ROME, November **25-26**, 2014

AUDITORIUM, MINISTRY OF HEALTH

EACS European AIDS Clinical Society MEETING

STANDARD of CARE for **HIV** and **COINFECTIONS** in **EUROPE**

Chairs: *A. Antinori, A. d'Arminio Monforte, C. Mussini*

Late Presentation in HIV infection

Amanda Mocroft
University College London
a.mocroft@ucl.ac.uk

Outline

- Definitions and diagnosis of late presentation
- Consequences of late presentation
- Late presentation across Europe
- Initiatives to reduce late presentation

Outline

- Definitions and diagnosis of late presentation
- Prevalence of late presentation
- Consequences of late presentation
- Initiatives to reduce late presentation

Many definitions reported

CD4 count	Country and year
CD4 < 350	England, 2000
CD4 < 200	UK 2000, 2005, 2006
	France 2006, 2007
	Italy, 2004
	Spain, 2005
CD4 < 50	UK 2004

Time until first ADE	Country and year
< 1 year	European survey, 2006
< 6 months	England, 2006 France, 1998 Italy, 2005
< 3 months	Sweden, 2005 England, 2000 France, 2004, 2007 Italy, 2000 Poland, 2006
< 8 weeks	Spain, 2002 Denmark, 2005
< 1 month	England, 2001 Italy, 2003
Concurrent AIDS	Poland, 2006 England, 2006 France, 2000

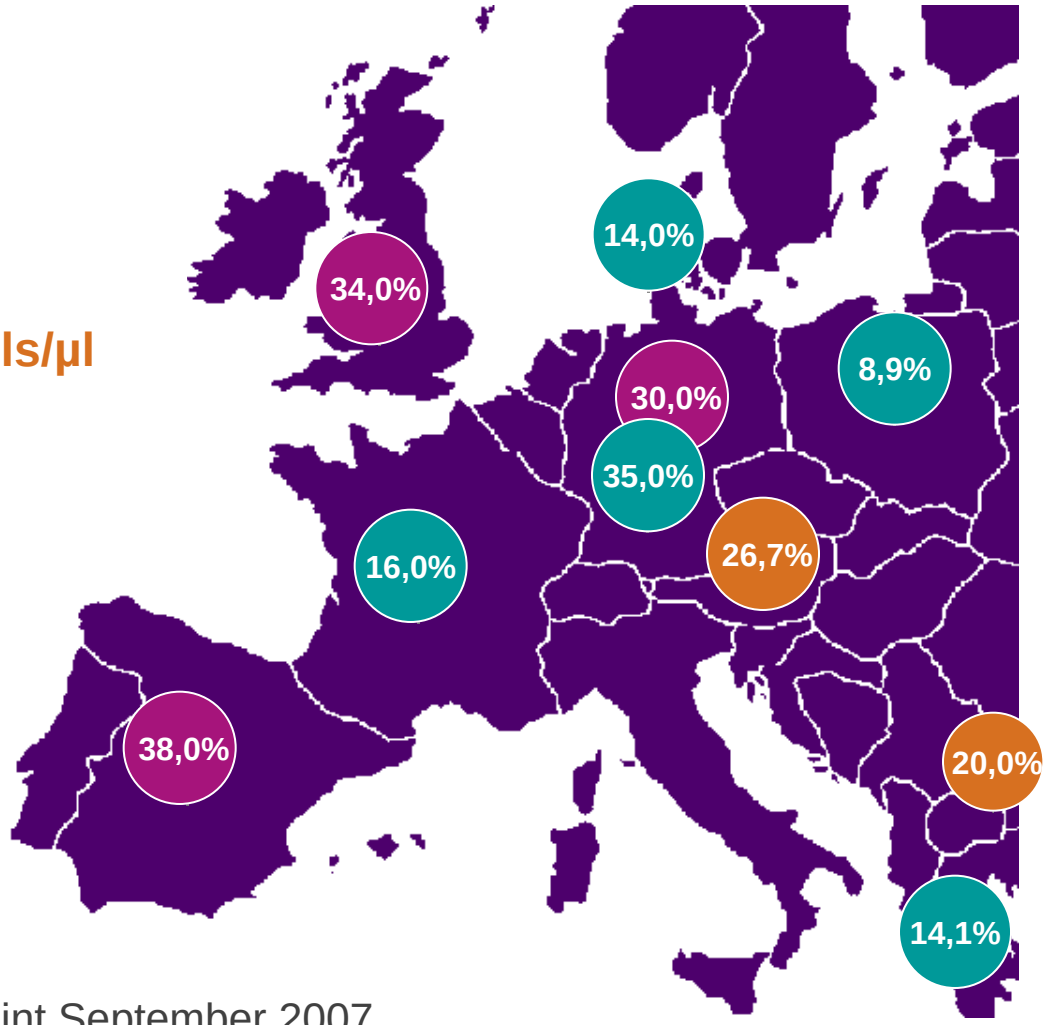
Why do we need a common definition?

- To monitor changes in rates of late presentation over time, and assess effectiveness of public health interventions
- To identify risk factors in a common way
- To permit comparisons between countries
- To correlate late presentation rates with country-specific interventions and/or policies for earlier diagnosis

Prevalence of Late Presentation : *Impact of definition*

Definition based on:

- **AIDS**
- **CD4 < 200 cells/µl**
- **AIDS and CD4 < 200 cells/µl**



Late Presenter (%), survey timepoint September 2007

Modified from: Adler A et al. AIDS Care; 2008

European Consensus definition

Late presentation: Persons presenting for care with a **CD4 count <350 cells/mL** or presenting with an **AIDS-defining event**, regardless of the CD4 cell count

Late presentation with advanced disease: Persons presenting for care with a **CD4 count <200 cells/mL** or presenting with an **AIDS-defining event**, regardless of the CD4 cell count

Antinori, *HIV Med* 2010

Outline

- Definitions and diagnosis of late presentation
- Consequences of late presentation
- Late presentation across Europe
- Initiatives to reduce late presentation

What are the consequences of starting cART late?

Short Term

Higher risk of mortality in the 1st year
ART CC and ART LINC, Lancet 2006; 367: 817–24

Reduced chance of viral supression
Waters L, HIV Med *2011* 12(5), 289–298.

Increased risk of hospitalization
Sabin CA, AIDS 2004; 18:2145–2151

More potential drug-drug interaction
Rockstroh JK, Antivir. Ther 2010.15 (S1), 25-30

More likely to have IRIS
Barber D, Nature Rev 2011 vol 10: 150

Long Term

Increased risk of non-AIDS events
Reekie, AIDS. 2011;25(18):2259-68

Increased risk of neurocognitive impairment
Ellis RJ, AIDS 2011;25(14):1747-51

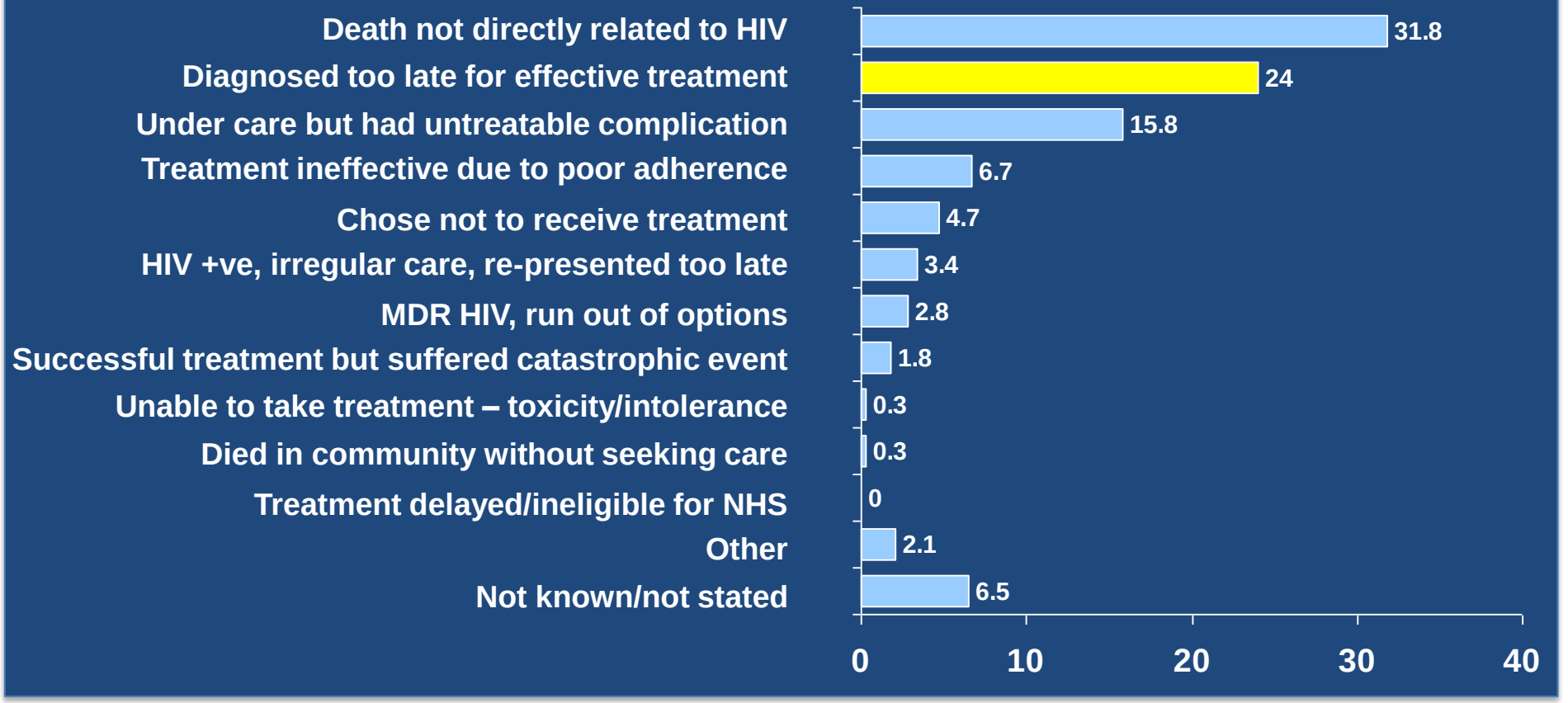
Potentially increased risk of HIV transmission
Cohen MS, N Engl J Med. 2011;365(6):493-505

Higher direct cost of care
RY Chen, et al; Clin Infect Dis 2006

Adapted from: Waters and Sabin, *Expert Rev Anti Infect Ther.* 2011

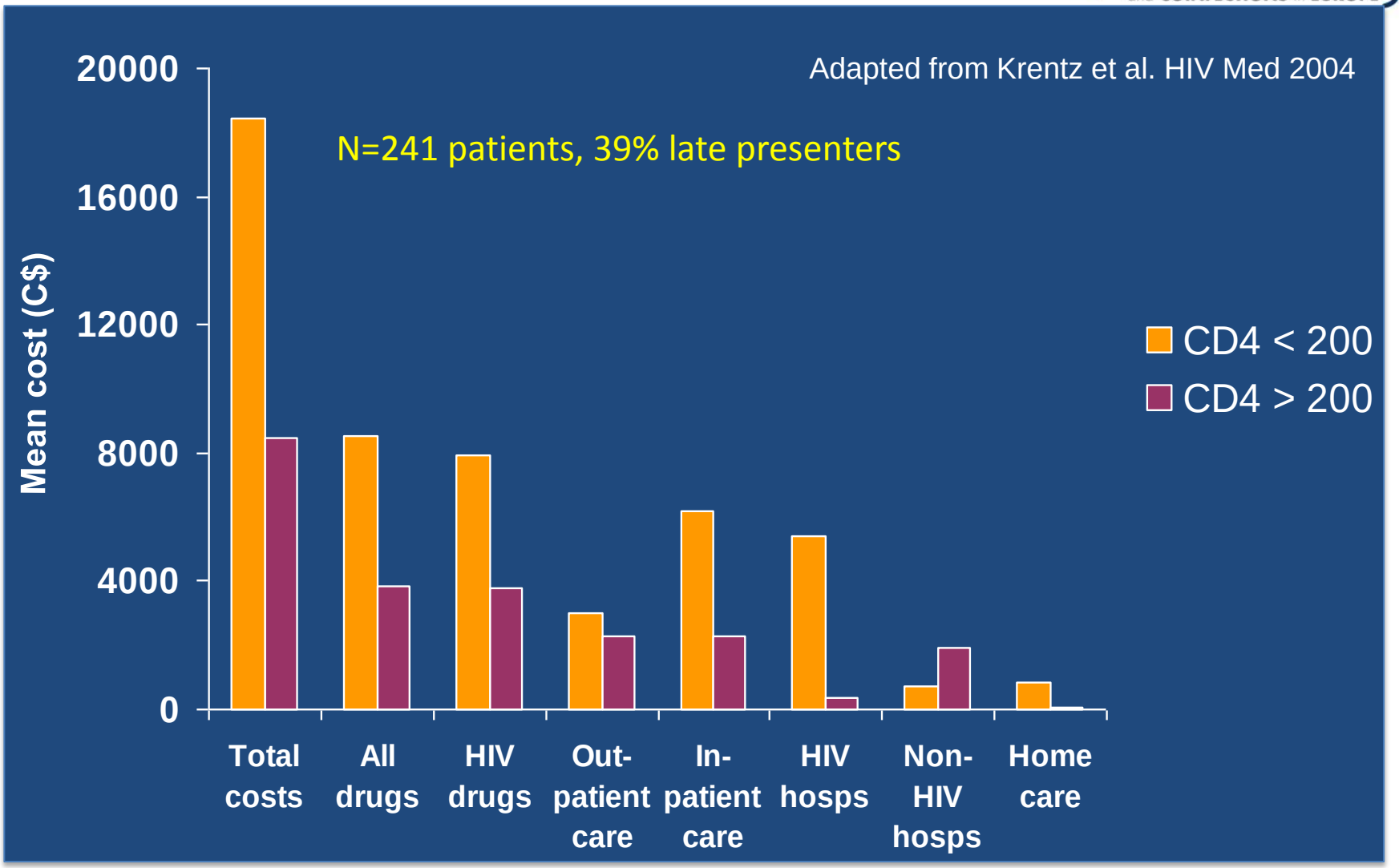
BHIVA audit: scenario leading to death

n = 387 deaths between October 2004 and September 2005



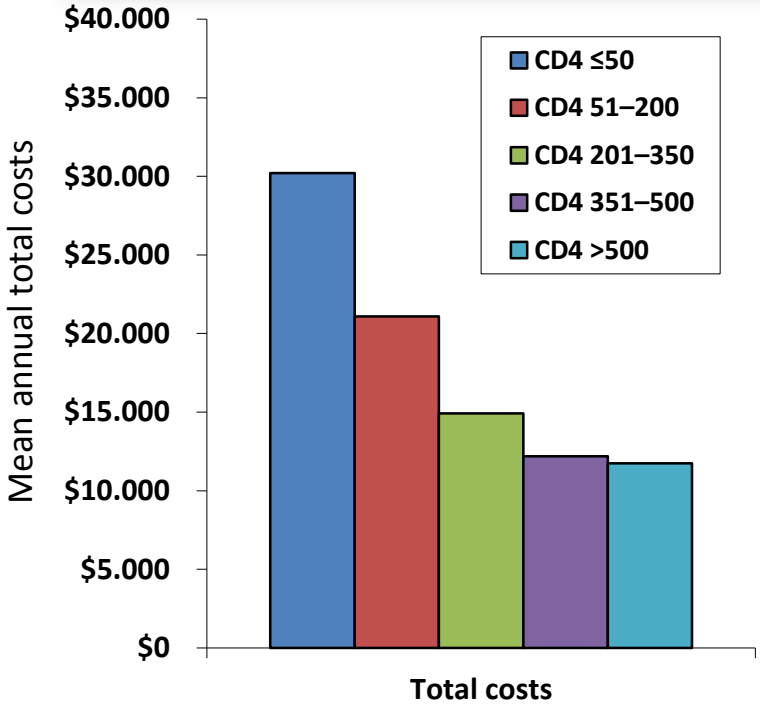
Adapted from Lucas. Clin Med 2008;8:250

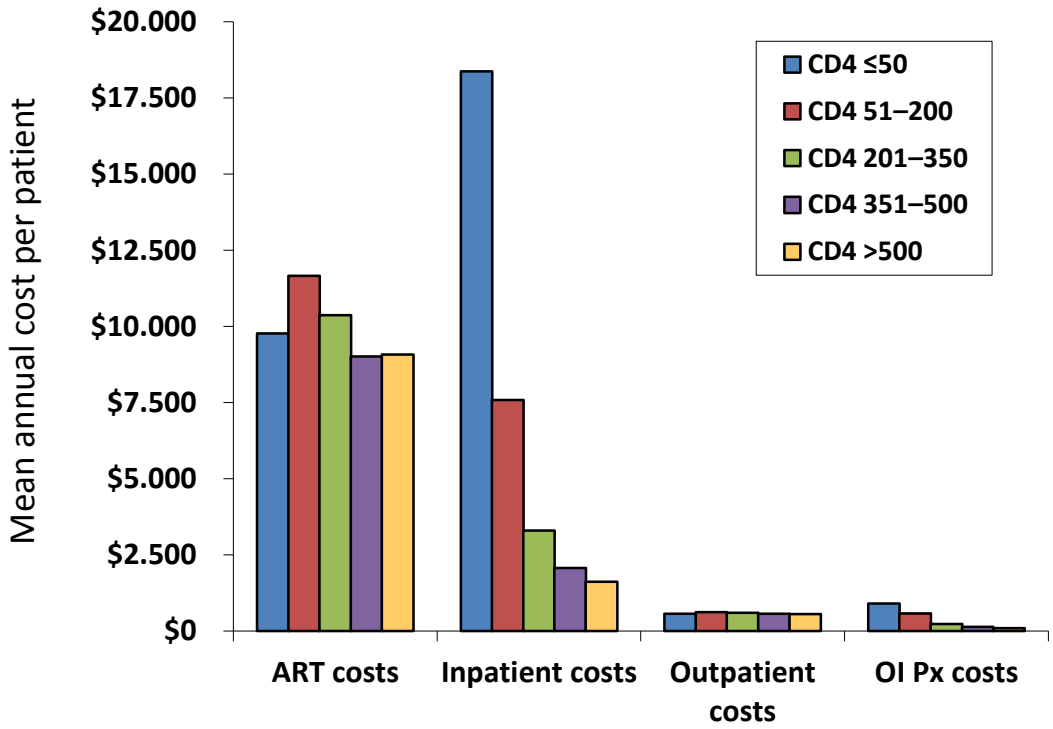
Estimated cost of late presentation in Canada – year following diagnosis



Higher cost of medical care for late presenters

Data for 10,433 patients from 7 primary HIV care sites



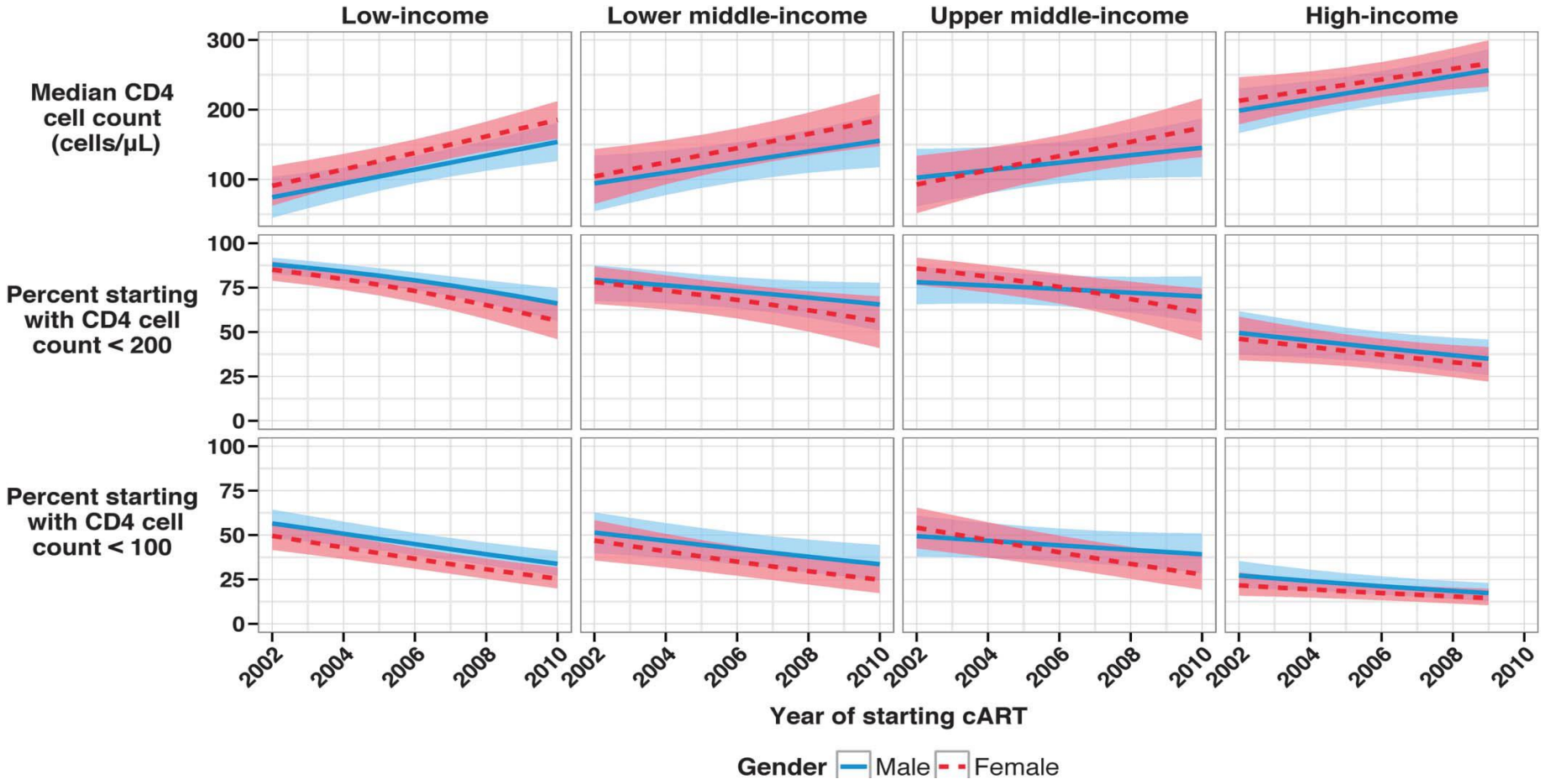


- Annual total cost of late care is ~2.5 times the cost of care for early therapy (CD4 >500)
- Inpatient costs attributed the most to the total cost in late presenters

Adapted from Gebo KA et al. *AIDS* 2010

Variation in CD4 count at starting cART

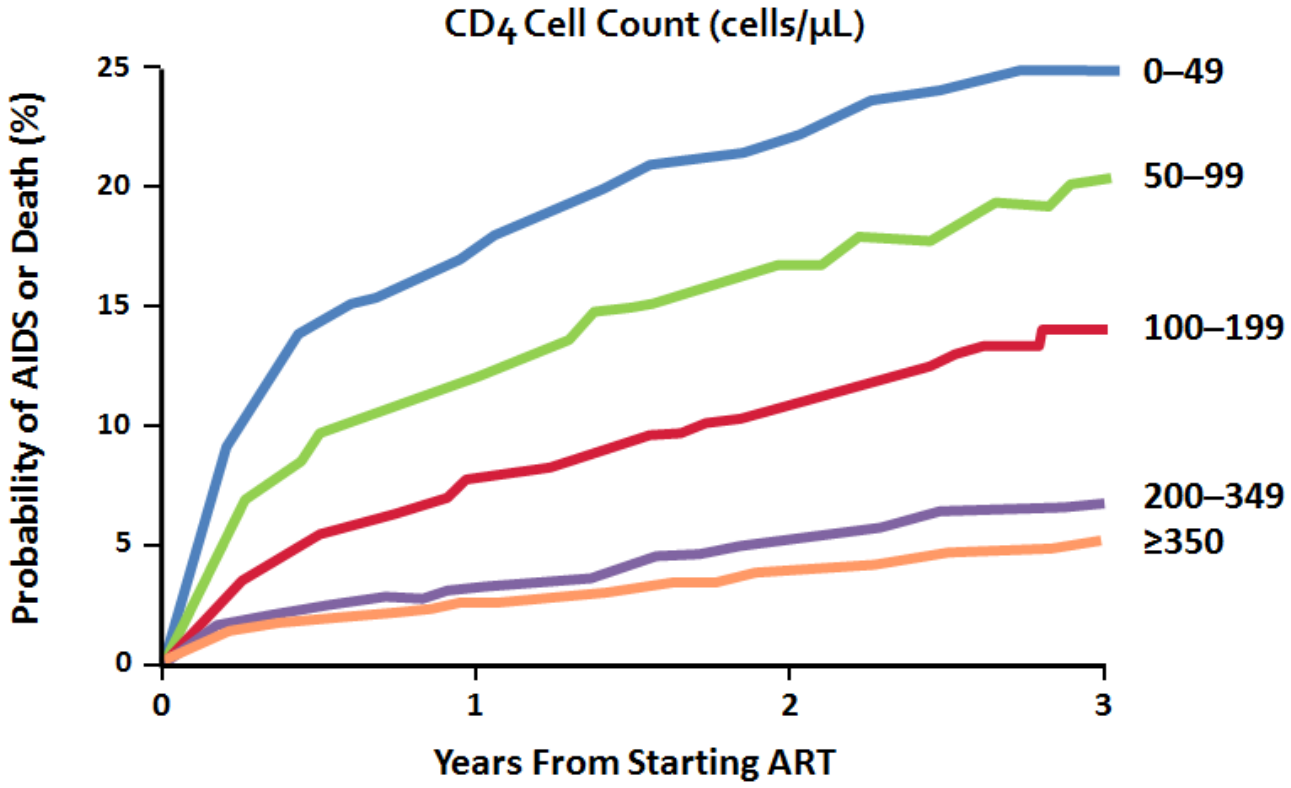
Based on 379,865 pts, LIC (<$1005), LMIC ($1006-$3975), UMIC ($3976-$12,275), HIC (>$12,175)



IeDEA and ARTCC collaboration; JAIDS 2014

Prognosis from starting ART according to pre-therapy CD4 cell counts and HIV-RNA levels

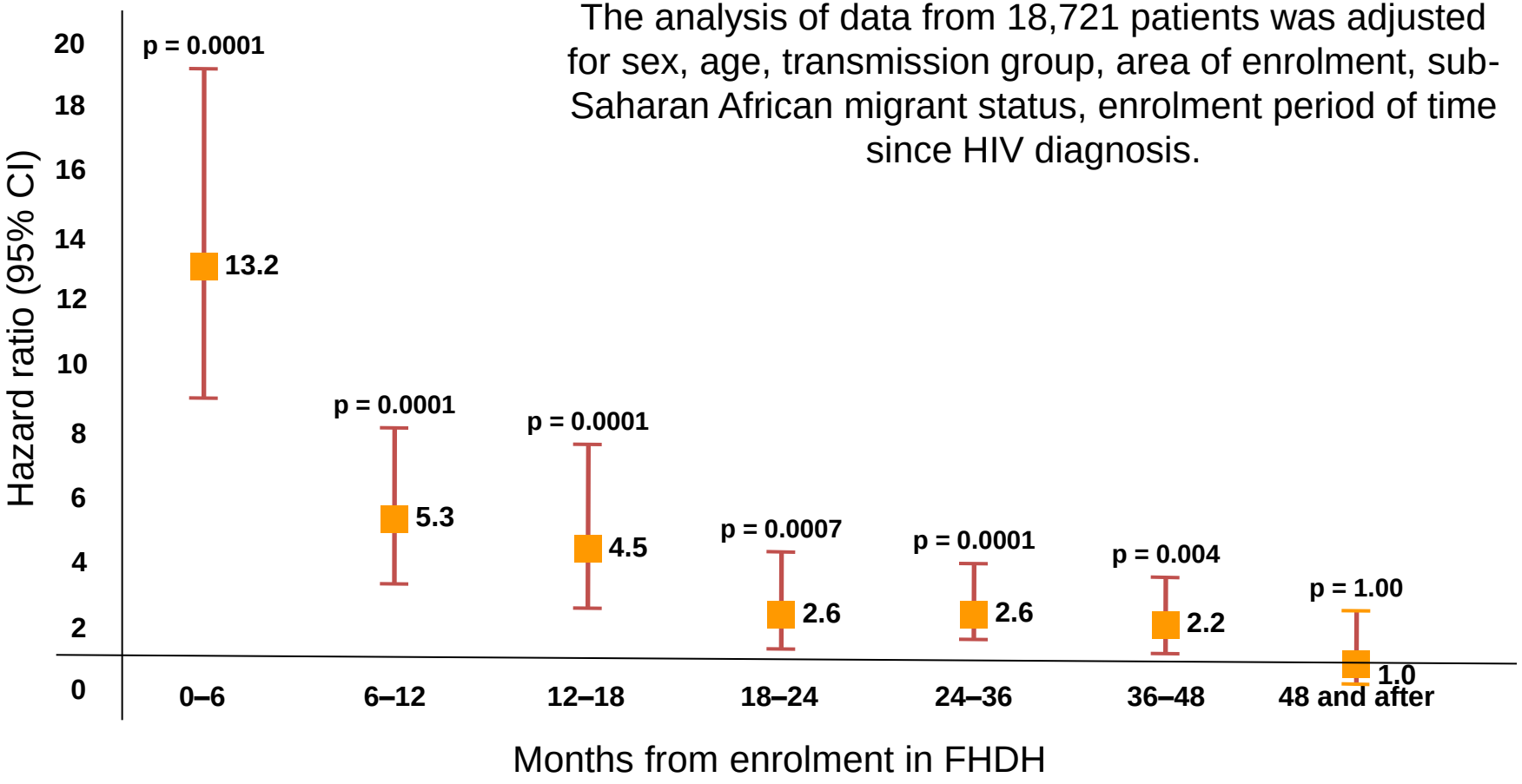
ART Cohort Collaboration, 13 cohort studies from Europe and North America. Analysis of adult patients starting HAART with a combination of at least three drugs (N=12,574)



Egger M et al. *Lancet* 2002;360(9327):119–129

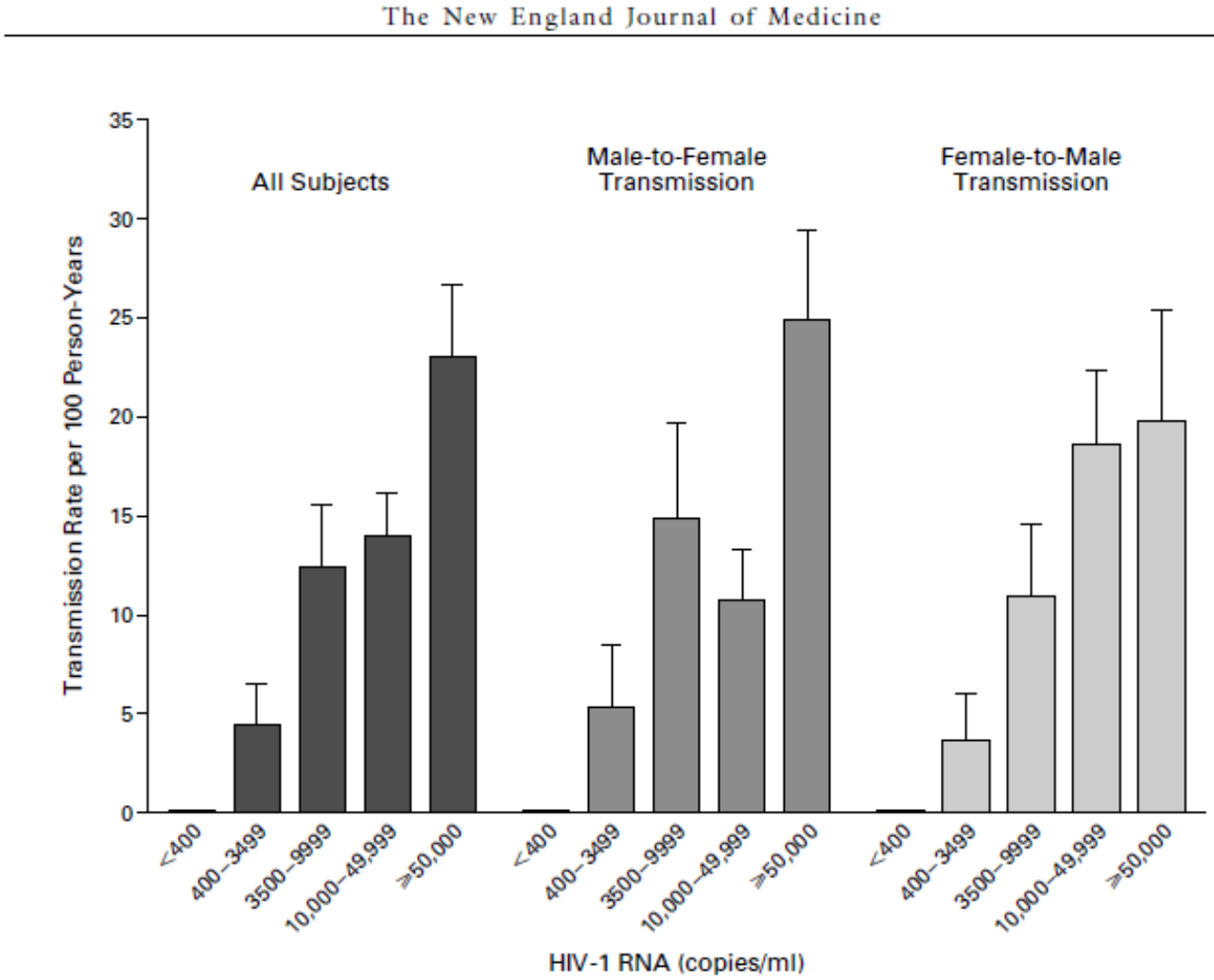
Mortality and delayed access to care in France

The analysis of data from 18,721 patients was adjusted for sex, age, transmission group, area of enrolment, sub-Saharan African migrant status, enrolment period of time since HIV diagnosis.



Adapted from Lanoy et al. Antiviral Therapy 2007

Onward transmission of HIV (1)

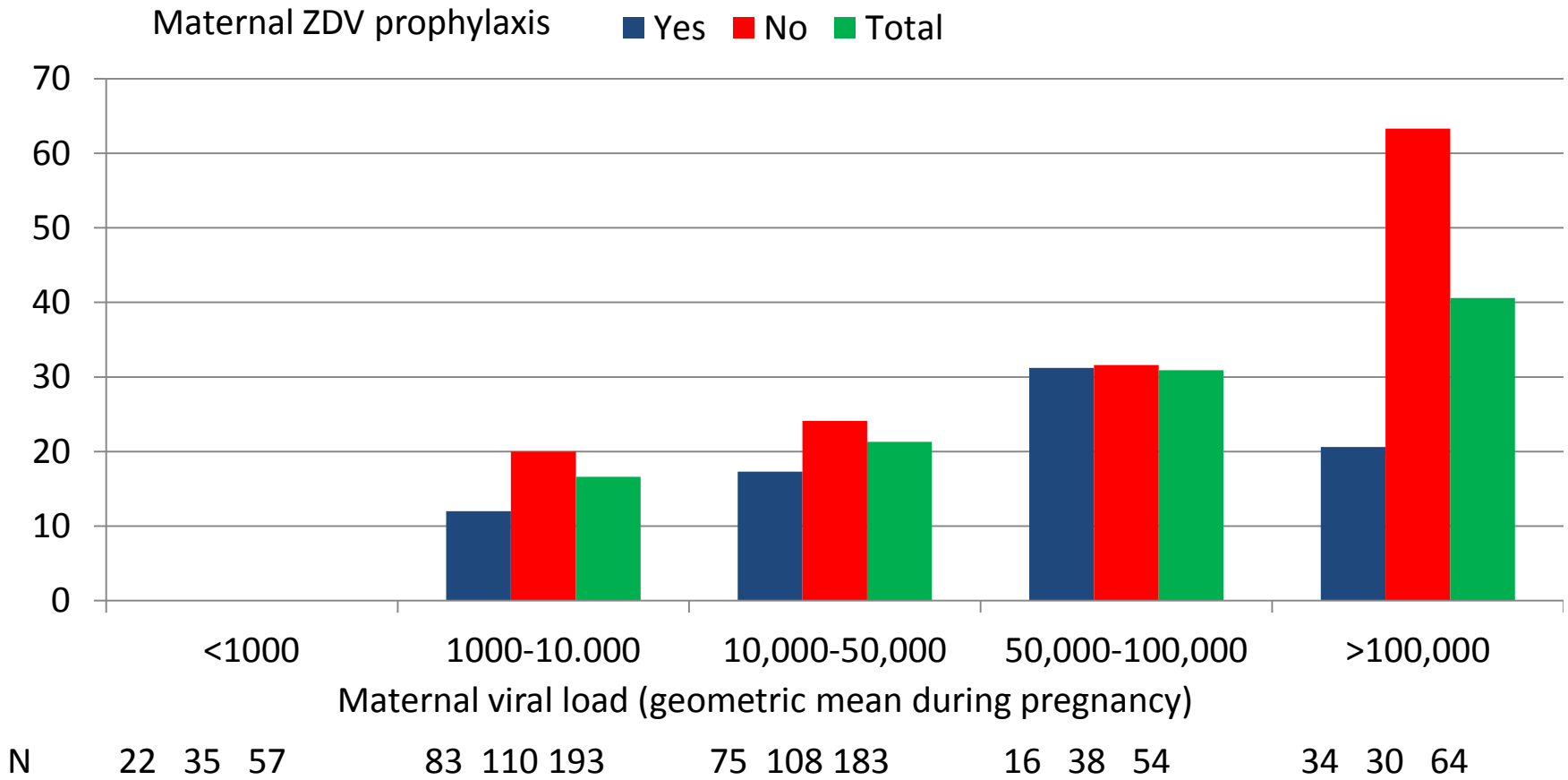


Quinn et al, *NEJM* 2000

- N=415 serodiscordant couples from 4 US states and Puerto Rico
- 90 HIV seroconversions over 30 mths FU
- none with VL < 1500 cp/ml

Onward transmission of HIV (2)

502 women from Rakai, Uganda, with singleton pregnancies; no transmissions to child when maternal VL < 1000 cp/ml

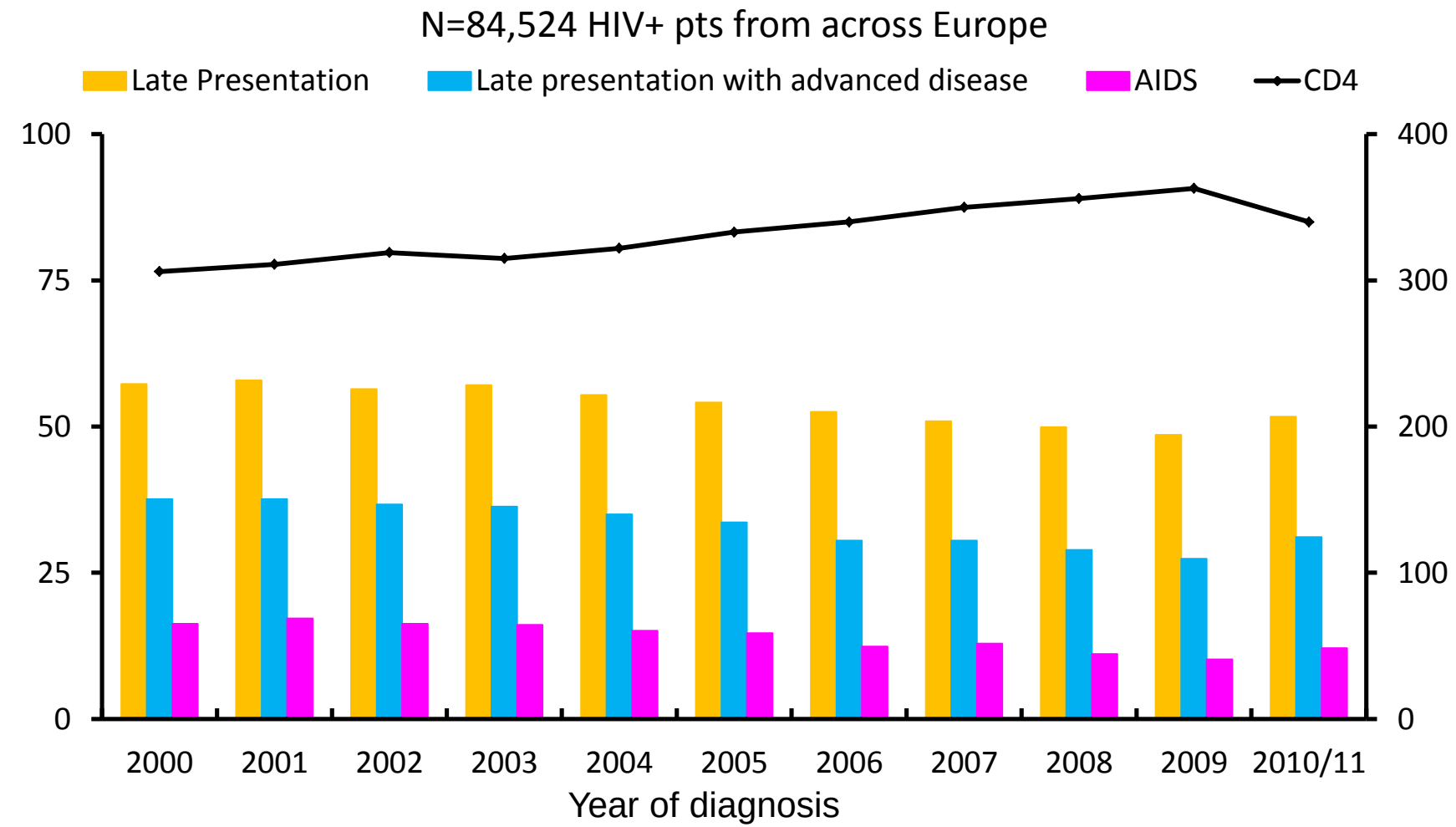


Adapted from Garcia et al NEJM 1999

Outline

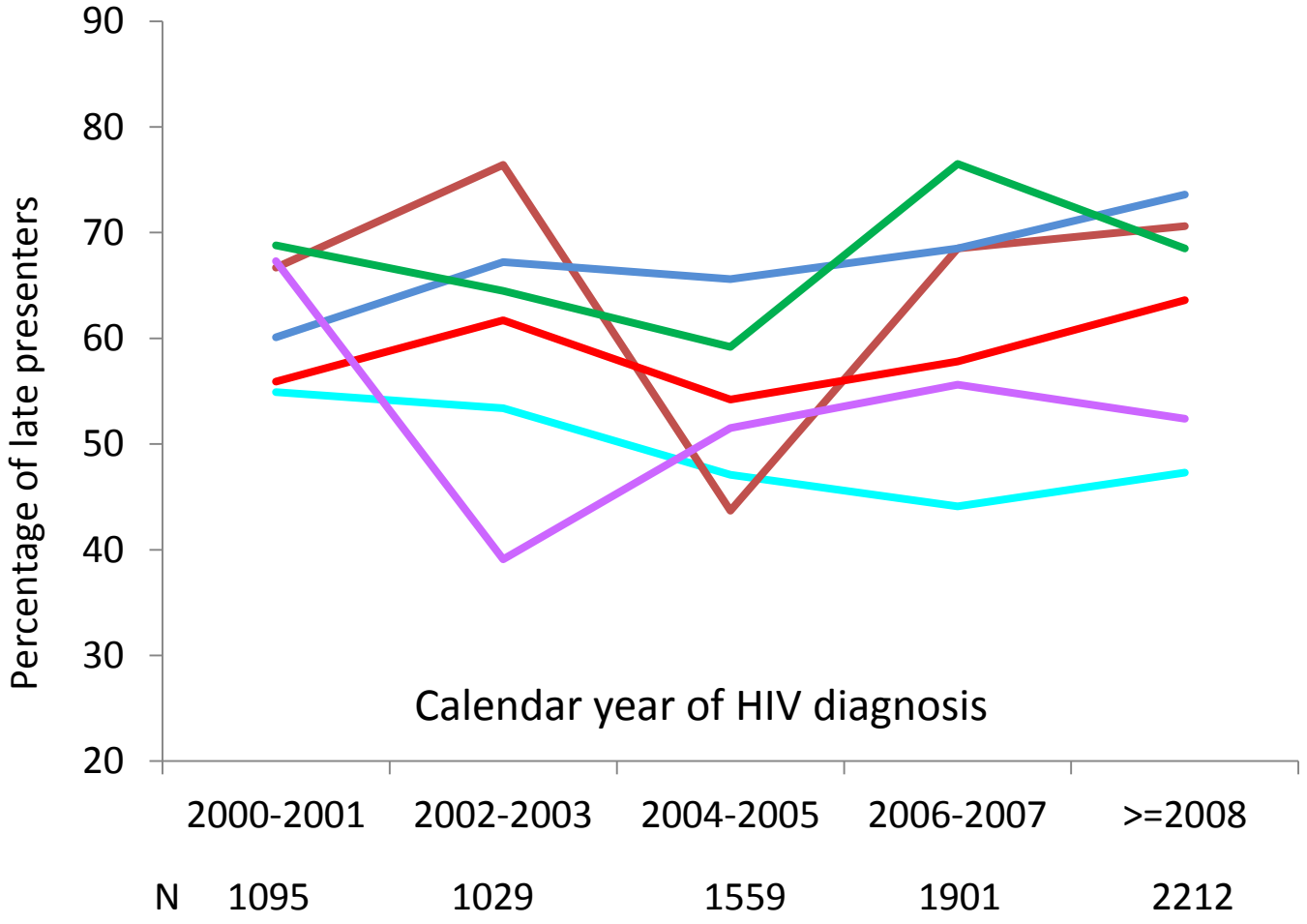
- Definitions and diagnosis of late presentation
- Consequences of late presentation
- Late presentation across Europe
- Initiatives to reduce late presentation

Changes over time in late presentation and CD4 count at HIV-diagnosis : COHERE 2000-2011



Mocroft et al, PLoS Med 2013

Changes in late presentation over calendar time in **Southern Europe**; stratified by HIV exposure group



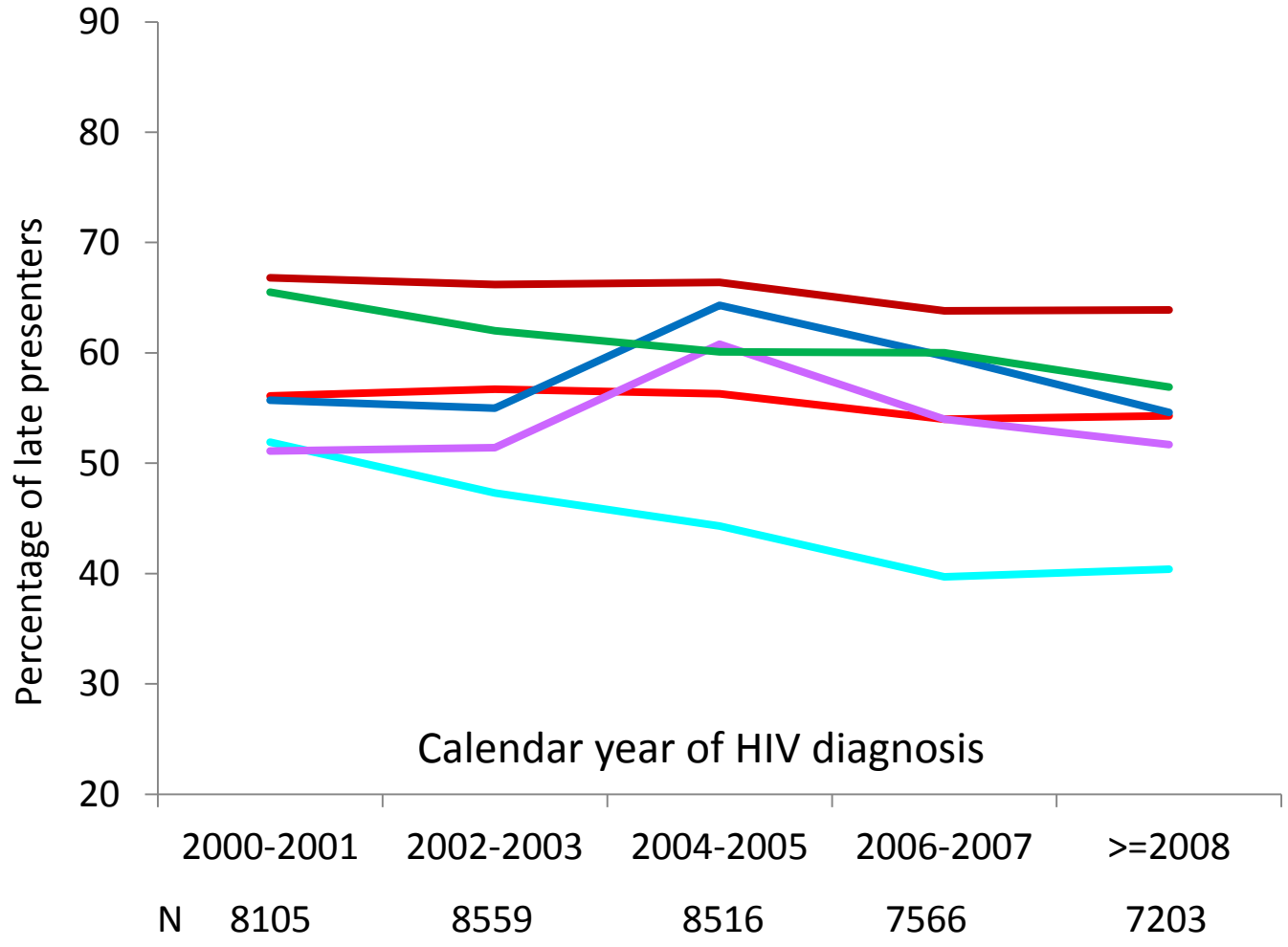
Adjusted*odds ratio (95% CI) of late presentation per calendar year later : Comparison of HIV exposure groups

MSM	1.00 (0.97-1.03)
M Het	1.03 (0.98-1.07)
F Het	1.06 (1.02-1.11)
M IDU	1.06 (0.99-1.13)
F IDU	0.92 (0.78-1.09)
Other	1.05 (0.98-1.11)

Mocroft et al, PLoS Med 2013

*Adjusted for age, delayed entry into care (≥3 months) after HIV diagnosis, region of origin, European region of care, and HIV mode of infection. MSM: males having sex with males. M; male. F; female. Het; heterosexual. IDU; injecting drug user

Changes in late presentation over calendar time in **Central** Europe; stratified by HIV exposure group



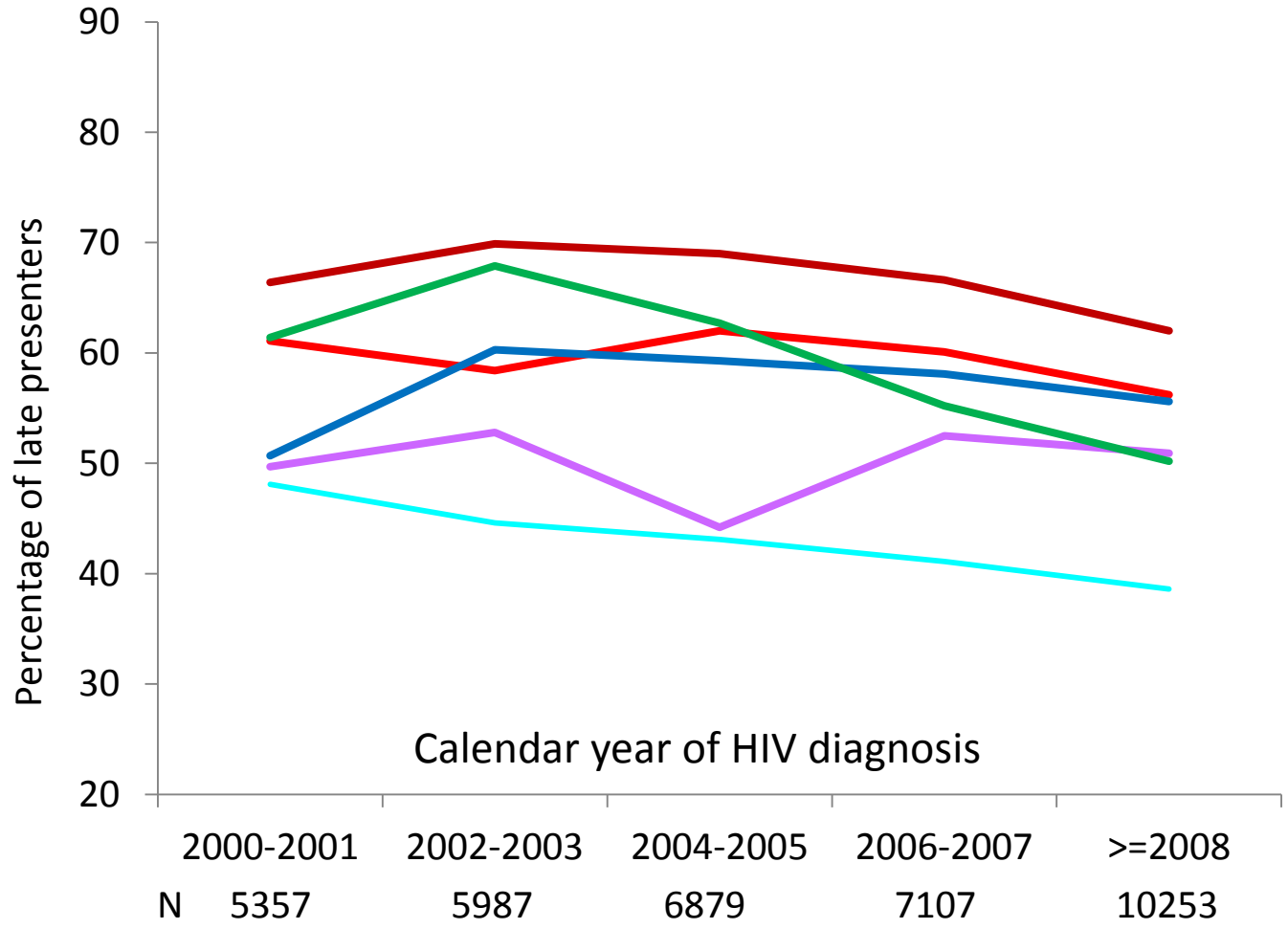
Adjusted*odds ratio (95% CI) of late presentation per calendar year later : Comparison of HIV exposure groups

MSM	0.93 (0.92-0.94)
M Het	0.97 (0.96-0.99)
F Het	0.98 (0.97-0.99)
M IDU	0.99 (0.95-1.03)
F IDU	0.98 (0.92-1.03)
Other	0.95 (0.93-0.98)

Mocroft et al, PLoS Med 2013

*Adjusted for age, delayed entry into care (≥3 months) after HIV diagnosis, region of origin, European region of care, and HIV mode of infection. MSM: males having sex with males. M; male. F; female. Het; heterosexual. IDU; injecting drug user

Changes in late presentation over calendar time in **Northern** Europe; stratified by HIV exposure group



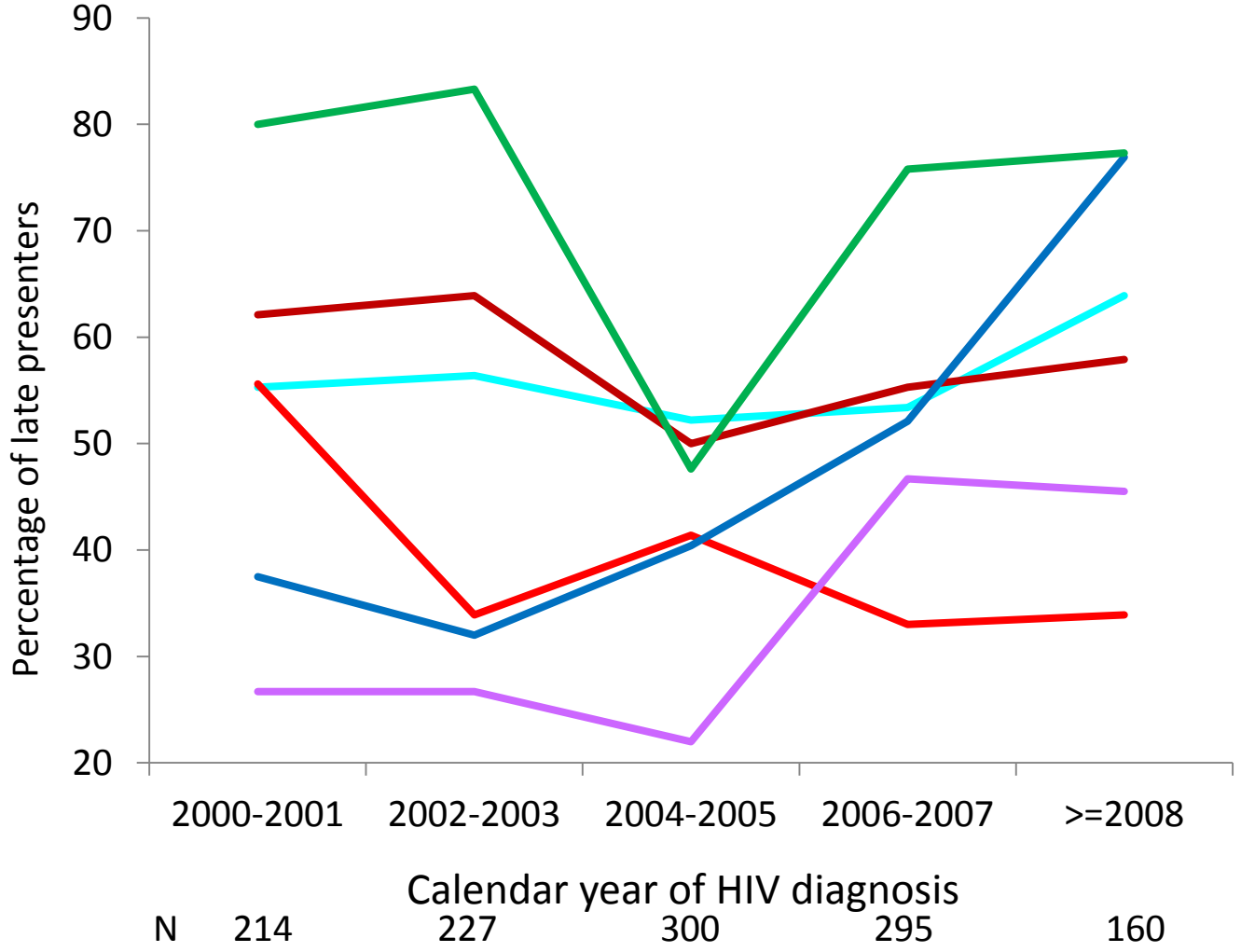
Adjusted*odds ratio (95% CI) of late presentation per calendar year later : Comparison of HIV exposure groups

MSM	0.95 (0.94-0.96)
M Het	0.96 (0.95-0.98)
F Het	0.97 (0.95-0.98)
M IDU	1.01 (0.97-1.04)
F IDU	1.00 (0.94-1.07)
Other	0.92 (0.91-0.94)

Mocroft et al, PLoS Med 2013

*Adjusted for age, delayed entry into care (≥3 months) after HIV diagnosis, region of origin, European region of care, and HIV mode of infection. MSM: males having sex with males. M; male. F; female. Het; heterosexual. IDU; injecting drug user

Changes in late presentation over calendar time in **Eastern** Europe; stratified by HIV exposure group



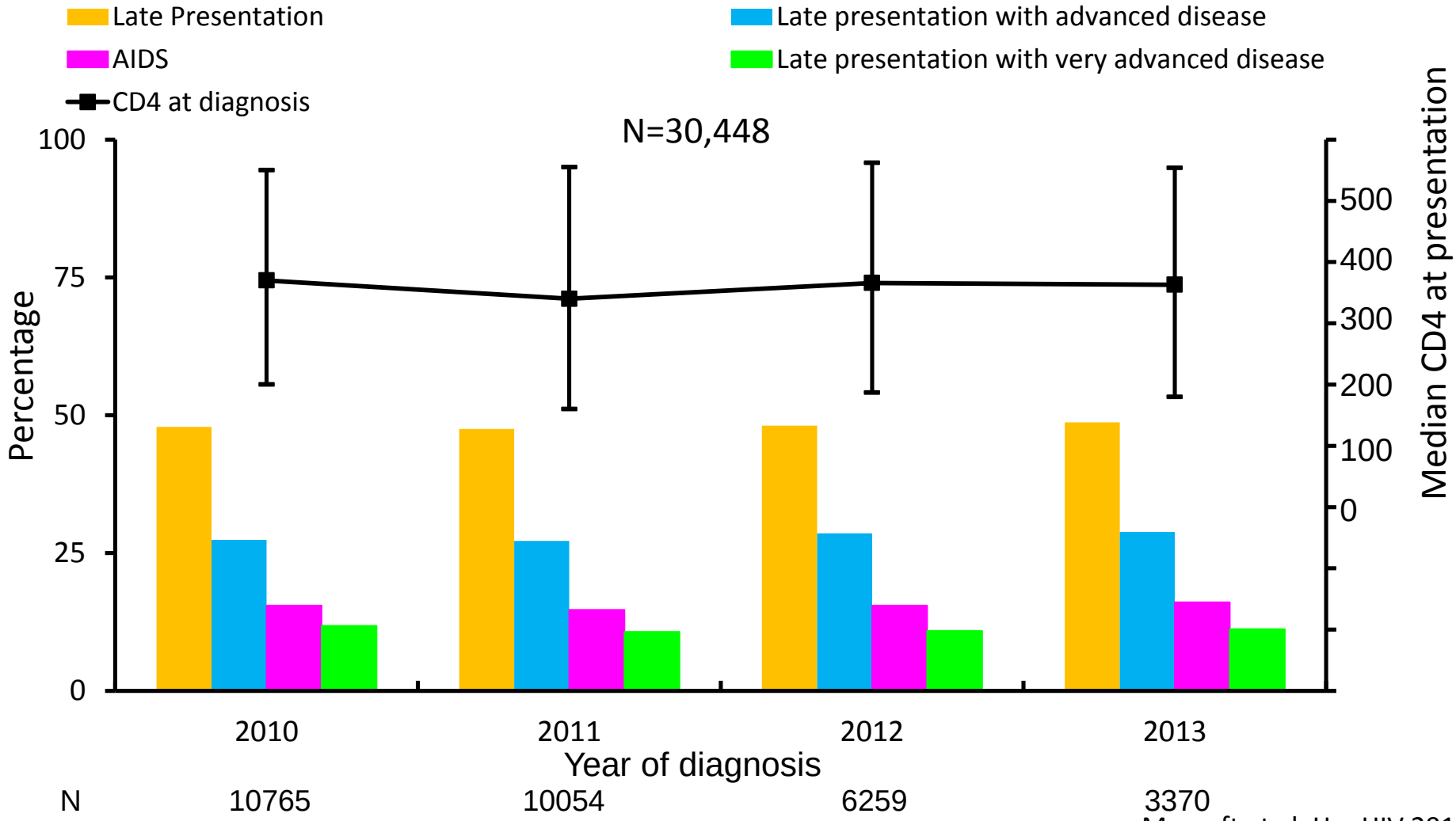
Adjusted*odds ratio (95% CI) of late presentation per calendar year later : Comparison of HIV exposure groups

MSM	1.03 (0.93-1.14)
M Het	0.97 (0.86-1.11)
F Het	0.89 (0.80-0.98)
M IDU	1.11 (0.98-1.25)
F IDU	1.12 (0.93-1.34)
Other	1.02 (0.83-1.26)

Mocroft et al, PLoS Med 2013

*Adjusted for age, delayed entry into care (≥3 months) after HIV diagnosis, region of origin, European region of care, and HIV mode of infection. MSM: males having sex with males. M; male. F; female. Het; heterosexual. IDU; injecting drug user

Changes over time in late presentation and CD4 count at HIV-diagnosis : COHERE 2010-2013



Mocroft et al, HepHIV 2014

Odds of late presentation per year later testing HIV+

N=30,448

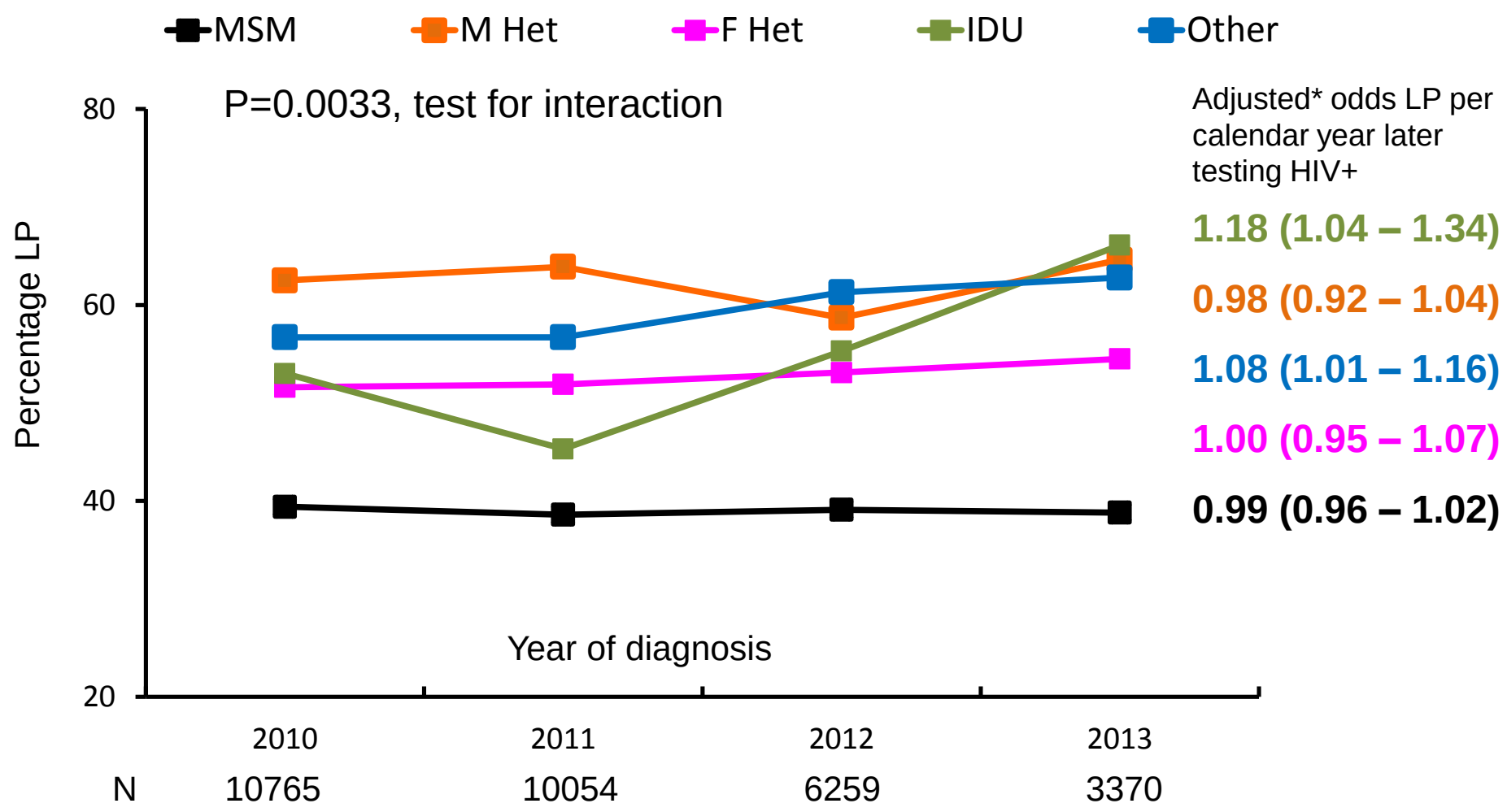
	Univariate			Multivariate*		
	OR	95% CI	P	OR	95% CI	p
Overall	1.01	0.99 – 1.03	0.40	1.00	0.98 – 1.03	0.84
Region						
South	1.00	0.95 – 1.05	0.95	1.00	0.96 – 1.06	0.87
Central	1.01	0.97 – 1.05	0.64	1.01	0.97 – 1.06	0.61
North	1.01	0.98 – 1.04	0.62	0.98	0.94 – 1.02	0.27
East	1.07	0.91 – 1.25	0.41	1.03	0.88 – 1.21	0.73

P=0.073, test for interaction

Late presentation: diagnosed with HIV with a CD4 count below 350/mm^3 or an AIDS defining event regardless of the CD4 count, in the 6 months following HIV diagnosis. *Adjusted for age, HIV exposure group, region of origin and age

Mocroft et al, HepHIV 2014

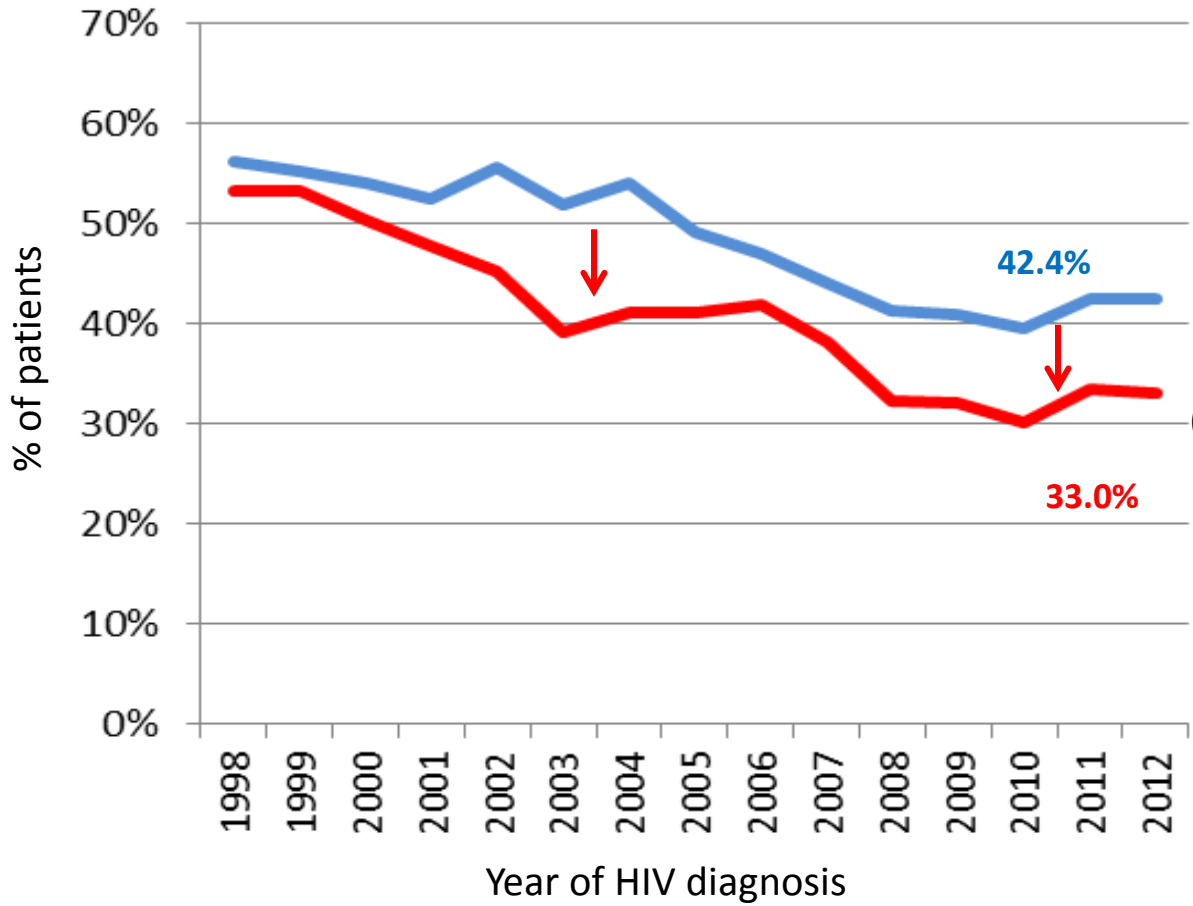
Changes over time in late presentation : HIV exposure group



*Adjusted for age, region of care, region of origin and age

Mocroft et al, HepHIV 2014

Reclassification of LP according to clinical stage



(*p*<0.001)

Cases considered as "LP" by the consensus definition were reclassified as "non-LP" if a recent infection (< 6 months) was reported by clinicians

Stauss et al, HepHIV 2014

Outline

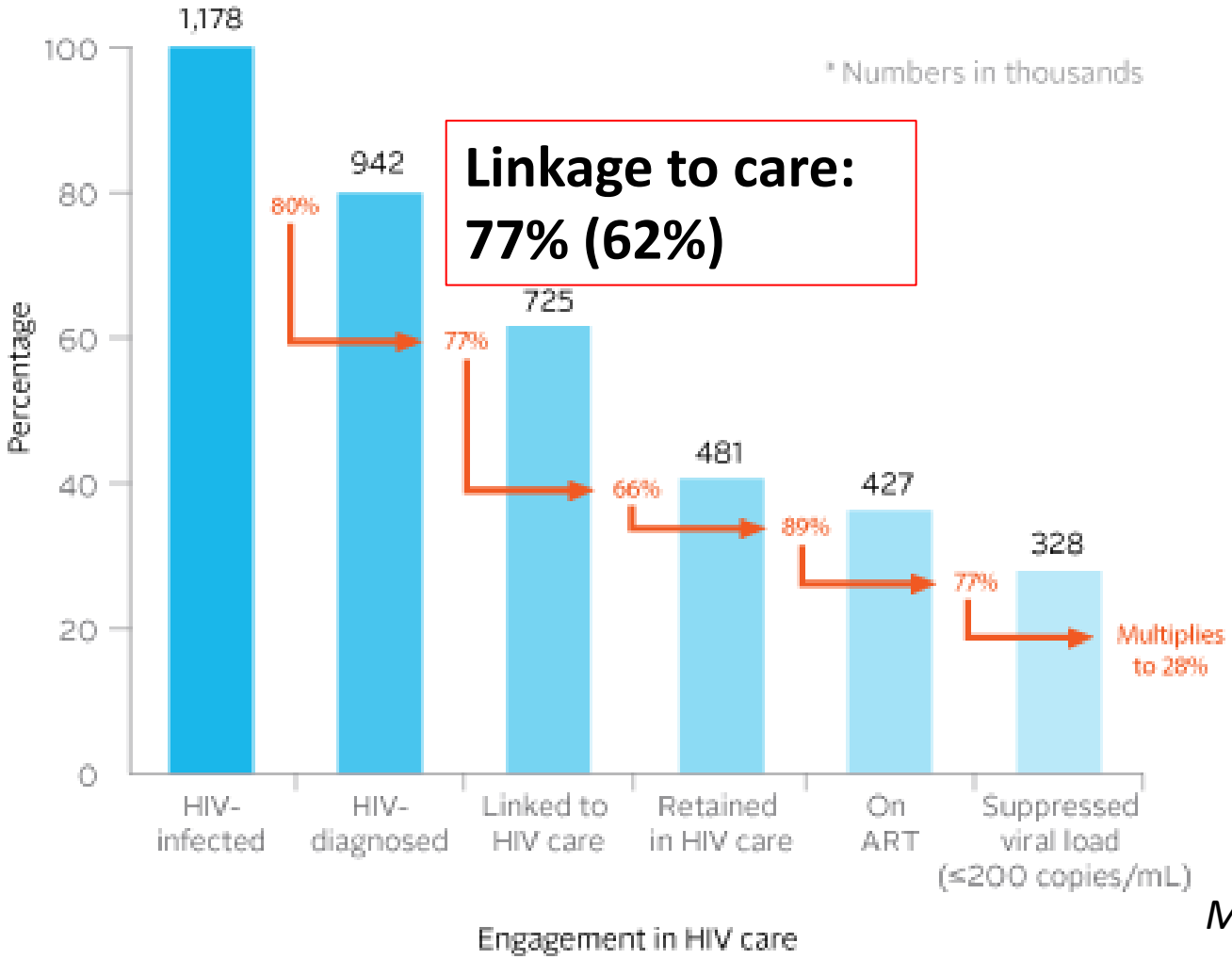
- Definitions and diagnosis of late presentation
- Consequences of late presentation
- Late presentation across Europe
- Initiatives to reduce late presentation

What can do be done to reduce numbers of late presenters?

- One third of the estimated 2.2 million HIV-positive people across the European region are unaware of their HIV status
- Approximately 50% of those diagnosed are late presenters
- Client-initiated testing strategies are not sufficient, provider-initiated evidence based testing strategies are needed

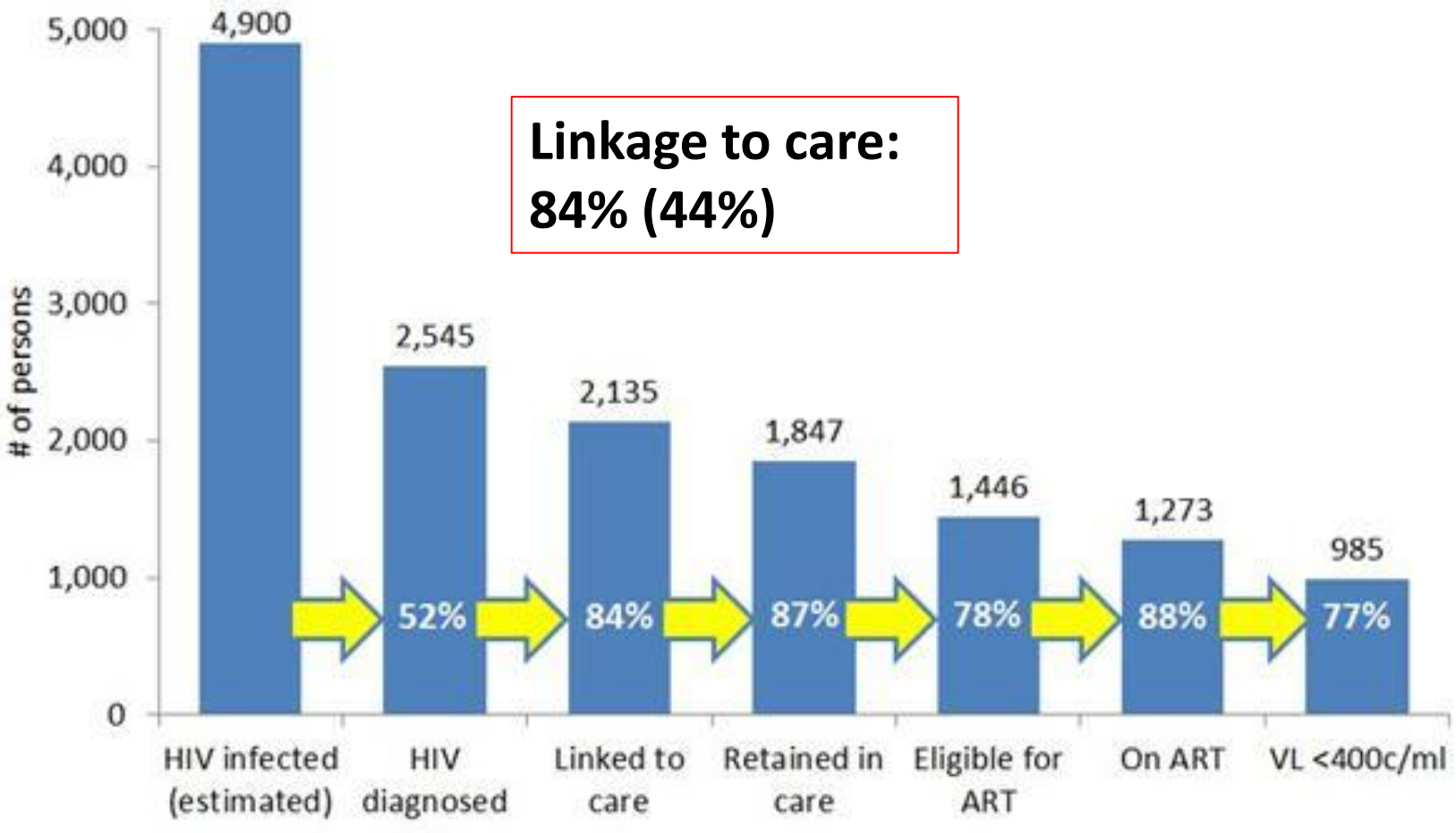
Kutsyna et al, HepHIV Conference, Barcelona 2014

Treatment cascade in United States



MMWR 2011

Treatment cascade in Georgia



Linkage to care: 84% (44%)

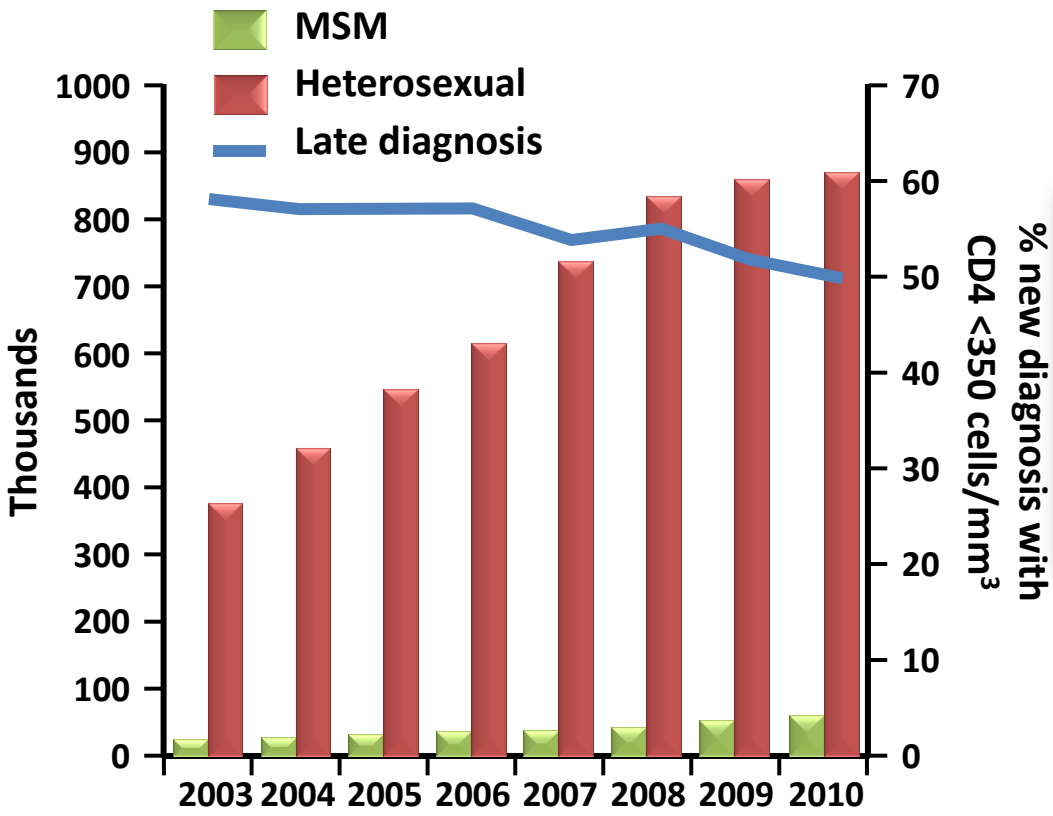
Adapted from Chkhartishvili, *HIV Med* 2014

Successful interventions for earlier HIV diagnosis

- Antenatal screening
- Increase in MSM testing
- Screening in GUM clinics
- Screening in TB clinics
- Screening among IDUs
- Indicator condition guided HIV testing

Increased HIV testing correlates with a reduction in late diagnosis of HIV

HIV tests among English STI clinic attendees vs overall UK late HIV diagnosis, 2003–2010



Late diagnosis: CD4+ count <350 cells/mm3

"The proportion diagnosed late (CD4 count <350 cells/mm3) remained high (50%) despite a slow and significant decline over the last decade"

Adapted from HPA. HIV in the United Kingdom: 2011 Report. London: Health Protection Services, Colindale. November 2011

What is indicator condition guided HIV testing?

- An approach using certain conditions, linked with an excess risk of being HIV positive, as indication for health providers to routinely offer an HIV test[1-3]
- Studies suggest that routine HIV testing remains cost-effective, when the undiagnosed HIV prevalence in a specific group, is > 0.1%[4]
- The concept of indicator condition guided HIV testing is an approach by which health care practitioners can be encouraged to test more patients based on indicator conditions rather than risk behaviour or group[3,4,5]

[1]AK Sullivan, PLoS ONE, 2013; [2]European Centre for Disease Prevention and Control (2010) ECDC guidance. [3]HIV in Europe Initiative. 2012; [4]Y Yazdanpanah, PLoS One 2010

HIDES II Study : Enrolment

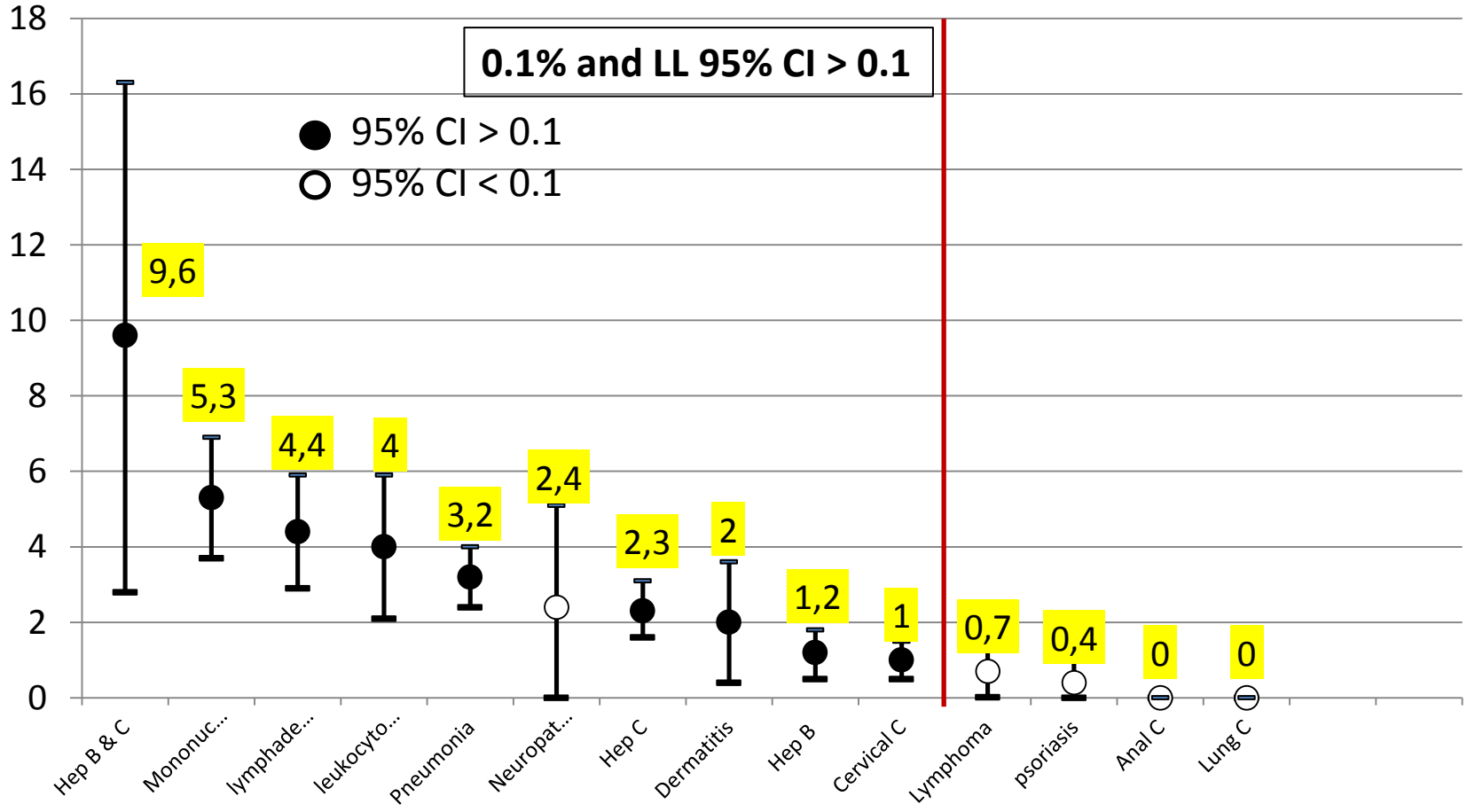
- 10139 patients were enrolled; of unknown HIV status and presenting for care with one of the surveyed conditions in one of the clinics.
- Excluded participants: 98 due to missing data; 569 due to age criteria <18 or >65, **N=9471** (93.4% of original)
- 42 clinics participated in 20 countries across 4 regions of Europe

Malignant lymphoma of any type; Cervical dysplasia or cancer (cervical CIN II and above), Anal dysplasia or cancer, Hepatitis B viral infection (acute or chronic), Hepatitis C viral infection (acute or chronic), Hepatitis B & C, Ongoing mononucleosis-like illness, Unexplained leukocytopenia and/or thrombocytopenia,(lasting at least 4 weeks), Seborrheic dermatitis/ exanthema, Pneumonia, admitted to hospital for at least 24 hours, Unexplained lymphadenopathy, Peripheral neuropathy of unknown cause, Primary lung cancer, Severe or recalcitrant psoriasis, newly diagnosed

Kutsyna et al HepHIV Barcelona 2014

HIV prevalence in the indicator conditions

Overall prevalence: 2.5: 95% CI 2.2 -2.8



Tested:	73	734	401	722	1881	84	1751	299	1126	1339	588	276	53	144
HIV+:	7	39	16	32	61	2	41	6	13	13	4	1	0	0

Kutsyna et al HepHIV 2014

Targeted, high-quality HIV testing

- Expand alternatives to traditional on-site, clinical HIV antibody testing which use **rapid tests and which provide testing in locations and in conditions that are convenient to clients**
- **Improve links and access to treatment, care and support**, and make the social, legal and policy environment more supportive
- Introduce **provider-initiated testing** and care in prenatal care and in certain other health-care settings
- Use **targeted campaigns to encourage the uptake of HIV testing**

Lazzarus et al, *HIV Med* 2010

Summary

- Late presentation to HIV care (diagnosis and linkage to care) remains common in Europe
- Late presentation has serious implications for the individual patient and for transmission of HIV
- The proportion of late presenters varies across Europe and across risk groups
- Access to HIV testing should be improved
- Provider-driven HIV testing in health care settings (indicator condition guided HIV testing)

Many thanks to those who shared slides

- Jurgen Rockstroh
- Andre Sasse
- Jens Lundgren
- Ole Kirk
- Galyna Kutsyna

Thank you for listening