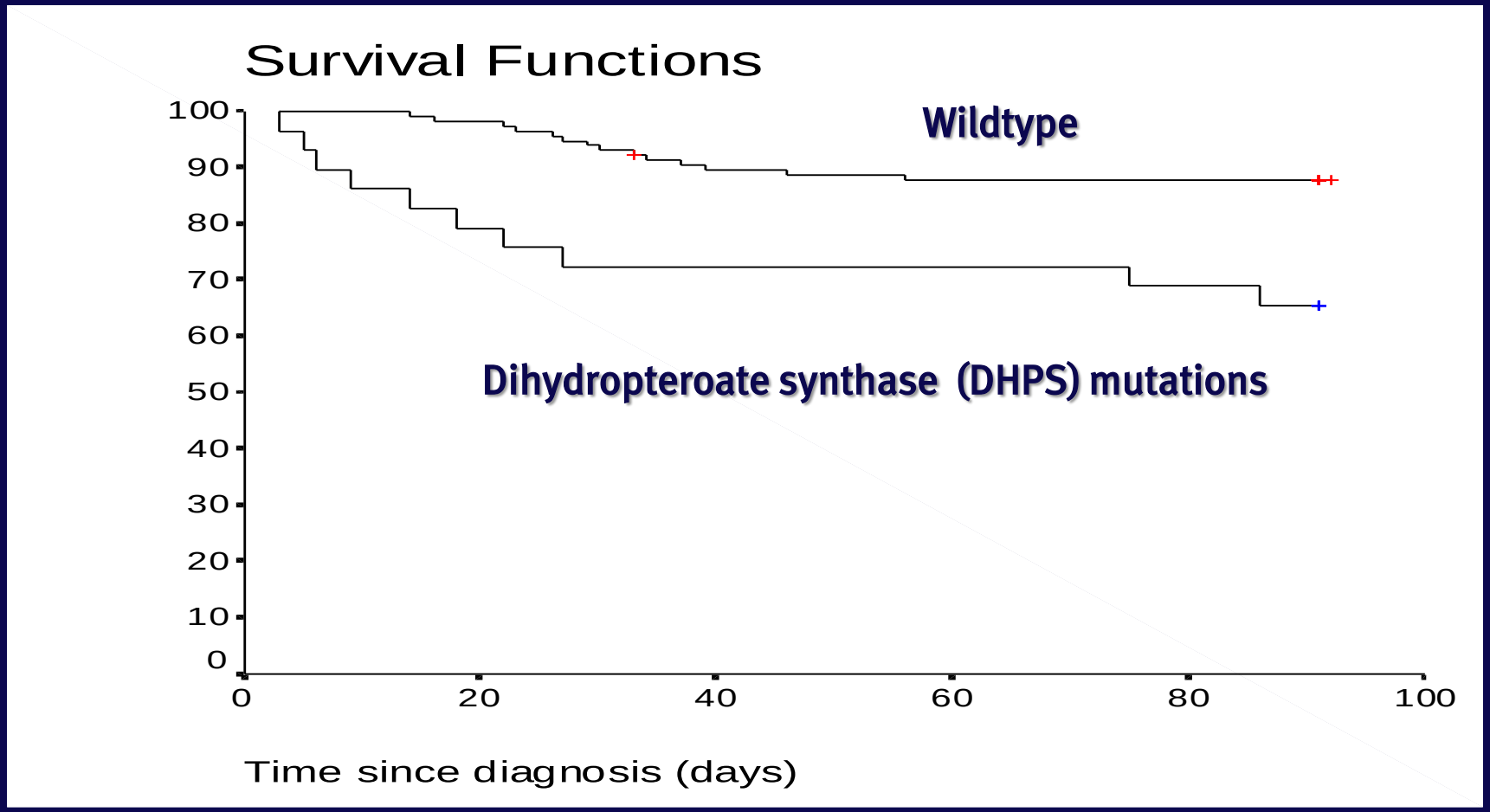
Discontinuation of Secondary PCP Disease-Specific Chemoprophylaxis After Immunological Recovery



- Persons: 325
- Median follow-up time: 13.2 months (7.0-19.0)
- Person-years of follow-up: 374.5
- Recurrent PCP: 0
- Incidence: 0 (0-1.23)* per 100 person-years

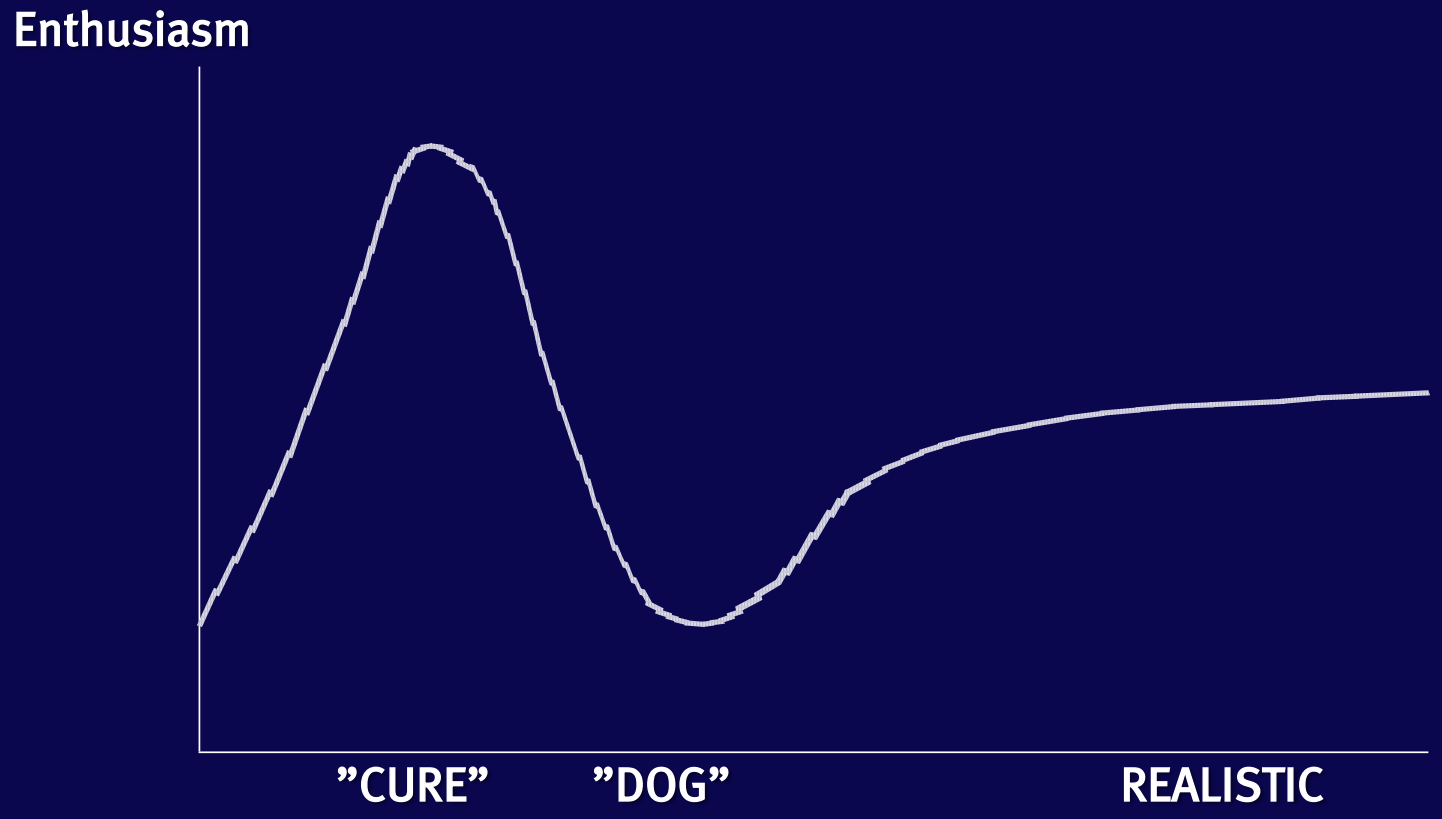
Ledergerber. NEJM 2001.

Resistance of *Pneumocystis jirovecii* to sulfa-drugs: 3 month mortality from date of diagnosis of PCP



Helweg-Larsen et al. Lancet 1999;354:1347

Enthusiasm for an agent as a function of time since first introduced



Textbook in Pharmacology, 1960's

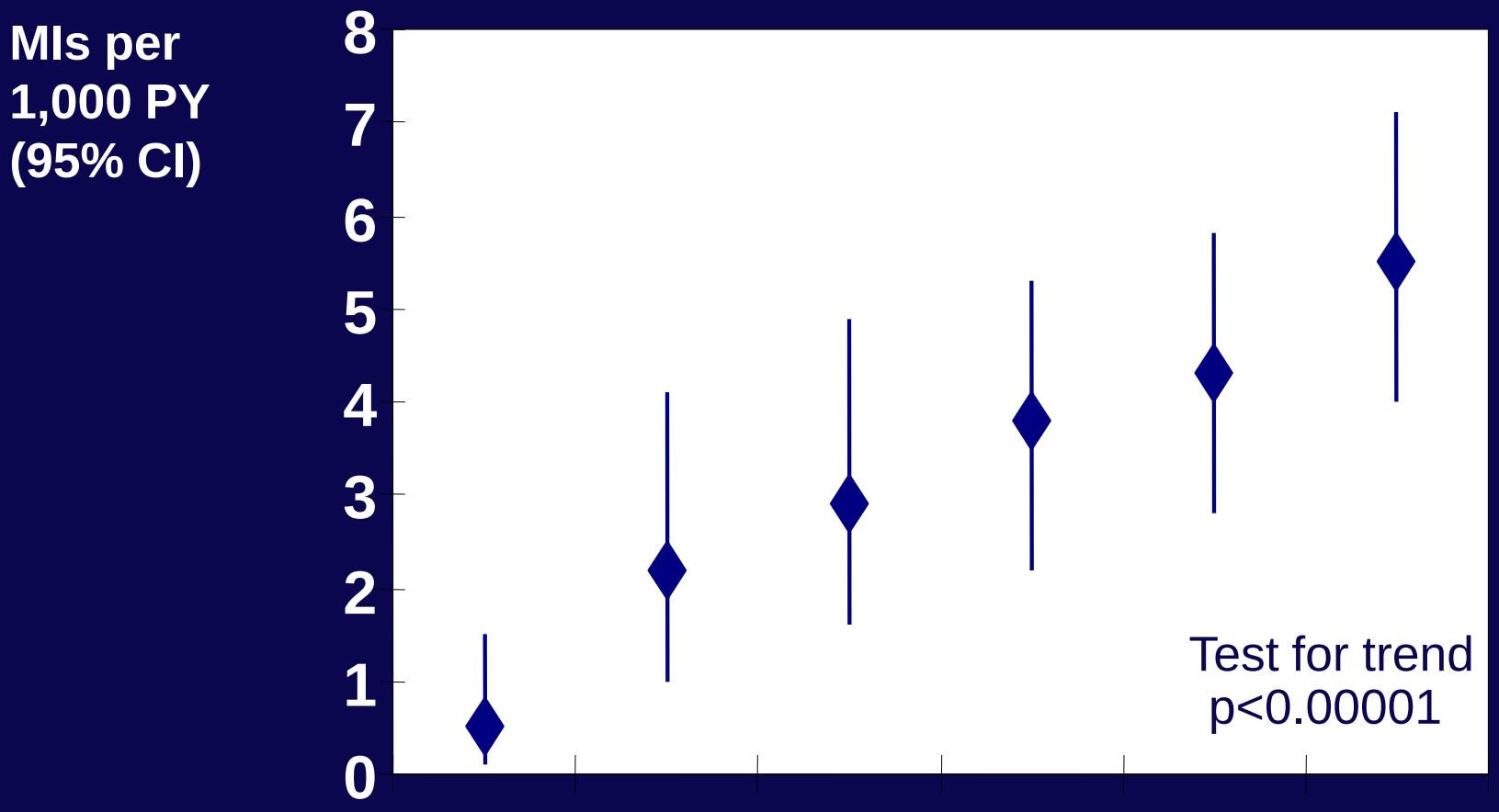
Example of toxicity “missed” in “official” system

- Abnormal fat distribution
  - 1995-97: Randomised trials evaluating efficacy/ toxicity of ARVs. Lipodystrophy not identified
  - Feb. ‘98: First report, Carr et al. (cohort study)
  - March ‘99: EMEA initiative (product labelling)
  - 2003: stavudine (and less so zidovudine) responsible

How best to address toxicity's of anti-HIV drugs in 1999

- Early onset of common event
  - Phase I/II/III trials
- Early onset of rare event
  - Meta-analysis of data from randomised trials
- Late onset of common event
  - Cohort studies (large size will increase power) and long-term randomised trials
- Late onset of rare event
  - Large size cohort studies and long-term randomised trials

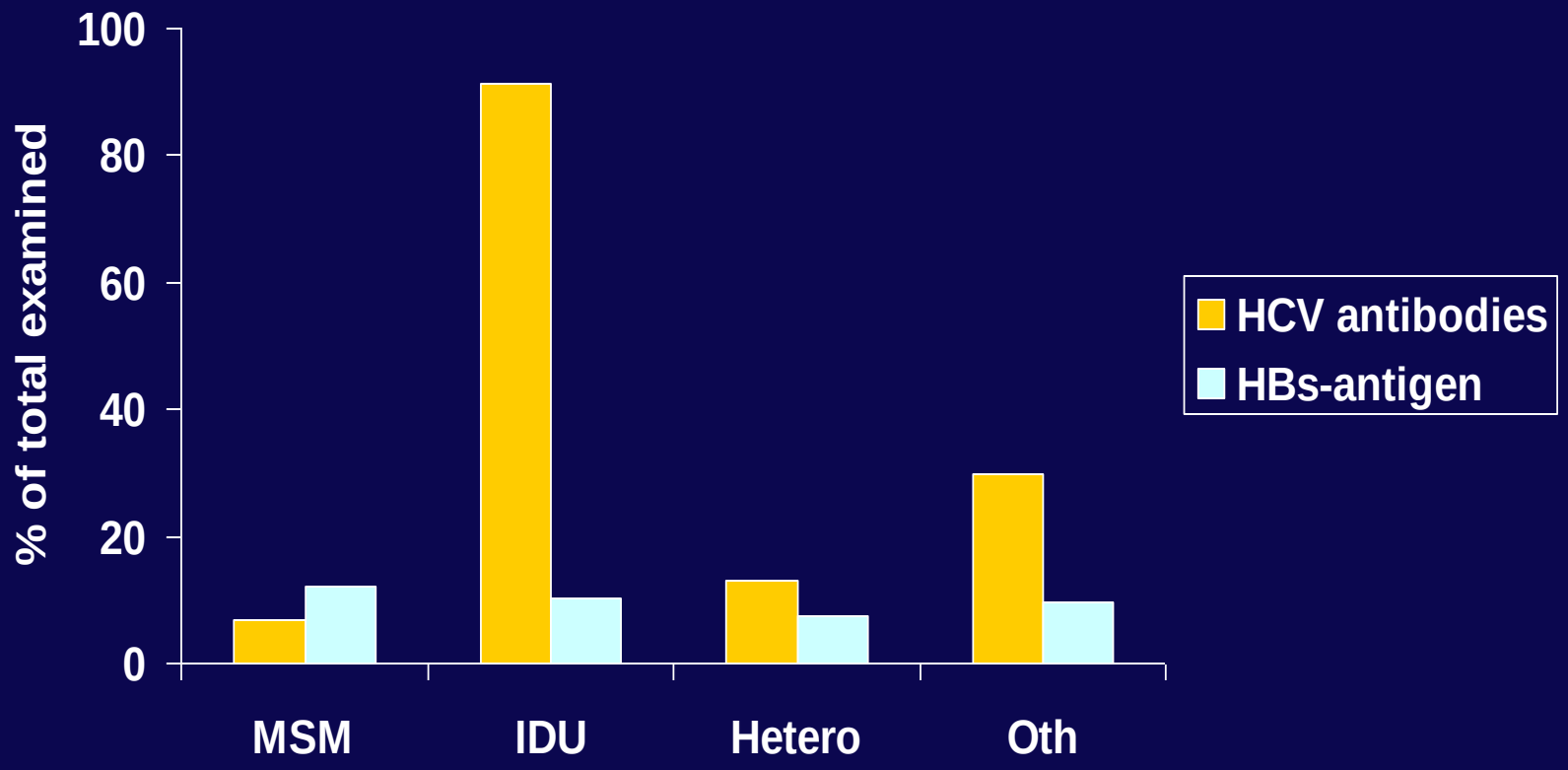
Antiretroviral drugs and risk of myocardial infarction



Years on cART	None	<1	1-2	2-3	3-4	>4	Total
No. MIs	3	9	14	22	31	47	126
No. PY	5,714	4,140	4,801	5,847	7,220	8,477	36,199

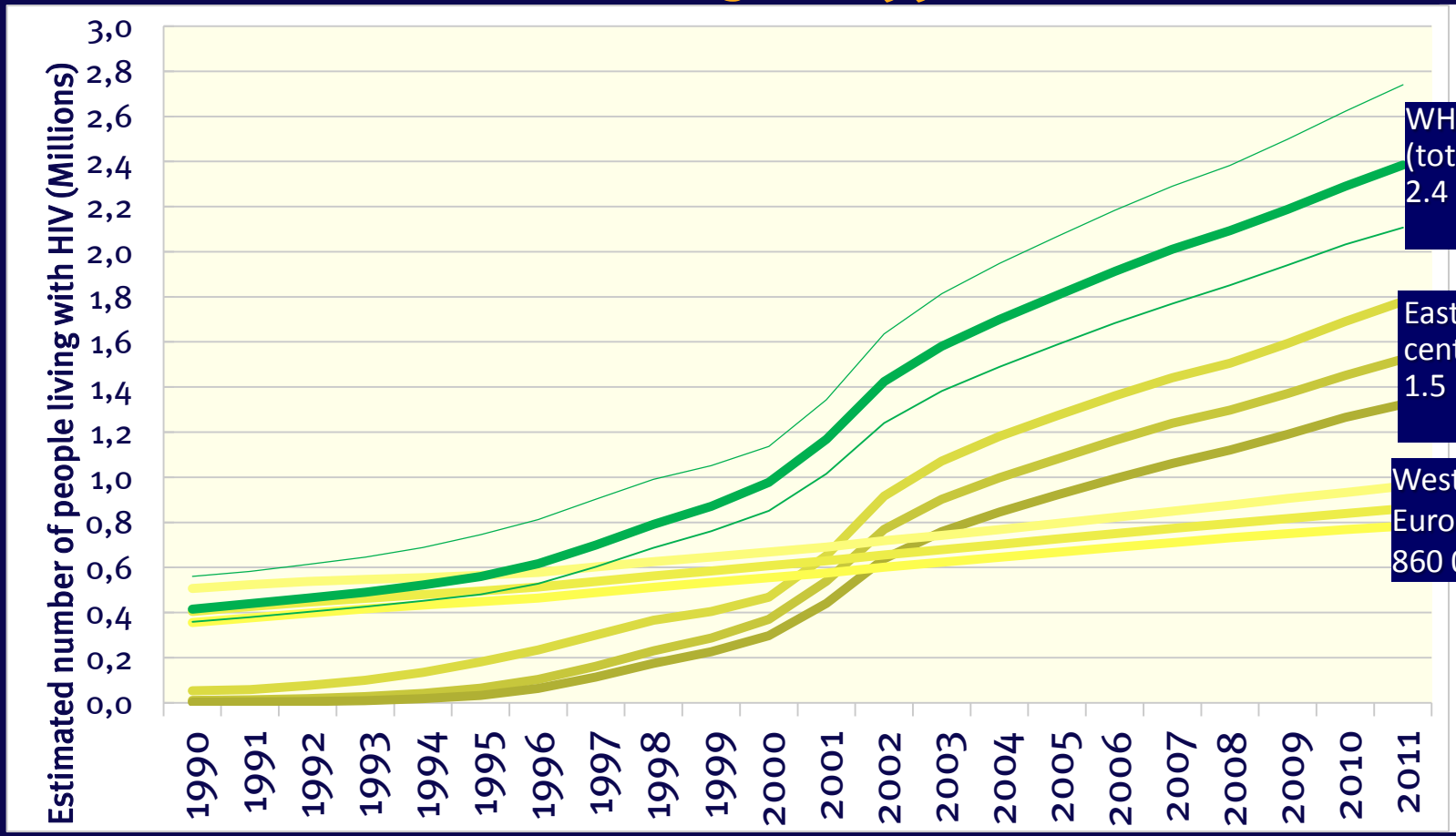
D:A:D study: Friis-Møller *et al*, *NEJM*, 2003

Prevalence of hepatitis



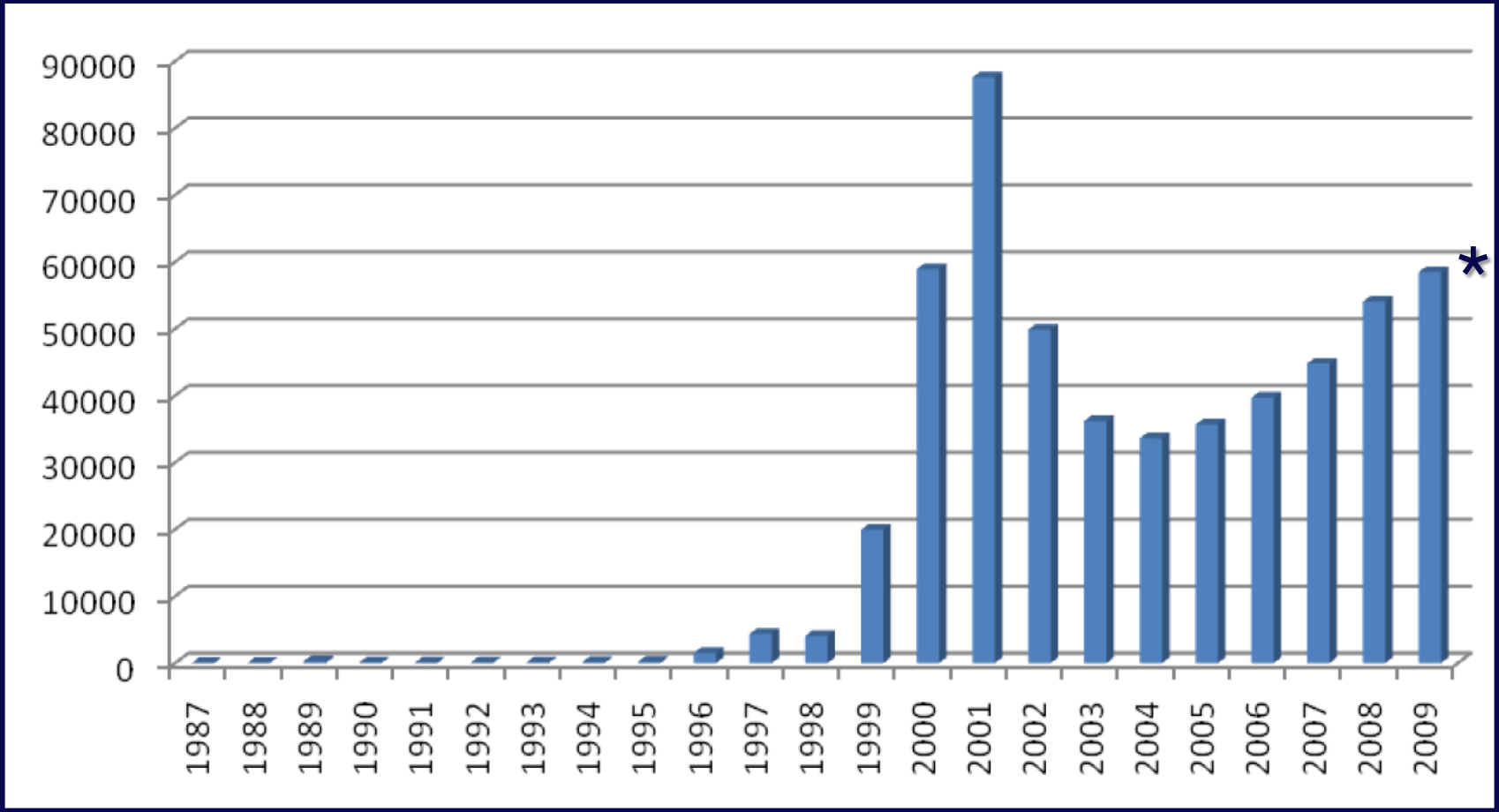
EuroSIDA: Soriano *et al*, JID 2002

HIV epidemic in eastern Europe and central Asia the fastest growing in the world:
Estimated number of people living with HIV in WHO European Region, 1990-2011



Source: UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2012.

The number of new cases of HIV infection in Russian citizens, 1987 - 2009

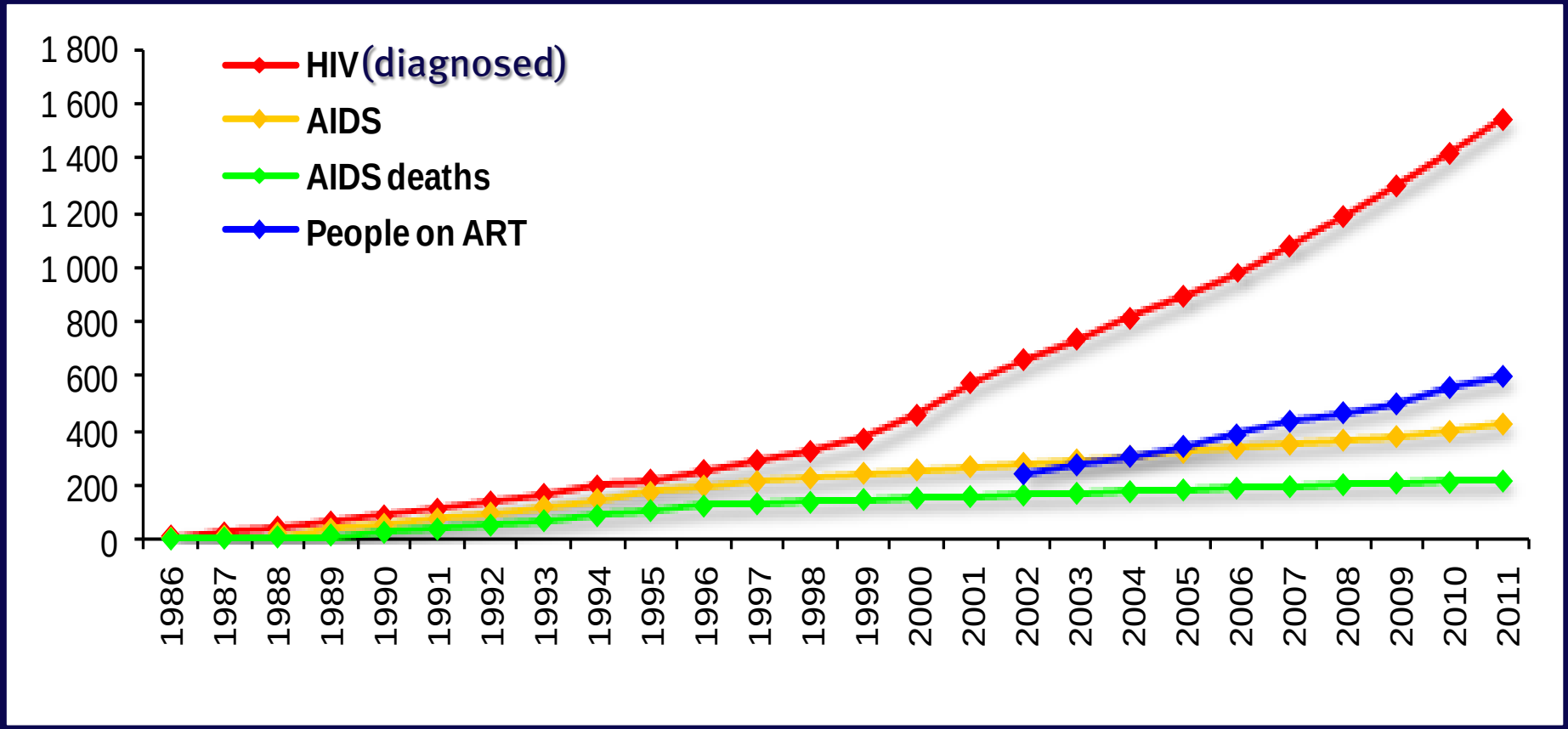


*: numbers continue to increase in 2010/11 (app 70,000)

20-25 million HIV tests per year – www. hivrussia.org

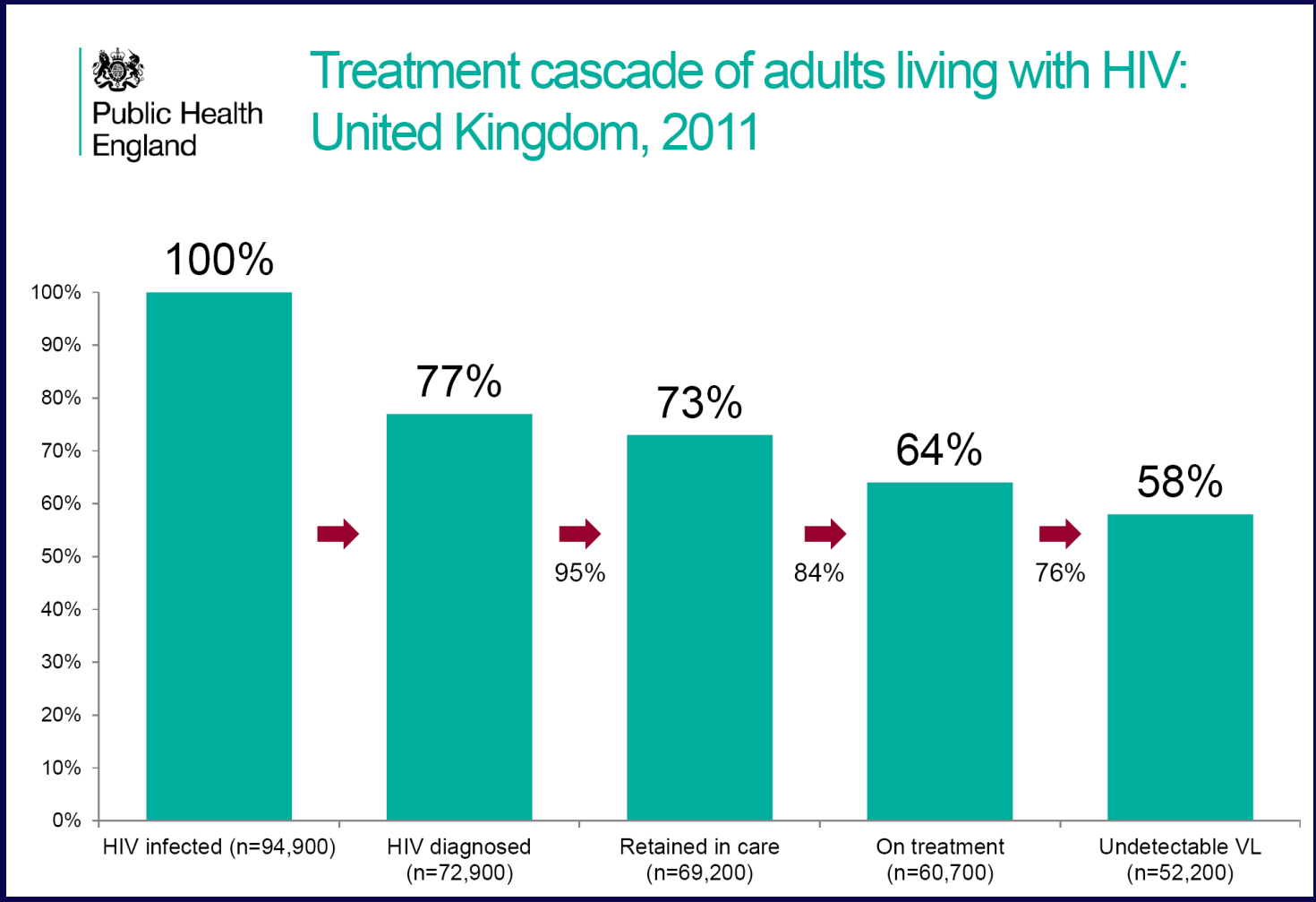
UNAIDS Country Report

Infection increasing faster than treatment: WHO European Region, 1985–2011



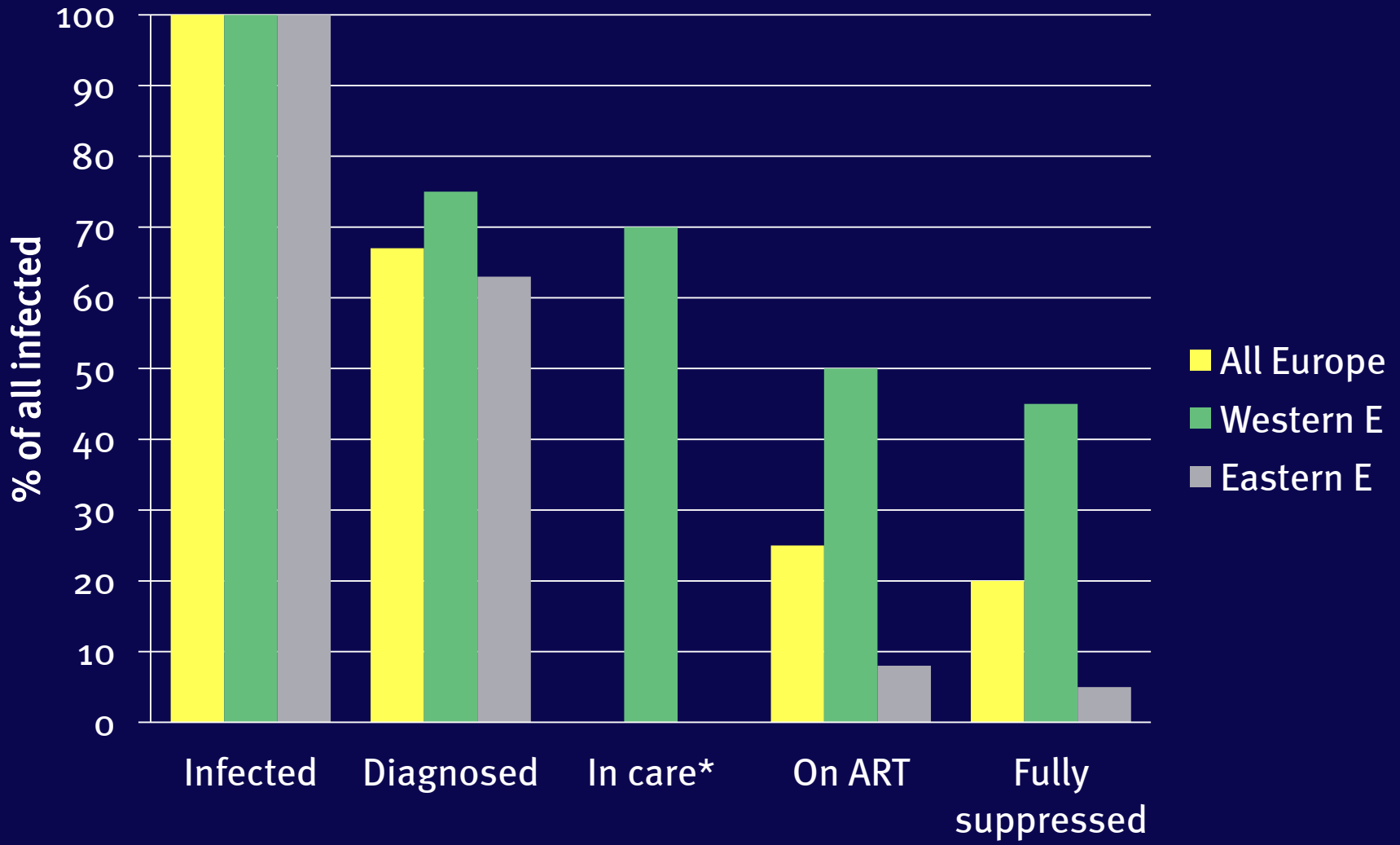
Sources: ECDC/WHO. HIV/AIDS surveillance in Europe 2011. Stockholm: ECDC; 2012; Federal Scientific and Methodological Center for the Prevention and Control of AIDS, Russian Federation; Ukrainian AIDS Centre, Ukraine; WHO/UNICEF/UNAIDS monitoring and reporting on the Health Sector Response to HIV/AIDS.

Lack of engagement/retention in care/initiation of cART



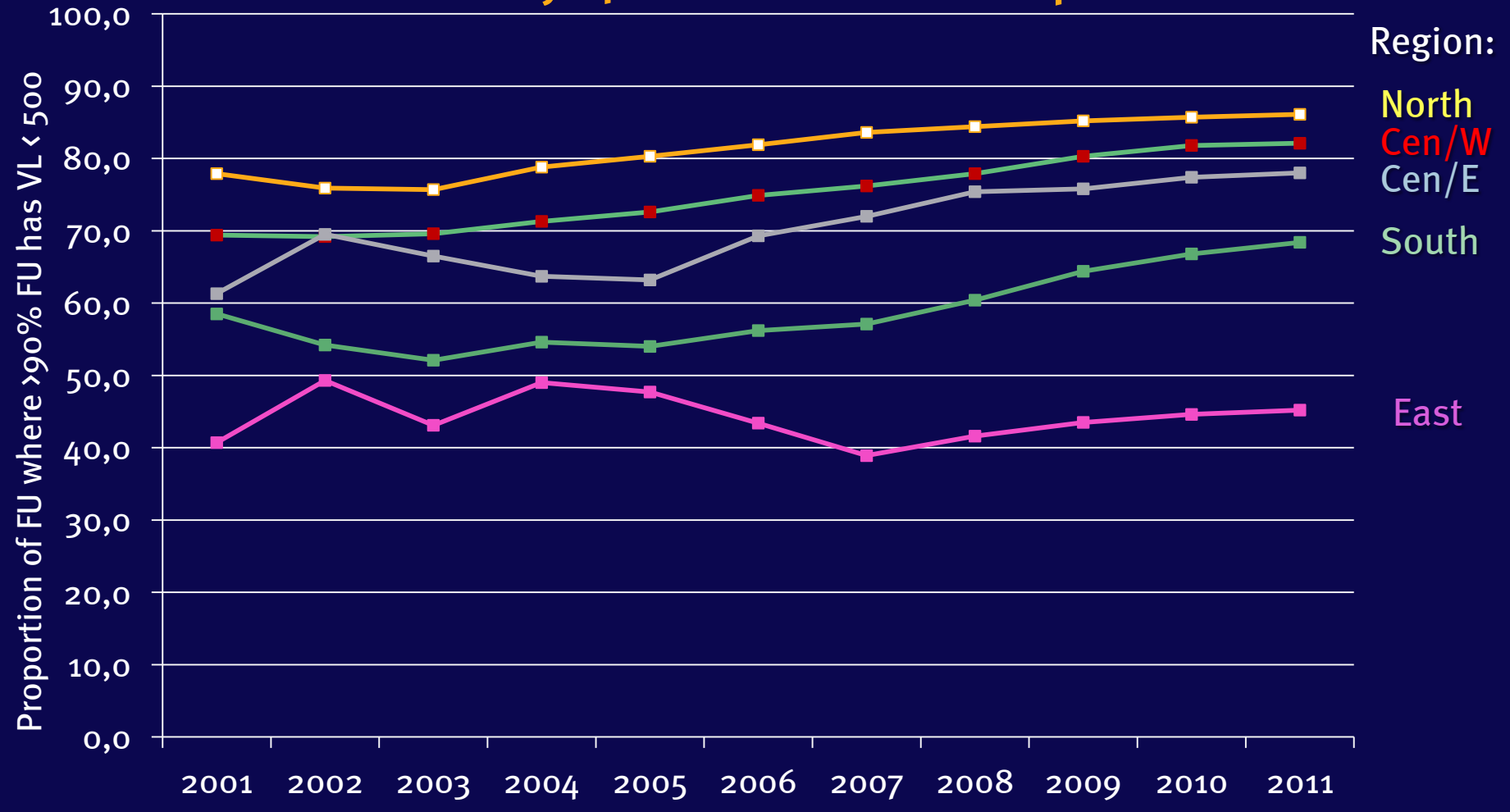
Delpech V. BHIVA Conference, 2013

Treatment cascade in Europe



*: incomplete data on number of persons in care in Eastern Europe

Durability of HIV suppression*: the key indicator to benchmark for good ART care varies by 40% across Europe



*: % of follow-up (FU) on ART where >90% FU has VL < 500

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EuroSIDA (unpublished)

Retention in care require health systems to manage all aspects of care:
poor opioid substitution therapy (OST) coverage in EE*

	# IDU	% of IDU receiving OST	# IDU HIV+ in 2010	# of HIV+ IDU on ART
Belarus	75,000	0,3%	10,500	?
Kazakhstan	186,000	0,1%	5,580	182
Lithuania	5,458	?	1,250	62
Moldova	25,000	1,4%	4,450	446
Russia	2 million	0%	?	?
Ukraine	375,000	2,1%	85,000	1732

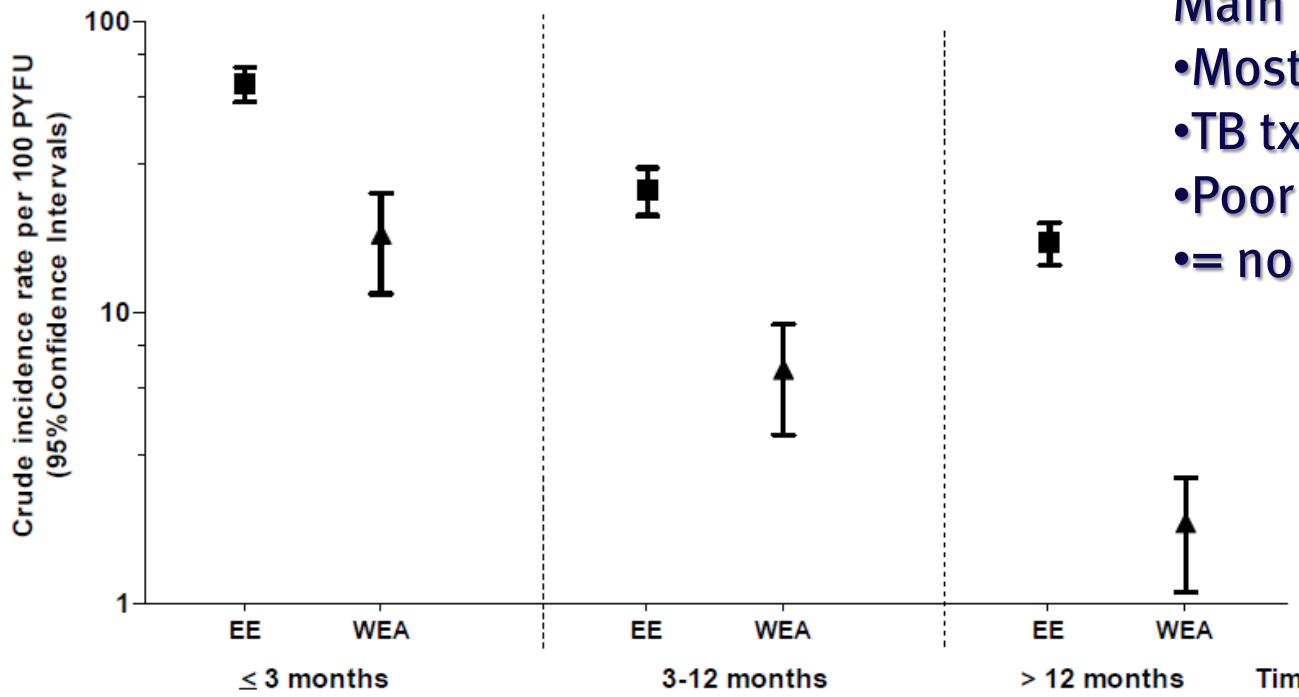
15,9 million IDU's globally – 80% in low-middle income countries

*: OST coverage in Western Europe: 30-60%

Petersen *et al.* Harm Reduction J, 2013

Mortality after TB in HIV+ remains high in Eastern Europe (EE)

but decreases markedly in Western Europe/Argentina (WEA)



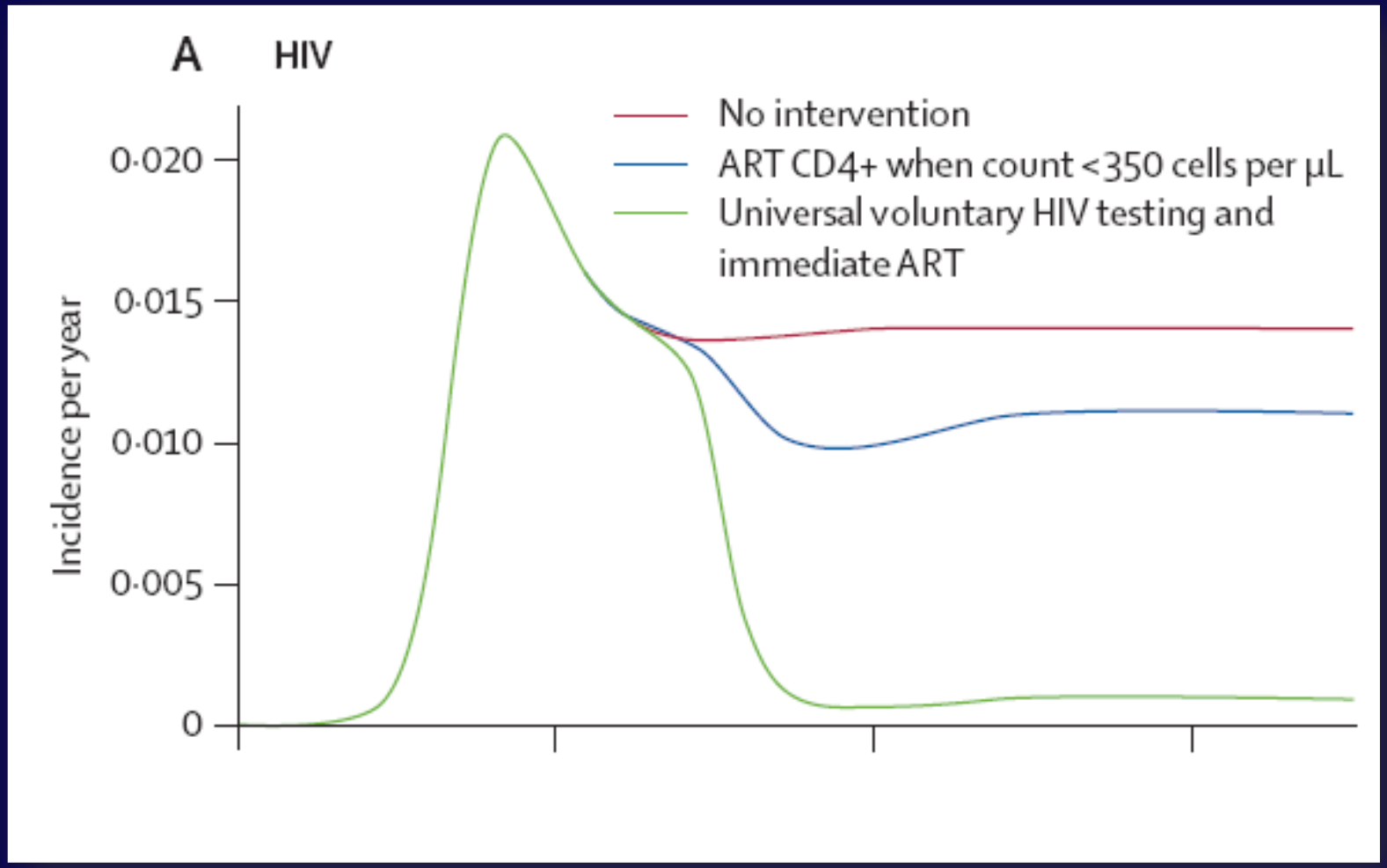
Main reasons:

- Most TB is MDR/XDR
- TB tx uncoordinated
- Poor retention in care
- = no ART

TB remains leading cause of deaths among HIV+ in EE

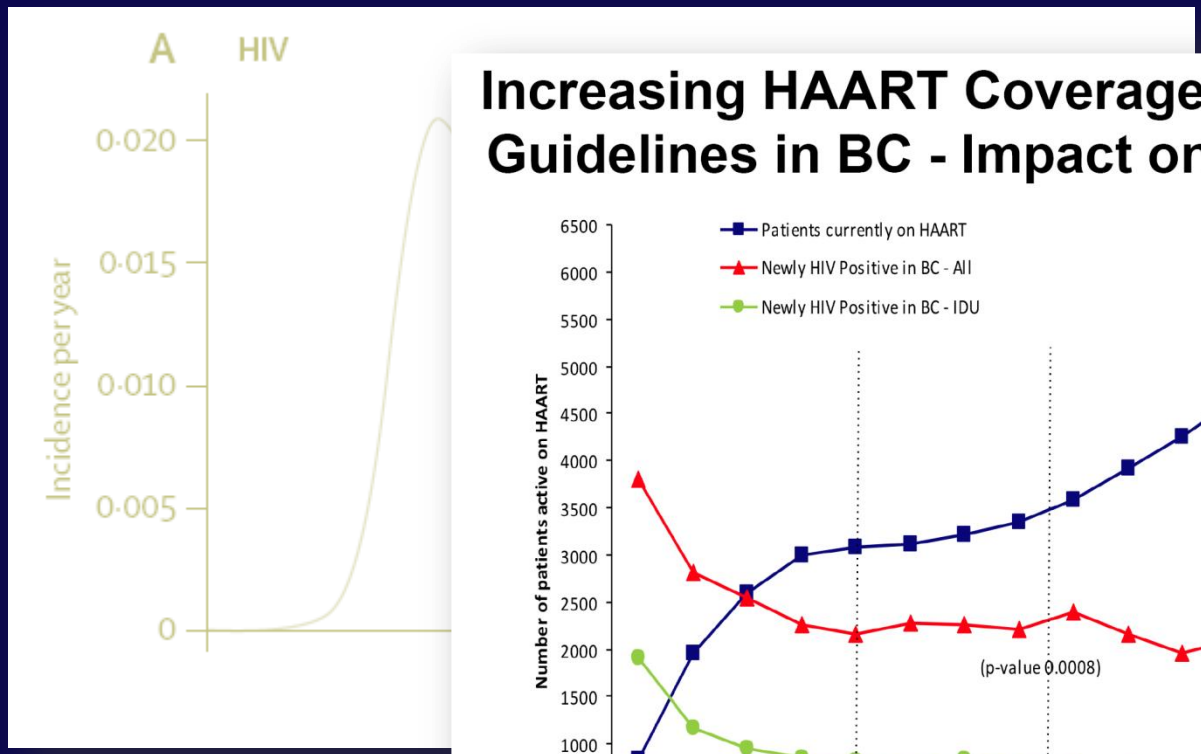
Podlekareva *et al*, ERJ 2013

Potential impact of cART on epidemic



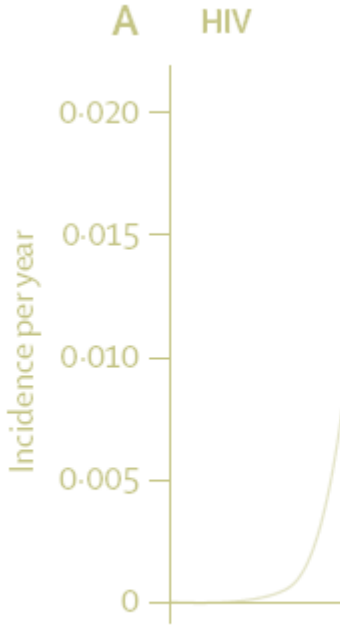
Granich RM et al. *Lancet* 2009

Potential impact of cART on epidemic



Granich RM et al. *Lancet* 2009;**373**:48-57; Montaner JS. TasP-Workshop, Vancouver 2012.

Potential impact of cART on epidemic



In MSM communities across Western Europe:

- Increasing ART coverage
- More condom-less sex
- Increasing HIV incidence

ART coverage – what is the target % required to get reproductive rate < 1 ?

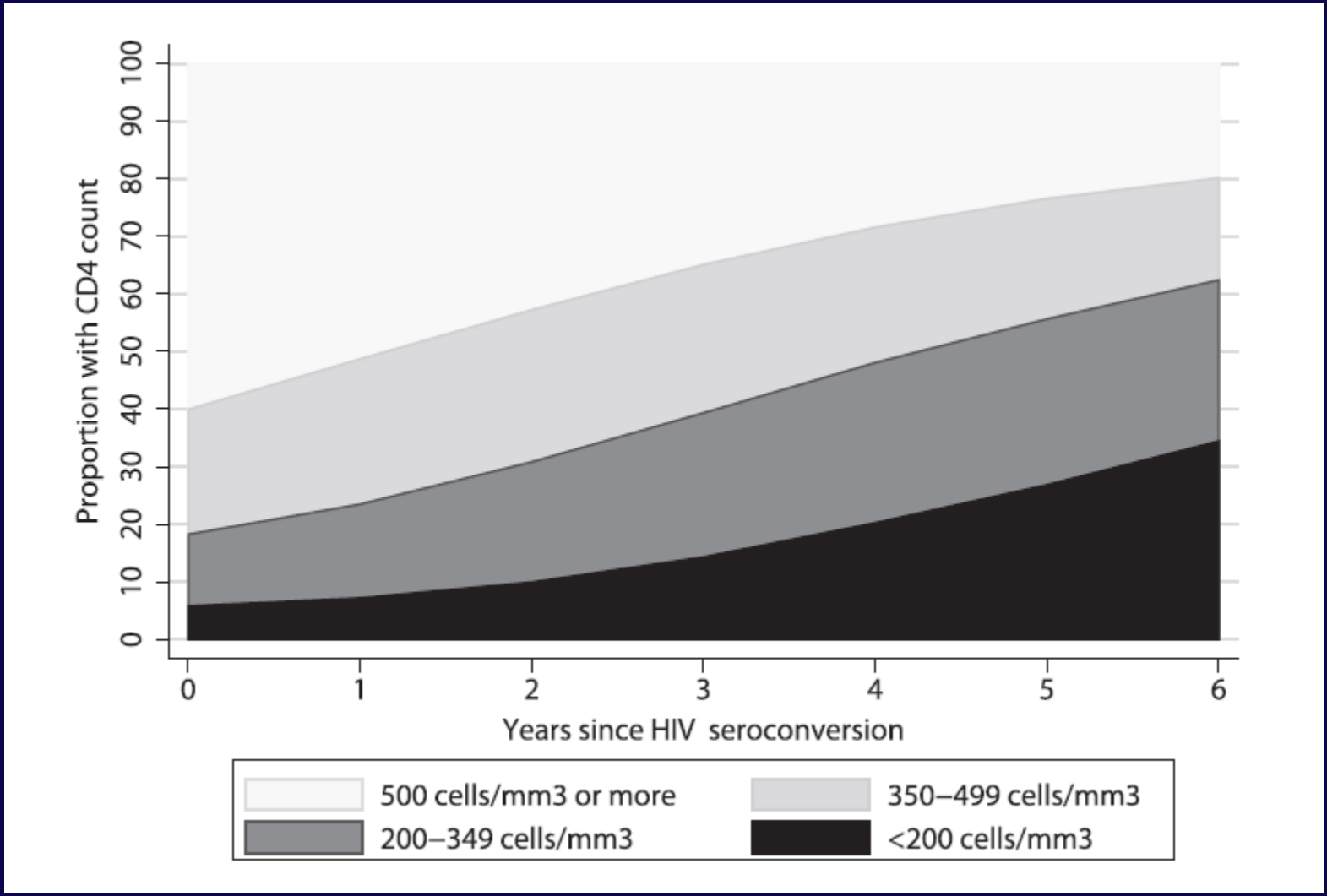
Granich RM et al. *Lancet* 2009;**373**:48-57; Montaner JS. TasP-Workshop, Vancouver 2012. Delpech Lancet 2012; Phillips et al, PLoS One 2013

When to START ART ?

Benefit to

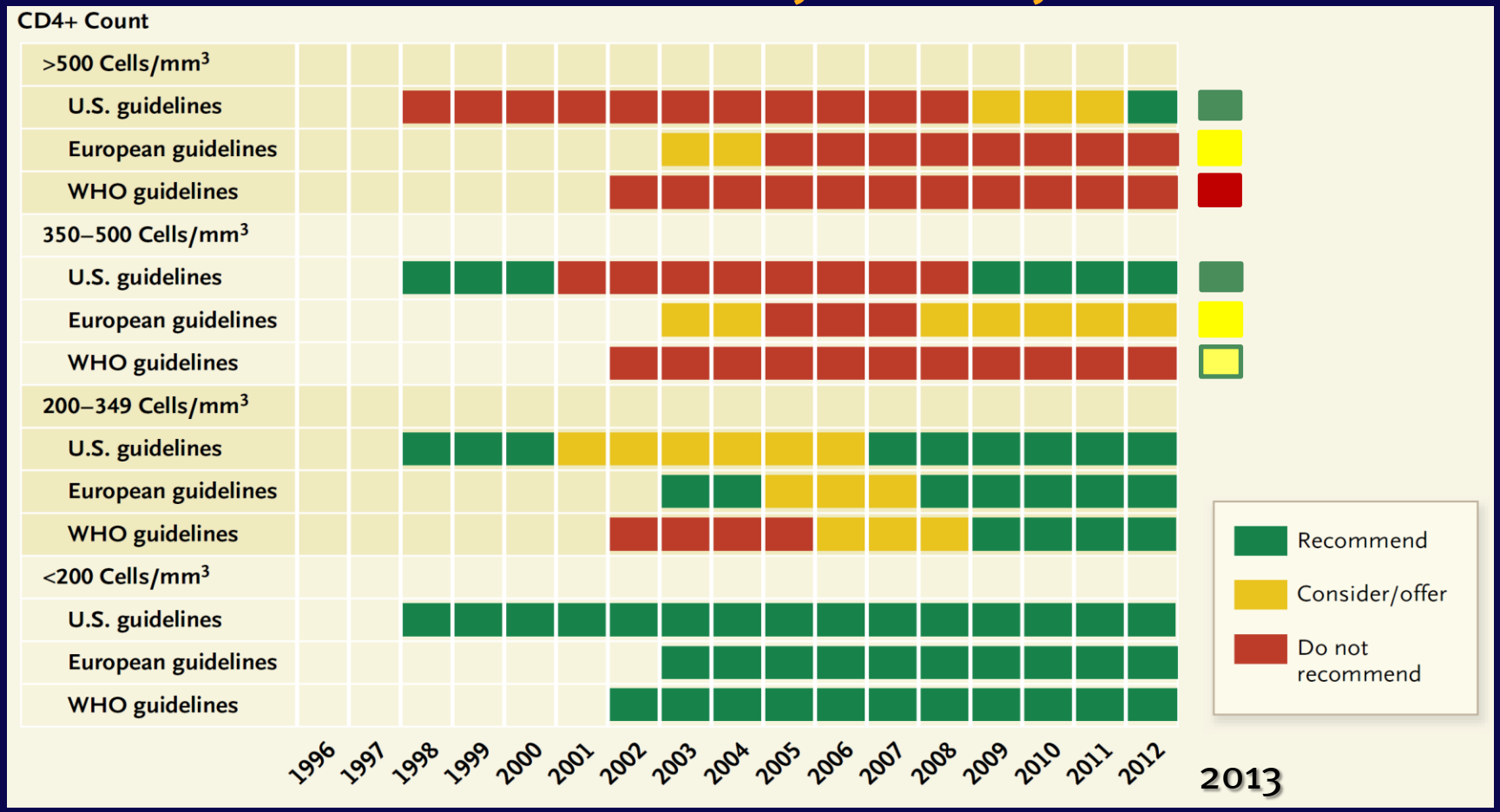
Individual vs
individuals sexual partner vs
societal benefit

Natural history of HIV: CD4 count distribution according to time from infection



Lodi et al; JID 2011

Guidelines Change but not in Synchrony



De Cock & El-Sadr, NEJM 2013

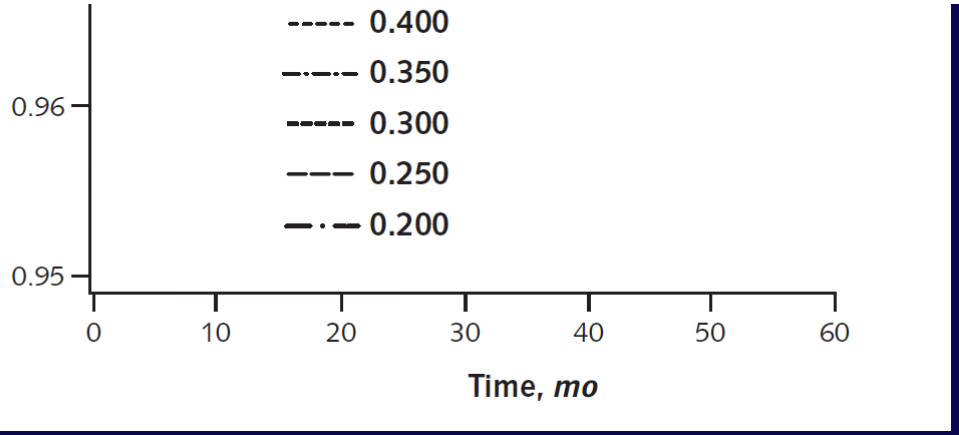
Survival after ART initiated at different CD4 count levels between 200-500: ”causal” modelling

Implication

Randomized, controlled trials are needed to better define the optimal time of initiation of combined antiretroviral therapy in HIV infection.

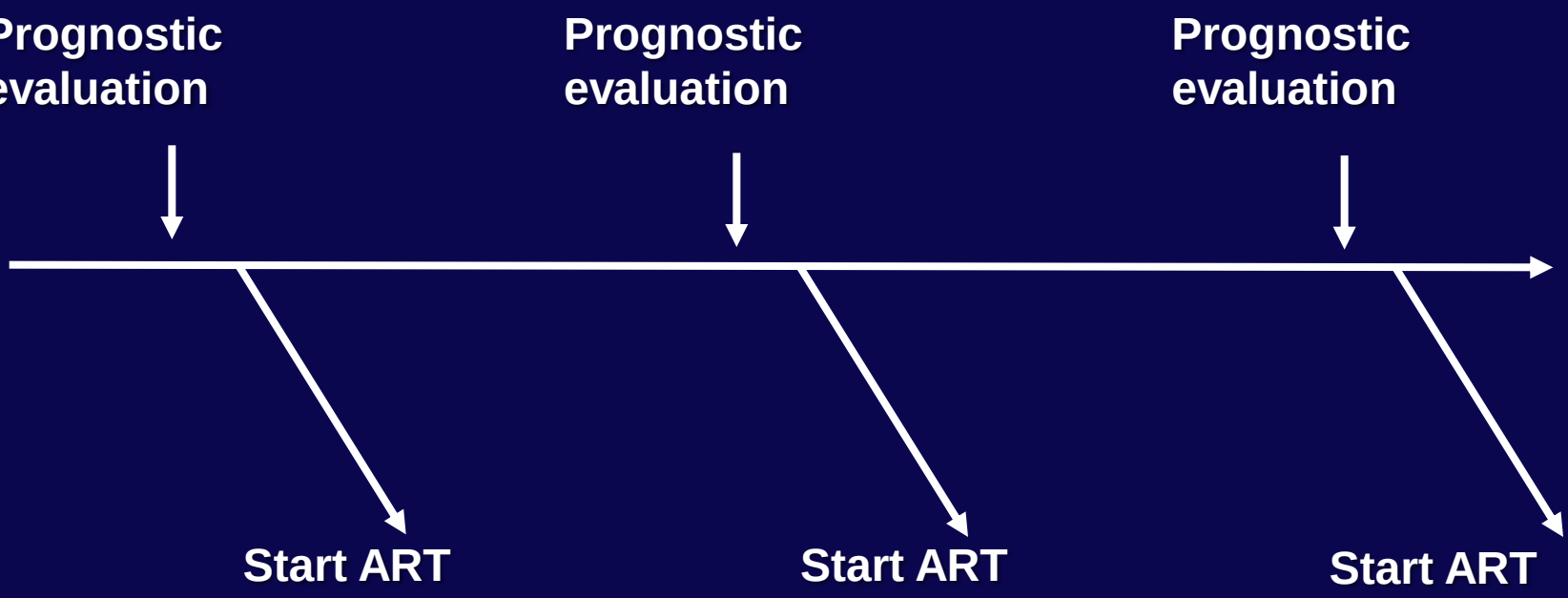
—*The Editors*

Propo
surviv



The HIV-CAUSAL Collaboration, Ann Intern Med 2011

The choice to make for asymptomatic treatment naïve patients



Talk in 2003

EDITORIAL REVIEW

Rating evidence in treatment guidelines: a case example of when to initiate combination antiretroviral therapy (cART) in HIV-positive asymptomatic persons

Caroline A. Sabin[a], David A. Cooper[b], Simon Collins[c] and Mauro Schechter[d]

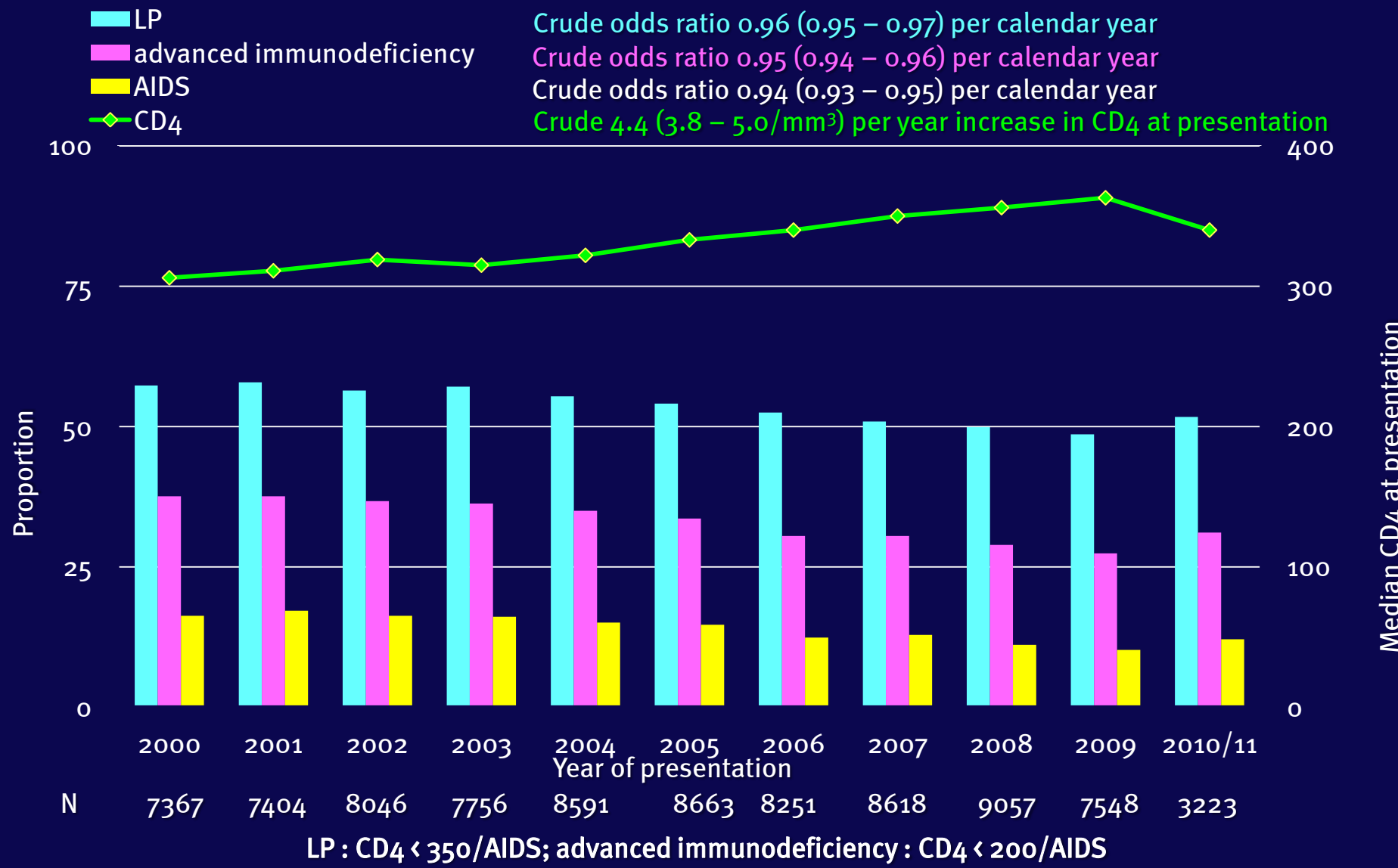
”Use of more stingent criteria, such as those proposed by the GRADE approach, would likely reach the conclusion that the evidence is insufficient to make firm recommendations
[for starting ART at CD4 of 500 vs deferring to 350 cells/µL].”

Major Guidelines for ART Initiation

Guideline	AIDS or HIV-Related Symptoms	CD4+ Cell Count < 200/mm³	CD4+ Cell Count 200-350/mm³	CD4+ Cell Count 350-500/mm³	CD4+ Cell Count > 500 cells/mm³
DHHS-USA, 2013	Yes	Yes	Yes	Yes[1]	Yes[2]
International AIDS Society-USA, 2012	Yes	Yes	Yes	Yes[1]	Yes[2]
British HIV Association, 2012	Yes	Yes	Yes	Defer [3]	Defer[3]
European AIDS Clinical Society, 2013	Yes	Yes	Yes	Consider[3]	Consider[3]
World Health Organization, 2013	Yes	Yes	Yes	Consider[4]	Defer[5]

(1) Strong strength recommendation based on observational data (A-II)
(2) Moderate strength recommendation based on expert opinion (B-III).
(3) But treat all HIV+ pregnant women, HBV co-infection, HCV co-infection, HIVAN, HIV related neurocognitive disorders, ITP, non-AIDS cancers and serodiscordant couples
(4) But treat individuals with CD4 < 350 a priority.
(5) But treat all HIV+ pregnant women ,TB co-infection with active disease and HBV co-infection with severe liver disease, and serodiscordant copuls

Late presentation by year of presentation



LP : CD4 < 350/AIDS; advanced immunodeficiency : CD4 < 200/AIDS

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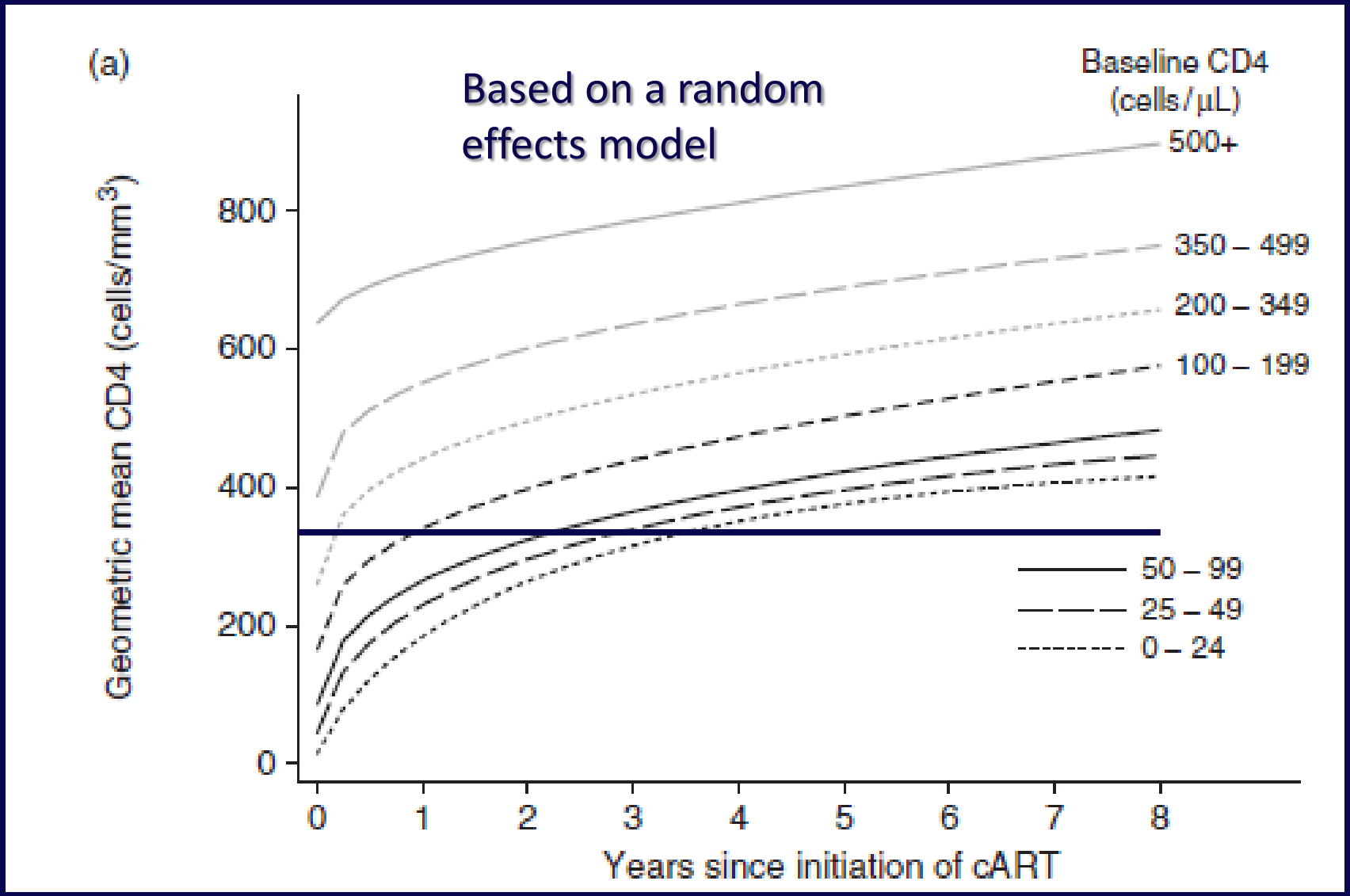
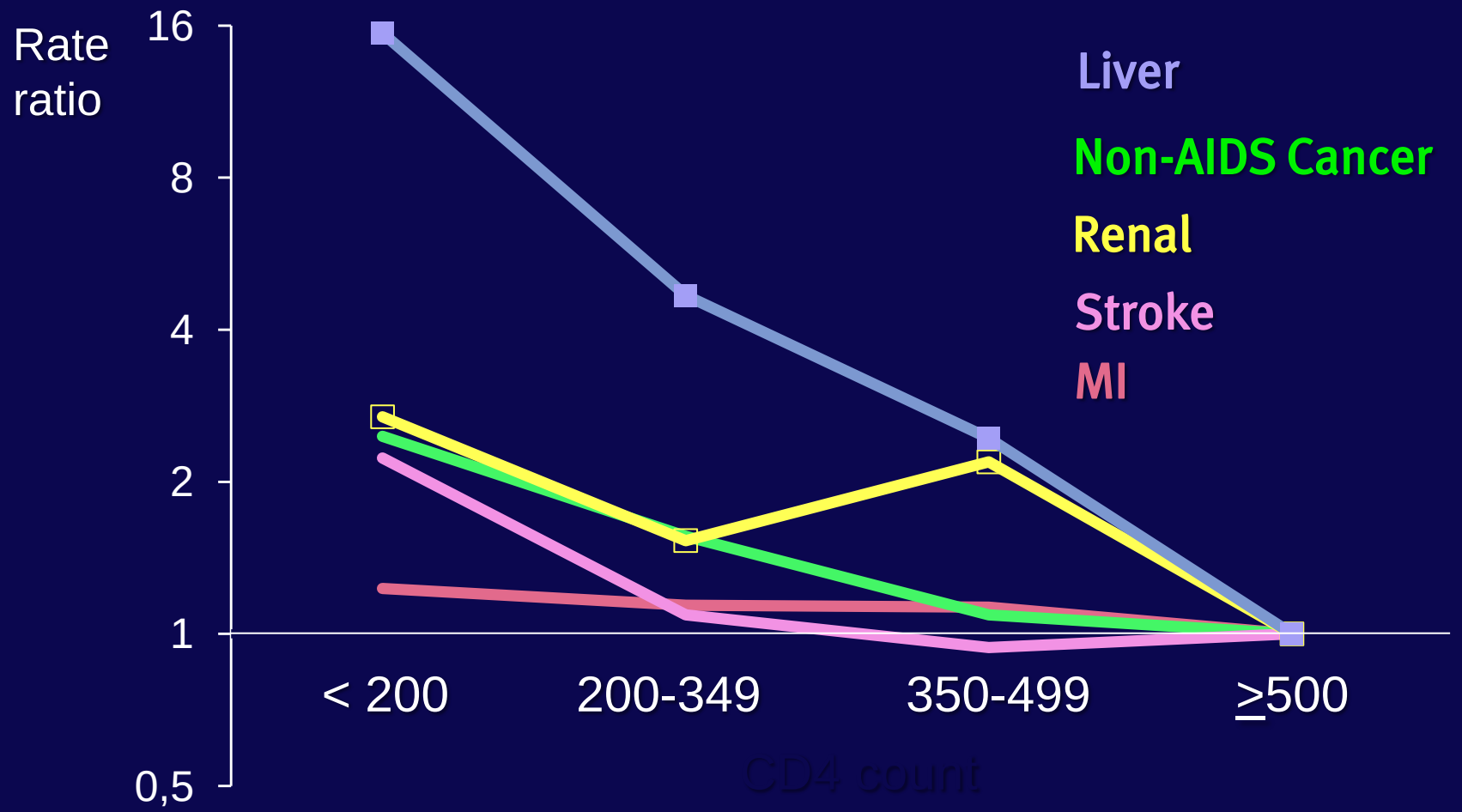
COHERE: Mocroft *et al*, PLoS Med 2013

CD4 count recovery on ART if fully virally suppressed



UK CHIC Study; Hughes et al, HIV Medicine 2010; see also Mocroft et al Lancet 2007

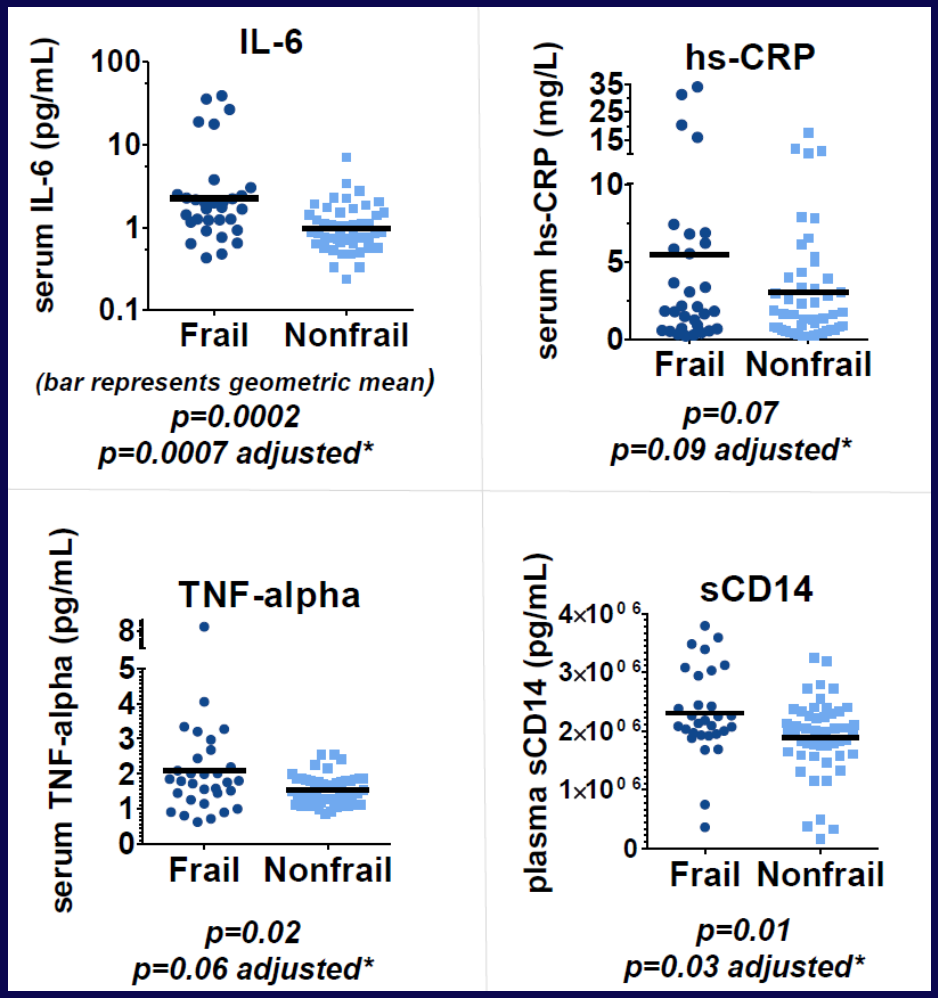
CD4 count and risk of non-AIDS disease events in people on ART with viral suppression: D:A:D



Trend highly statistically significant in all cases except for MI

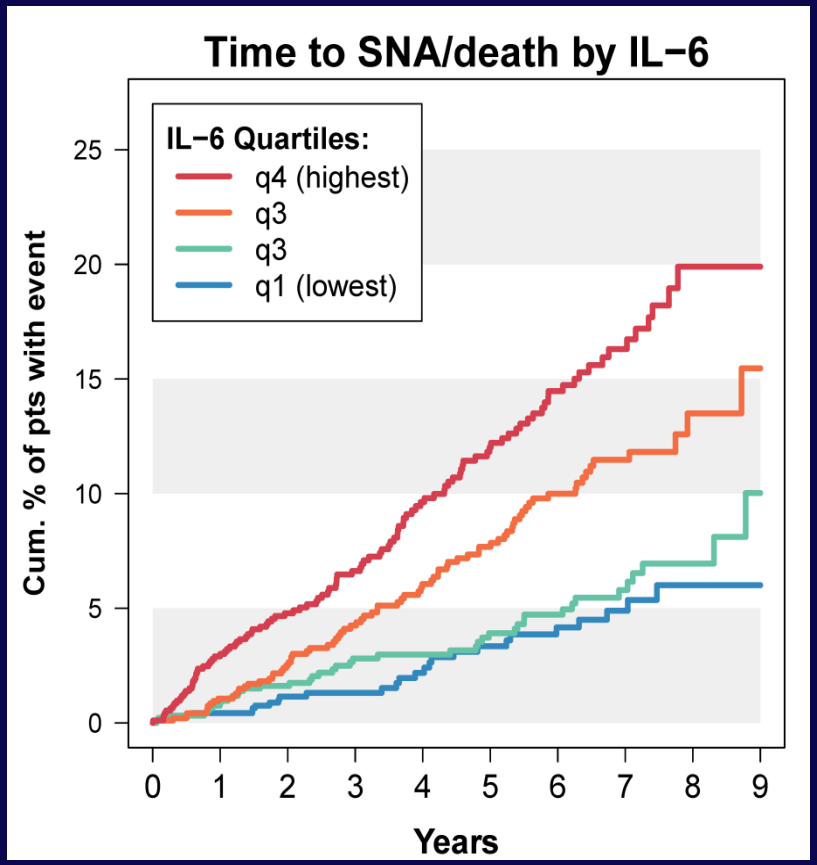
Source: D:A:D (Weber et al, Arch Intern Med 2006 – updated)

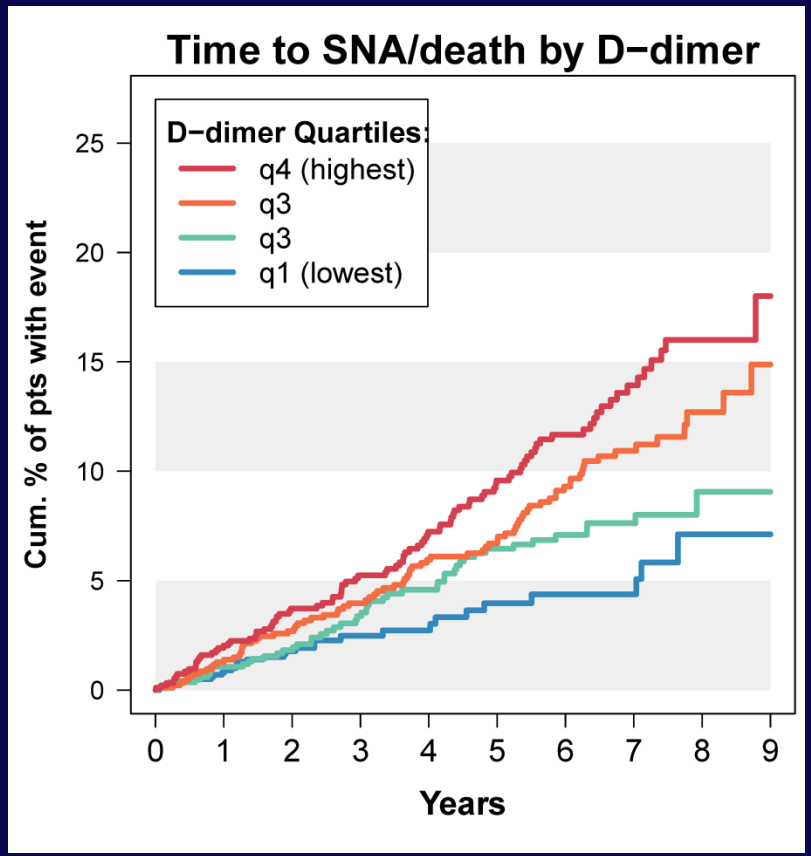
Frailty in treated HIV infection associated with elevated levels of T cell activation, (the classic geriatric syndrome) IL-6, CPR, TNF-alpha and sCD4



Erlandson, JID 2013

A single measurement of IL-6 or D-dimers predicts morbidity or mortality over next decade

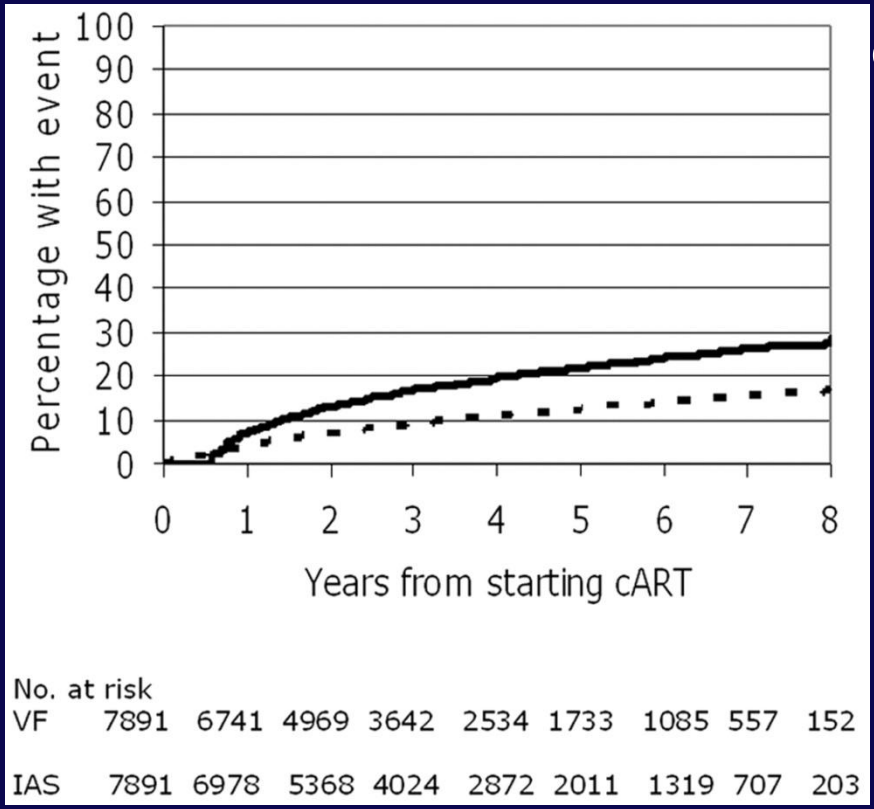




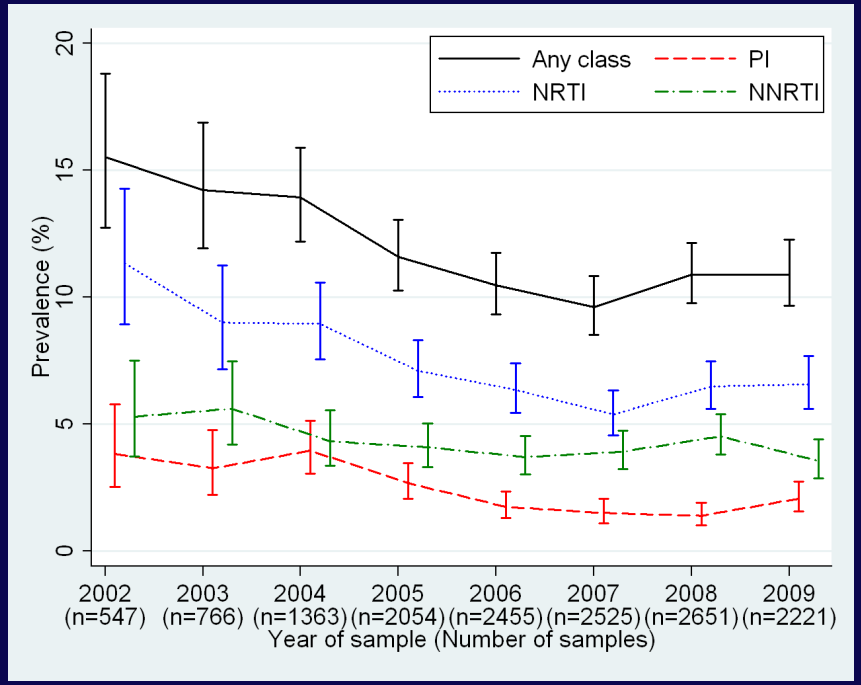
insight

Is resistance likely to be a problem?

Time to virological failure (bold line) and ≥1 IAS mutation (dotted line) after starting cART - UK CHIC/UK HDRD[1]



Prevalence of transmitted drug resistance over time, stratified by drug class - UK HDRD[2]



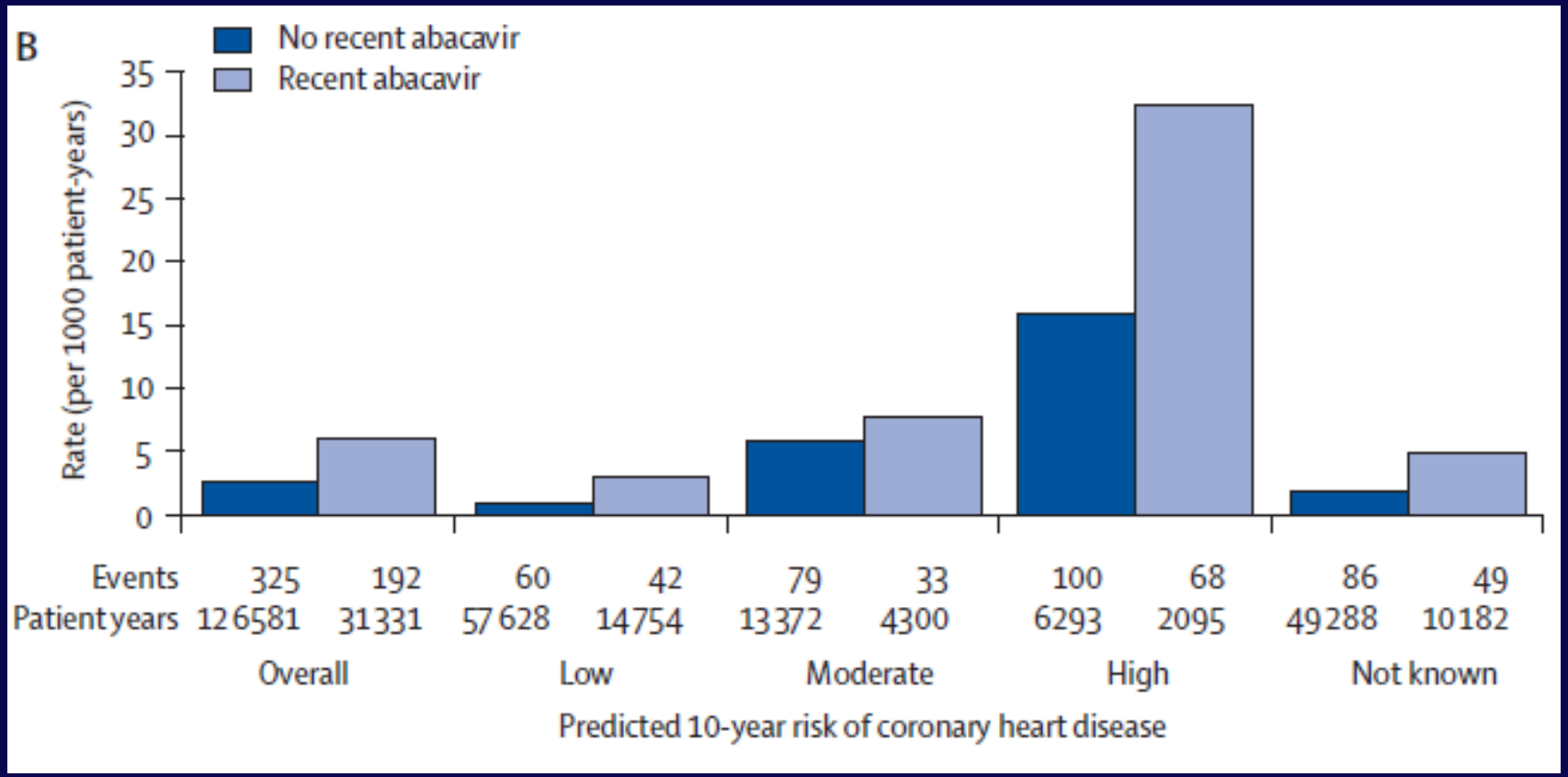
[1]Cozzi-Lepri A *et al.* CID 2010; [2]Dolling D *et al.* BMJ 2012

Changing natural history ?: Impact of year of seroconversion on viral load setpoint and CD4 loss

	Viral load set-point (log_{10} cps/ml)		CD4 loss (cells/mm^3 per year)	
Year	Coefficient	95% CI	Coefficient	95% CI
1996-99	0	-	0	
2000-03	0.12	(0.02, 0.23)	-0.46	(-0.68, -0.25)
2004-05	0.15	(0.03, 0.26)	-0.44	(-0.67, -0.20)
2006+	0.01	(-0.09, 0.12)	-0.18	(-0.42, 0.05)

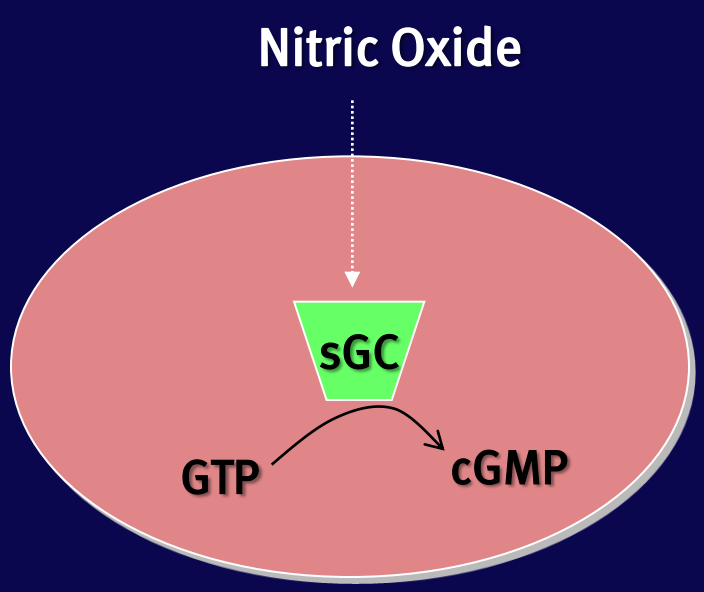
CASCADE: Touloumi et al. PLoS ONE 2013

Unanticipated association between abacavir use and raised risk of myocardial infarction

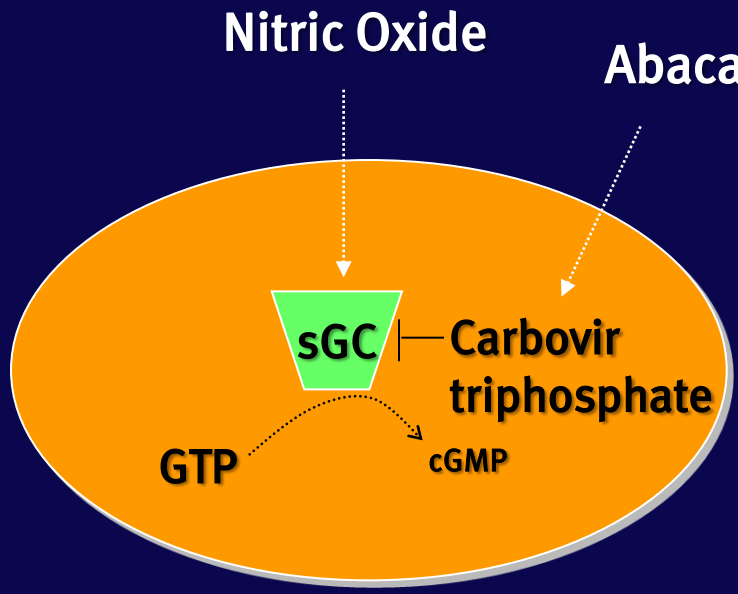


D:A:D Lancet 2008

Abacavir, a Competitive Inhibitor of Guanylyl Cyclase (sGC), Increases Platelet Reactivity



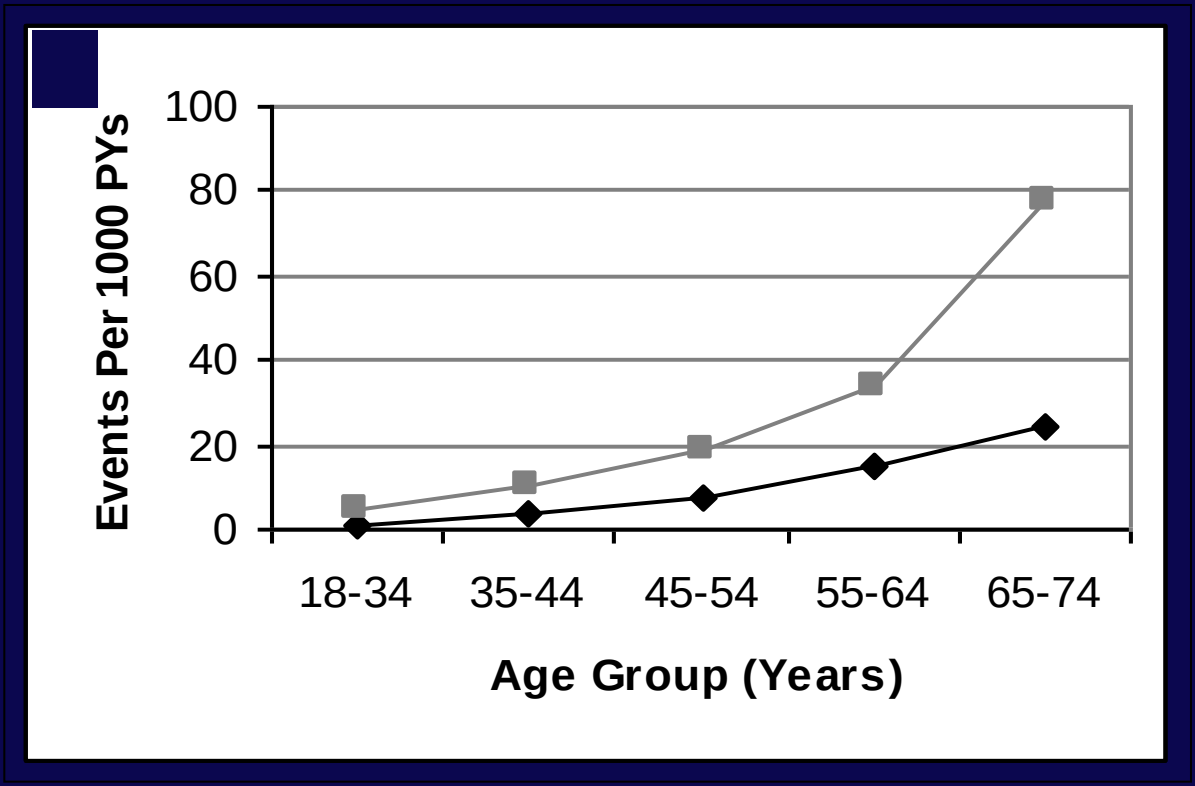
Inactive platelet



Increased platelet activity
Increased MI risk

Baum et al, JID 2011

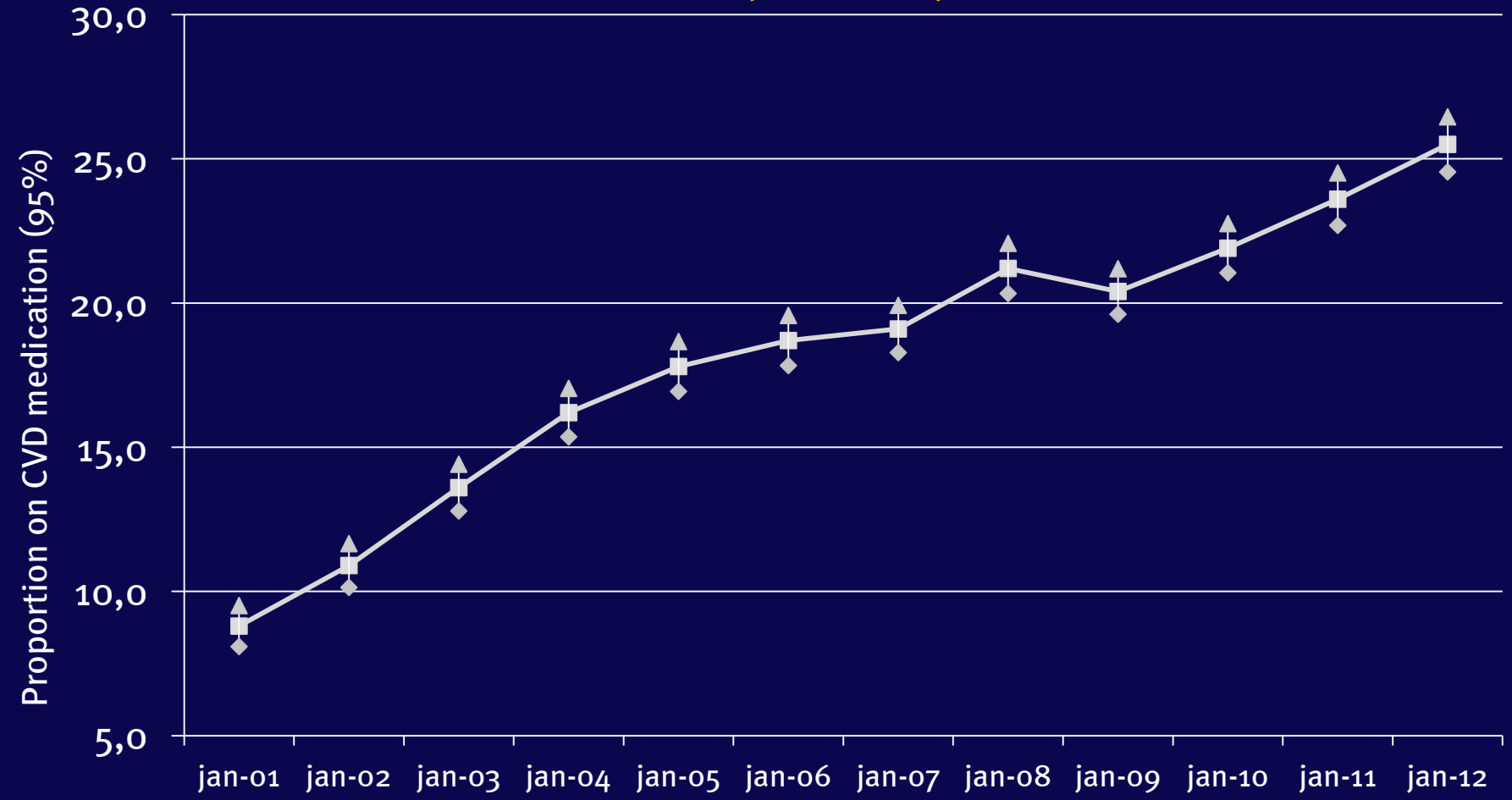
The excess risk of CAD in HIV disease increases with age, suggesting that problems will become more apparent in next decade



RR adjusted for age, gender, race, hypertension, diabetes, and dyslipidaemia

Triant VA et al, J Clin Endocrinol Metab, 2007

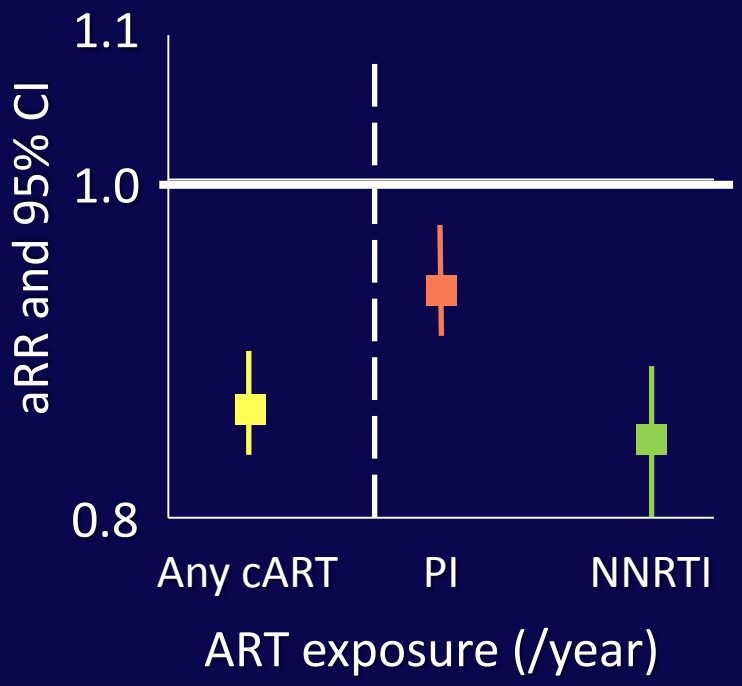
Proportion of patients on anti-CVD medication
1st January each year



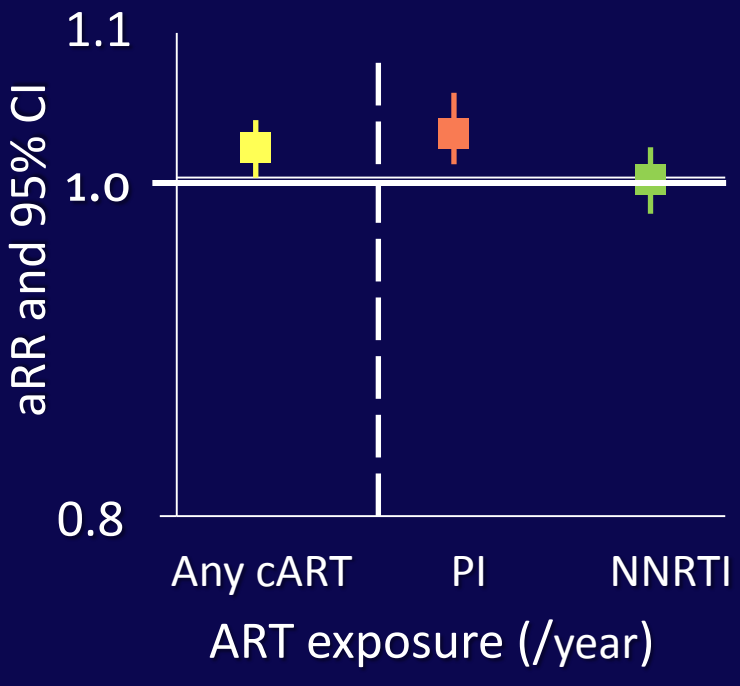
N under follow-up	jan-01	jan-02	jan-03	jan-04	jan-05	jan-06	jan-07	jan-08	jan-09	jan-10	jan-11	jan-12
	6106	6474	6879	7402	7538	7745	8843	8493	10034	9018	8369	8003

ART exposure and AIDS- and non-AIDS-defining cancer

AIDS-defining cancer (n = 1,151)



Non-AIDS-defining cancer (n = 1,091)



Adjusted for age, sex, cohort, HIV mode of acquisition, ethnic group, calendar year, body mass index, any prior cancer, prior AIDS diagnosis, prior AIDS cancer, smoking status, HCV and HBV status

D:A:D: Bruyand et al CROI 2013 Also Chao *et al*, AIDS 2012, Piketty *et al* J Clin Oncol 2012

Depressive symptoms and current treatment for depression

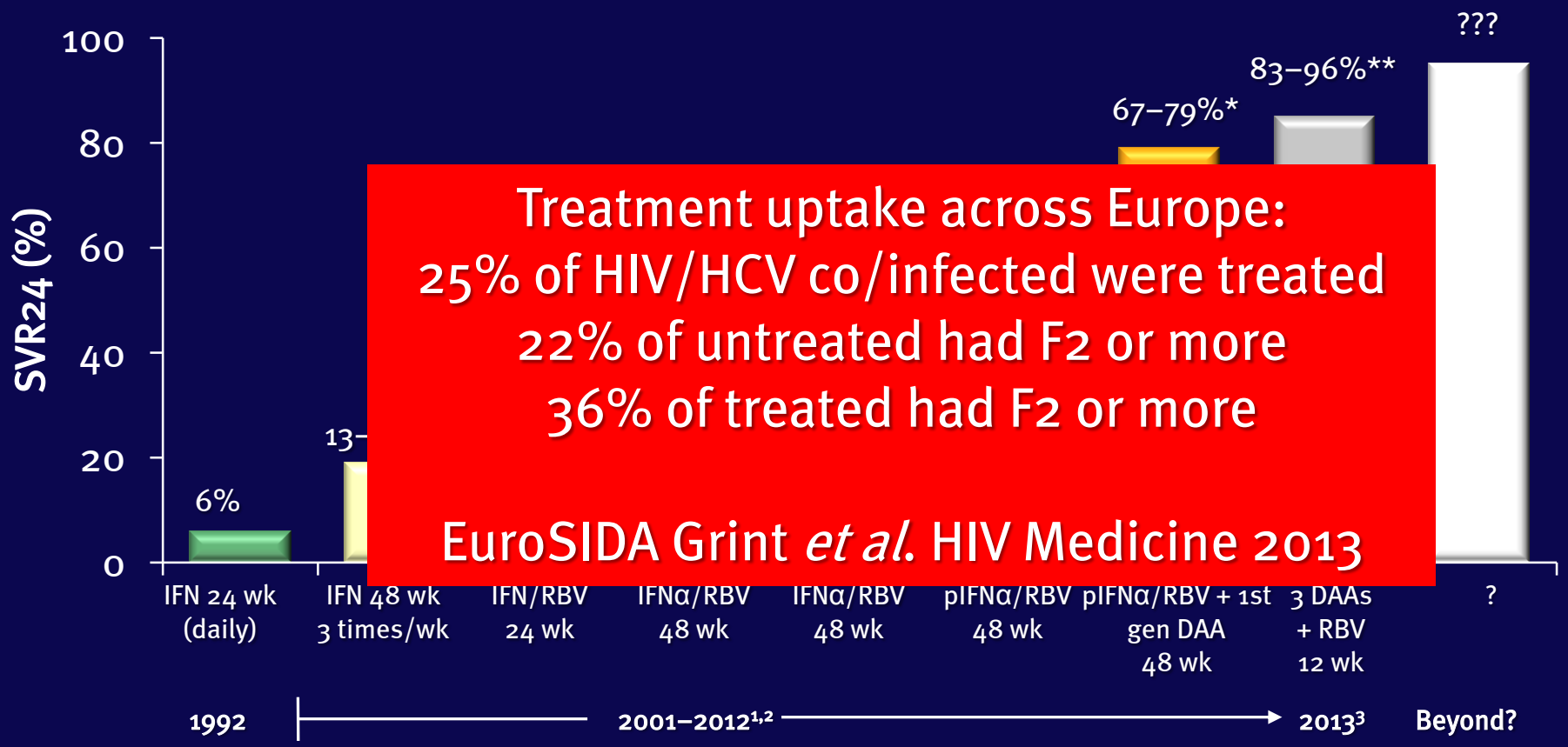
PHQ-9 Depressive Disorder status	Current treatment for depression?*	N
PHQ-9 DD (N=579)	YES NO	241 338
No PHQ-9 DD (N=1596)	YES NO	200 1396
TOTAL		2175

***Medicine or other therapy for depression**

- Total prevalence of depression (treatment or symptoms): 35.8% (779/2175)
- Among those with evidence of depression, 43.4% (338/779) were not receiving any treatment for depression

ASTRA study: Lampre *et al*, BHIVA, 2012

Cure success in HCV: the era of direct-acting antivirals (DAAs)



Treatment uptake across Europe:
25% of HIV/HCV co/infected were treated
22% of untreated had F2 or more
36% of treated had F2 or more

EuroSIDA Grint *et al.* HIV Medicine 2013

*In patients with HCV genotype 1; ** In treatment-naïve patients; IFN, interferon; RBV, ribavirin; SVR, sustained virologic response

1. Adapted from Manns MP, et al. Gut 2006;55:1350–59. 2. Tran TT. Am J Manag Care 2012;18(14 Suppl):S340–9. 3. Kowdley KV, et al. EASL 2013. Abstr 3. Available at: www.clinicaloptions.com/Hepatitis/Conference%20Coverage/Amsterdam%202013/Viral%20Hepatitis/Capsules/3.aspx. Accessed 25Jul13

Challenges in care when DAA becomes standard-of-care treatment for HCV

- Will likely be expensive
- Most pivotal trials done in persons with Fo-F1
  - F3/F4 stand to benefit the most but also more ADR – avoid repeat of problems w/ 1st generation PI's

Factors	Platelet count >100,000/mm^3	Platelet count ≤100,000/mm^3
Serum albumin		
≥35 g/L	3.4% (10/298)	4.3% (3/69)
<35 g/L	7.1% (2/28)	44.1% (15/34)

Hézode et al.
J Hepatol 2013

- Eastern Europe: app 800,000 HIV+/HCV+
  - access projected low – priority on ART earlier

Quality of care:

Define settings implementing
best standard of care

Benchmark own performance
(by use of indicators of care)

Degree of insufficient care
(not poor vs good care)
so targeted approach to improve care

Strengths and challenges within Europe to provide "good" care for HIV+ persons

- Strengths
  - When working well HIV care is very good (optimal ?)
    - experienced clinics w/ broad availability of medicine + no/minimal fee for care
- Challenges
  - Financial and political "instability" – erosion of good standard
  - Public health policies sometimes contra-productive
    - e.g. not wise to exclude diagnosed HIV+ from care
  - Available evidence - diversity in quality
    - Linkage and retention in care
    - Medicines for HIV, coinfections, comorbidities, addiction
  - Need for continent-wide benchmarking of quality to find "hot-spots" of good and poorer care

Task shifting

- If we don't figure it out – funders of health systems will
- In countries using
  - public health approach to care:
    - From doctors to nurses to assistants to community
    - Well integrated (out of necessity often) and evidenced based
  - Individualized care:
    - In stable well-treated HIV+ person – risk of viral failure is low
    - Interval between visits to HIV clinic progressively longer
    - General practitioners progressively involved with care
      - Define roles and responsibilities
      - Who is overall responsible for care
      - How to delegate responsibilities for component of care ?
      - How to oversee quality of care ?

Future: paradigm shift in HIV care

- Considerations
  - HIV care requires experience and high case load
  - Countries will centralized care have high retention and durable suppression rates
  - Task shifting could erode this success
- HIV specialist oversee care in “uncomplicated” patients provided by
  - General practitioners
  - Nurses in “own” outpatient clinic (physically located either within medical facility or in community)
  - Email clinic in Brigton (Whetham *et al*, EACS PS8/6)
    - electronic surveillance flagging abnormal course of follow-up

Summary

- Cohort studies instrumental to understand risk and benefits from ART
  - Consequences of lack of use of ART
  - Balance discussion on public health use of ART prevention
  - “Misused” in contemporary discussion on WTS
- Future role
  - Transmission and prevention
  - Issues from longer use of ART (good or bad)
  - Pathogenesis and host-response – biobank incl host DNA
  - Rational use of DAA for HCV
  - Best handling of emerging MDR/XDR TB

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