The epidemiology of late presentation

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Declaration of possible conflicts

I have received funding for travel, honorariums for provision of training courses and for participation on advisory boards and Data Safety and Monitoring Commitees for the following companies:

- Gilead Sciences
- Bristol-Myers Squibb
- Janssen-Cilag

HIV positive patients first presenting with an AIDS defining illness: characteristics and survival

- 97/436 (22%) patients presented with an AIDS defining illness coincident with their first positive HIV test, 1991-1993
- ‘Subjects who are HIV positive and present late are a challenge to the control of the spread of HIV infection because they progress from asymptomatic HIV infection to AIDS without receiving health care’

Poznansky MC. *BMJ* (1995); 311:156-8.

Content of talk

- What do we mean by late presentation and how common is it?
- The need for a consistent definition
- What are the risk factors for late presentation?
- What are the clinical and financial implications of late presentation?
- Encouraging earlier diagnosis

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What do we mean by a late presenter?

- Individuals who are diagnosed and/or present for clinical care at late stages of infection

What do we mean by a late presenter?

- Individuals who are diagnosed and/or present for clinical care at late stages of infection
  - Presentation with a low CD4 count
    - <50 cells/mm^3?
    - <200 cells/mm^3?
    - <350 cells/mm^3?
  - Presentation with clinical AIDS
  - Presentation shortly prior to death
  - Presentation with CDC stage ‘B’/ WHO stage 3/4 disease
  - Presentation during hospitalisation
  - Testing for clinical suspicion rather than for routine reasons

Late presentation – resource-rich settings

Definition	Reported frequency
CD4 <50 cells/mm^3	10% - 55%
CD4 <200 cells/mm^3	26% - 85%
CD4 <350 cells/mm^3	54% - 63%
Low CD4 and/or AIDS event	29% - 59%
Clinical events/hospitalisations alone	13% - 42%

Late presentation – wider afield

- Venezuela[1]
  - 40% of 225 patients had CDC stage B/C event at diagnosis
- Brazil[2]
  - Almost all 377 newly diagnosed patients showed signs of late diagnosis
- Southern Thailand[3]
  - 55% of 402 patients diagnosed with symptomatic HIV infection, 2004-2005
- Uganda[4]
  - 40% of 2584 patients presenting to clinic had WHO stage 3/4 disease
- Mexico[5]
  - 43% of 342 interviewed patients had AIDS +/- CD4 <200 cells/mm^3

[1]Bonjour MA. *AIDS Res Ther* (2008); 5:6; [2]Sampaio S. Braz J Infect Dis (2007); 11:395-8; [3]Thanawuth N. *AIDS Care* (2008); 20:43-50; [4]Kigozi IM. *JAIDS* (2009); 52:280-9; [5]Carrizosa CM. *AIDS Pat Care STDs* (2010); 24:333-40.

Other explanations for wide variation

- Time interval between positive HIV test and clinical event/low CD4 count
- Exclusion of seroconverters
- Exclusion of those with no CD4 measurement
- Exclusion of those who have died
- Exclusion of other groups (e.g. prisoners, those too sick to complete questionnaire)
- Study setting – inpatient/specialist referral centre vs. outpatient clinic

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The need for a consistent definition

- Lack of consistent definition has hampered attempts to assess trends over time and to identify risk factors

Identifying risk factors – the impact of different definitions of late presentation

	Definition of late presentation			
	CD4 <200 cells/mm^3		Diagnosis in hospital	
Risk factor	OR (95% CI)	p-val.	OR (95% CI)	p-val.
Age (/10 years older)	1.72 (1.12, 2.64)	0.01	1.79 (1.07, 3.12)	0.03
Female	1.30 (0.51, 3.35)	0.59	6.74 (2.08, 21.81)	0.001
Uninsured	1.06 (0.46, 2.45)	0.89	2.99 (0.99, 9.00)	0.05

Adapted from Mugavero MJ. *Am J Med* (2007); 120:370-3.

Identifying risk factors – the impact of different definitions of late presentation

Risk factor	Definition of late presentation		
	AIDS ≤3 months of diagnosis	CD4 <200 cells/mm^3	Diagnosis during hospitalisation
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Heterosexual	1	1	1
MSM	0.67 (0.50, 0.91)	0.32 (0.21, 0.50)	0.42 (0.31, 0.56)
IDU	-	0.24 (0.08, 0.73)	-
Blood products	0.10 (0.03, 0.42)	-	56.28 (16.2, 195.3)
Not known	0.48 (0.30, 0.76)	-	-

Wong K-H. *AIDS Pat Care STDs* (2003); 17:461-9.

The need for a consistent definition

- Lack of consistent definition has hampered attempts to assess trends over time and to identify risk factors
- General aim is to provide indication of number of HIV-positive individuals who are not yet linked into care
- Consideration of outcomes that occur further down the clinical pathway (e.g. AIDS and death more than a few months after diagnosis) may reflect different aspects of patient engagement, e.g. retention in care, uptake/adherence to HAART

Choosing a definition

- If aim is to identify those at imminent risk of further morbidity/mortality, definition based on low CD4 would be recommended
- However, this may fail to identify all patients at high risk of clinical progression, and thus definition based on both clinical and immunological criteria may be preferable
- For raising public health awareness of late presentation, or for identifying patients who could be eligible for treatment, a higher CD4 threshold may be desirable

A European consensus definition[1-3]

Advanced HIV disease:

Diagnosis of HIV with a CD4 cell count <200 cells/mm^3 and/or an AIDS-defining illness within first three months

Late presentation:

Diagnosis of HIV with a CD4 cell count <350 cells/mm^3 and/or an AIDS-defining illness within first three months

[1]UK CHIC. *AIDS* (2010); 24:723-7; [2]Antinori A. *HIV Med* (2011); 12:61-4; [3]HIV in Europe. www.hiveurope.eu

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Who presents late?

Late presentation more common in:

- Those not perceived to be at high risk of HIV infection
- Those who are not routinely offered HIV testing
- Disenfranchised groups (e.g. immigrants)
- Those born in a country other than the one of residence
- Those of lower socio-economic status
- Older individuals
- Men (in some studies)
- Those experiencing logistical barriers to testing

Who presents late?

- New HIV diagnoses at 6 university-affiliated clinics in France, 1996-2006
- Late presentation associated with:
  - Age >30 years
  - Mode of infection other than MSM
  - Co-infection with hepatitis B or C
  - Living in a couple with children
  - Diagnosed prior to 2003
- Risk factors did not appear to have changed over time

Delpierre C. *Eur J Pub Health* (2007); 18:345-7.

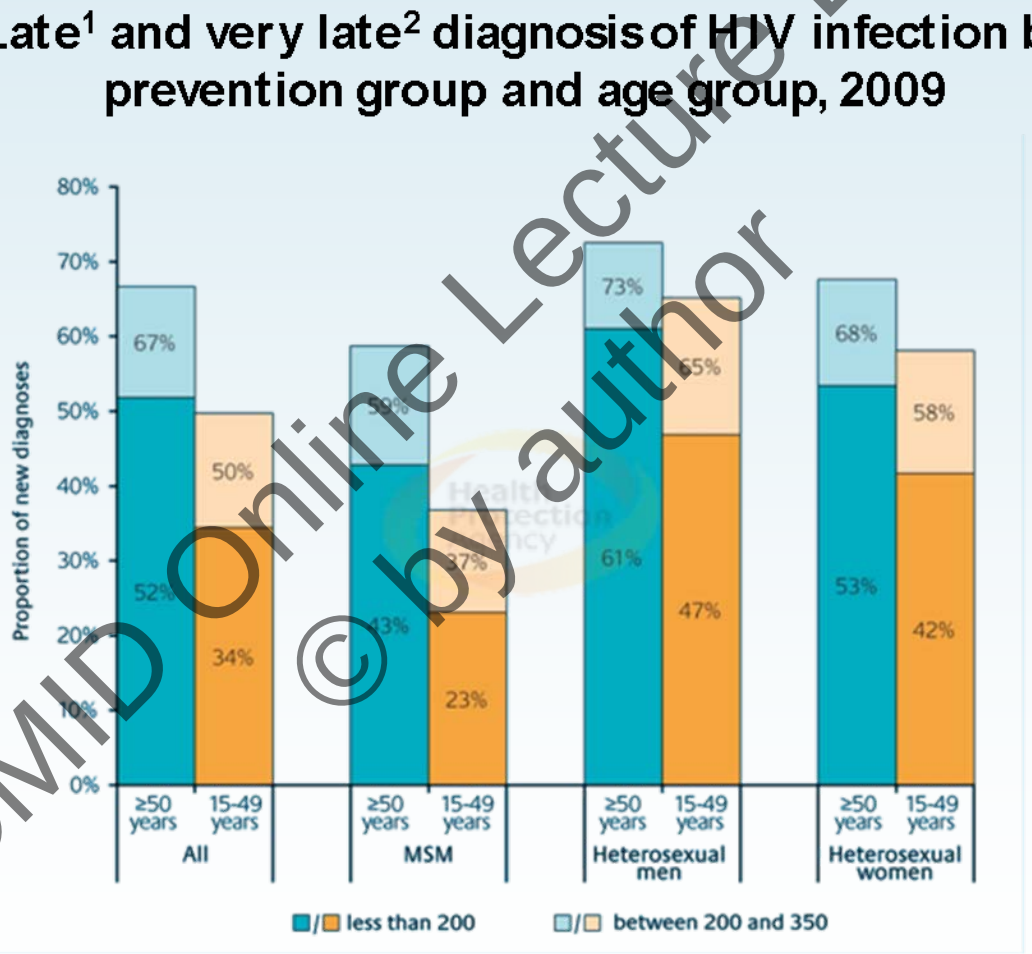
Who presents late?

225 individuals newly diagnosed with HIV, Venezuela; late presentation (CDC B/C event) occurred in 40%

	Adjusted OR	95% CI
Age ≥30 years	**5.34**	**1.70, 16.76**
Male heterosexual	**1**	
Male homosexual	**0.22**	**0.05, 0.92**
Female	**0.23**	**0.05, 1.06**
Partner thought to be unfaithful	**0.08**	**0.01, 0.56**
≥25km to clinical centre	**16.69**	**3.02, 92.11**

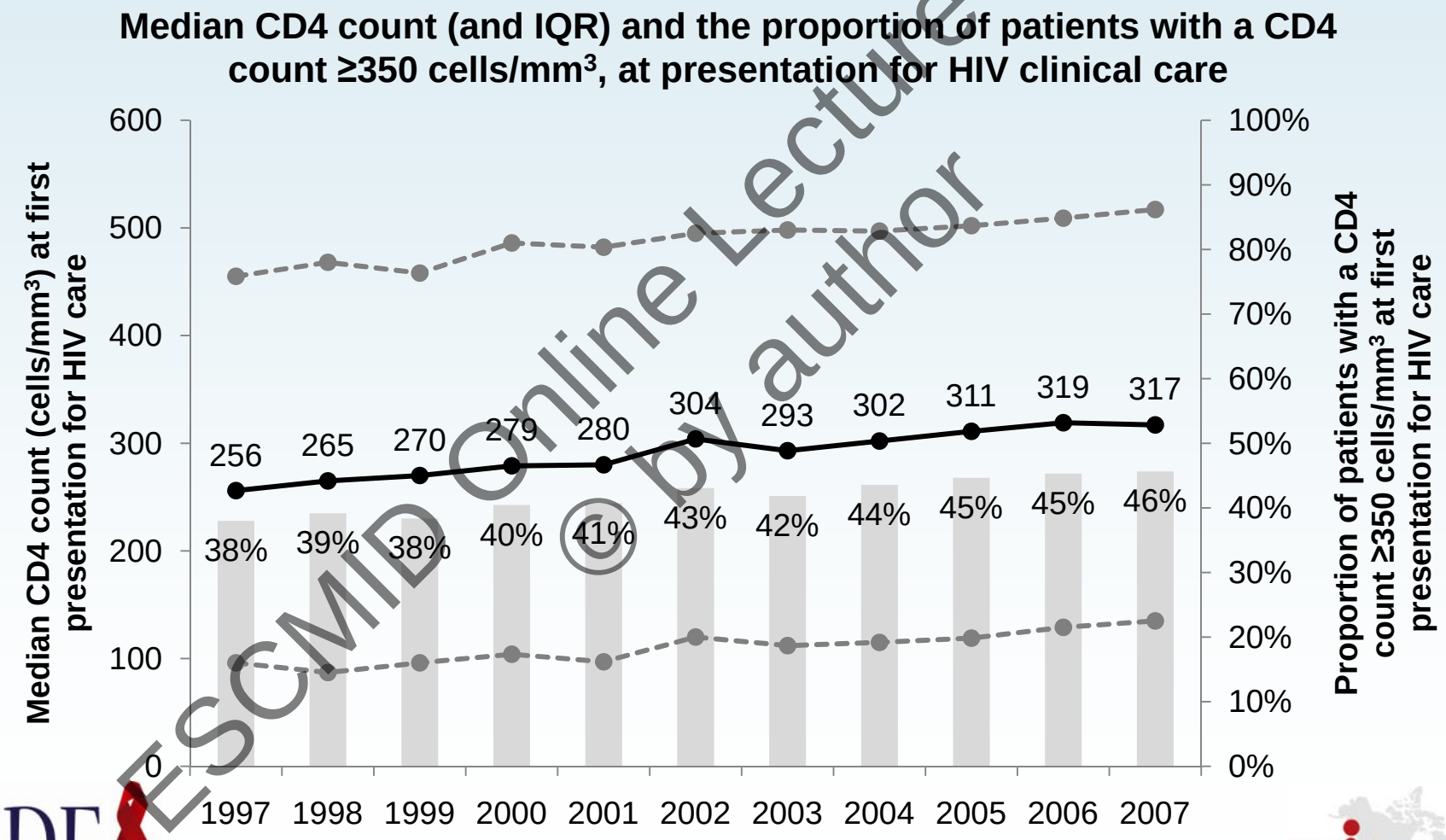
Bonjour MA. *AIDS Res Ther* (2008); 5:6.

Who presents late?



Health Protection Agency – Centre for Infections, 2011

Changes over time – North America[1]

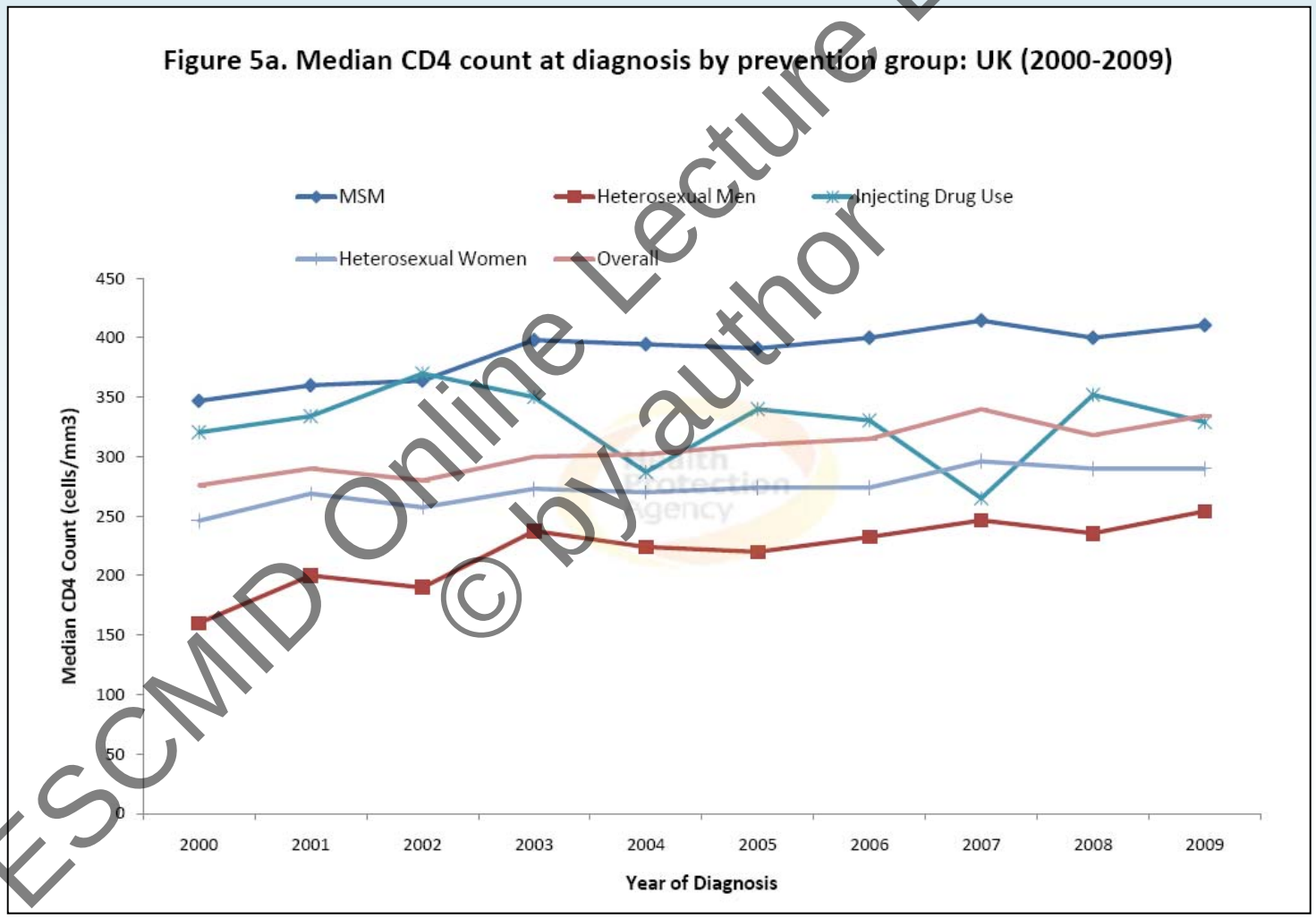


IeDEA International epidemiologic Databases to Evaluate AIDS

NA-ACCORD

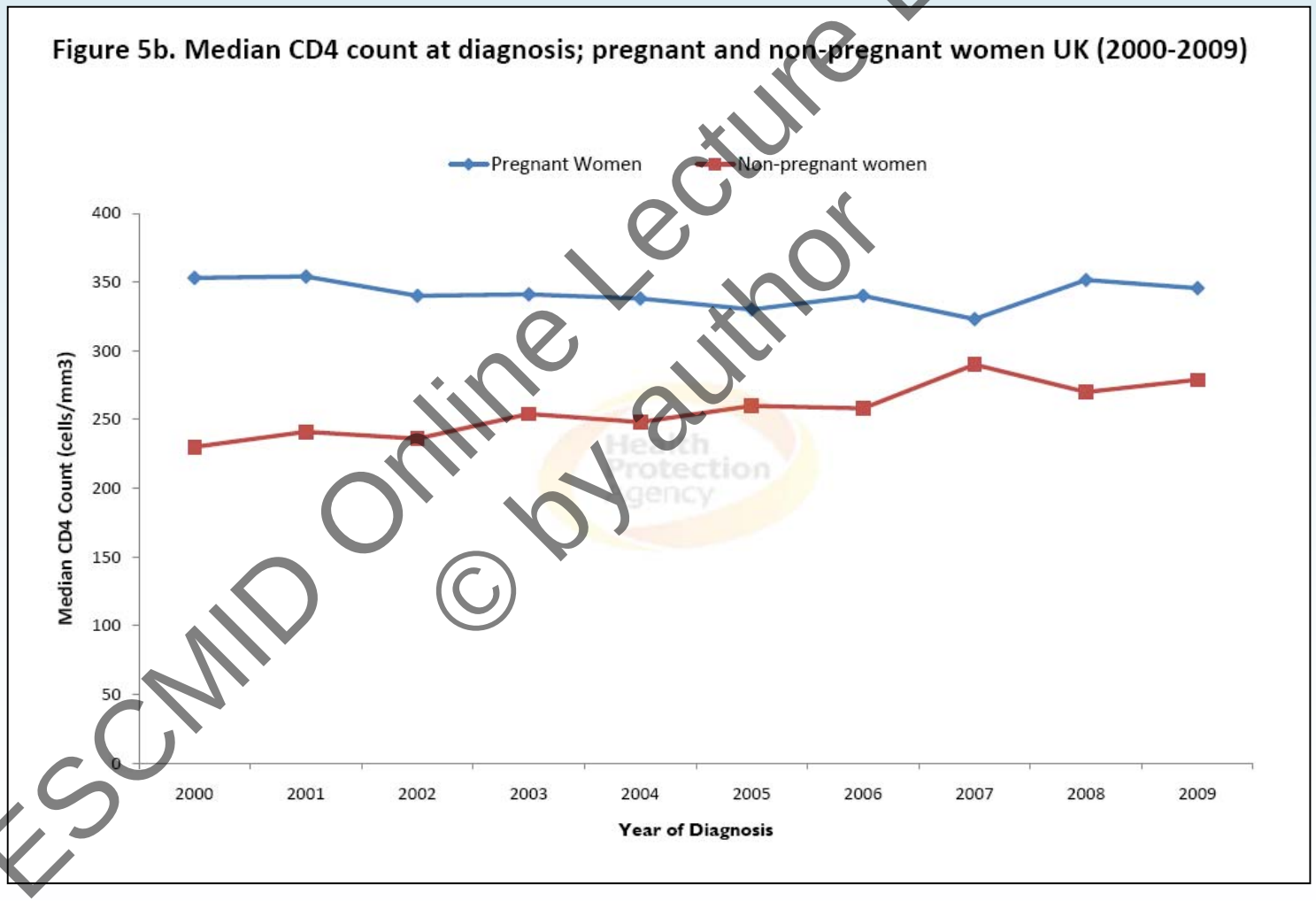
Althoff KN et al. *Clin Infect Dis* (2010); 50:1512-20.

Changes over time – UK[1]



[1]Health Protection Agency – Centre for Infections, 2011.

Changes over time – UK[1]



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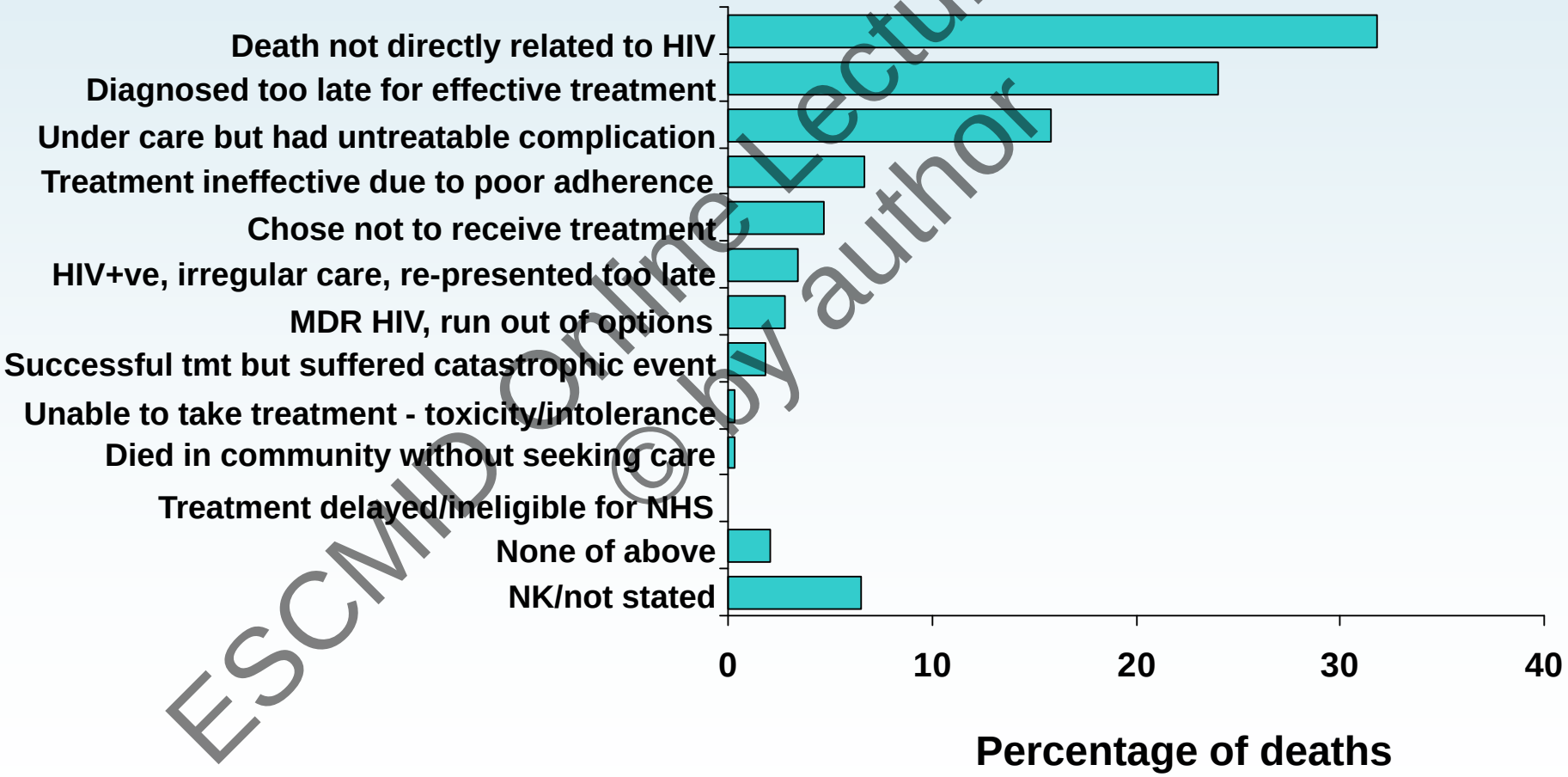
BHIVA audit - scenario leading to death among 387 deaths from 10/04-09/05



Lucas SB. *Clin Med* (2008); 8:250-2.

Mortality in late and non-late presenters. France

Mortality rate (per 1000 PYRS)	Late presenters	Non-late presenters
n	2023	4782
Overall	5.6	1.7
During first year after diagnosis	24.4	0.3

Delpierre C. *Eur J Pub Health* (2007); 18:345-7.

The potential impact of earlier diagnosis

- Dutch MSM[1] presenting with CD4<200 cell/mm^3 at 75% increased risk of death in first 3 years on cART compared to those presenting with CD4 ≥350 cells/mm^3
- If Dutch MSM all entered care with CD4 ≥350 cells/mm^3, mortality in first 3 years on cART could be cut by 20%

[1]Smit C. *PLoS ONE* (2008); 3:e1949;

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- In UK[2,3], earlier diagnosis may have reduced short-term mortality by 84% in MSM, and by 56% in those infected heterosexually

[1]Smit C. *PLoS ONE* (2008); 3:e1949; [2]Chadborn TR. *AIDS* (2005); 19:513-20; [3]ChadbornTR. *AIDS* (2006); 20:2371-9.

Cost of care after HIV diagnosis

- Mean annual costs in year after diagnosis, Canada[1]
  - Late presenters C$18,488
  - Non-late presenters C$8,455
- Estimated excess cost of late presentation (C$9,723) largely attributable to differences in HIV-related hospital care costs (15x higher for late presenters)
- US Study[2]: Analysis of 8348 newly diagnosed patients attending HIV clinic participating in HIV Research Network
- Late presenters (CD4 $\leq$200 cells/mm^3) experienced higher cumuative expenditure, even after 7-8 years in care

[1]Krentz HB. *HIV Med* (2004); 5:93-8; [2]Fleishman JA. *Med Care (*2010) ; 48:1071-9.

Contribution of late presentation to epidemic

- HIV RNA strong predictor of HIV transmission
- Untreated individuals have higher viral loads than treated individuals and are unlikely to make major changes to sexual behaviour
- Those unaware of their HIV infection are 3.5 times more likely to transmit HIV to partners than diagnosed individuals[1]
- Earlier diagnosis, and hence earlier treatment, may has the potential to lead to major public health benefits

[1]Marks G. *AIDS* (2006); 20:1447-50

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CDC Recommendations for HIV Testing in Healthcare Settings

- Routine voluntary testing for patients ages 13 to 64 years in healthcare settings
  - Not based on patient risk
- Opt-out testing
  - No separate consent for HIV
  - Resulting in increases in HIV testing rates
- Pretest counseling not required
- Repeat HIV testing left to discretion of provider, based on risk
- Within the US, 34 states are neutral to supportive of the CDC guidelines while 11 states have taken steps to reduce regulatory barriers
  - 6 states passed legislation (2007)

HIV testing guidance: core principals

- Voluntary, confidential, undertaken with informed consent
- Access to treatment, care and prevention services
- Political commitment
- Reduce stigma
- Remove legal and financial barriers
- Access to HIV testing is an integral part of national strategies
- Involvement of stakeholders

HIV testing guidance: developing a national strategy

Whom to test?	Know your epidemic: which groups are most at risk?
Where to test?	Make testing available in a variety of settings.
When to test?	Provide guidance on testing frequency.
How to test?	Raise public and professional awareness, ensure confidentiality; train the workforce; provide pre-test discussion to ensure informed consent, etc.

Ensure access to HIV treatment, care and prevention

Summary

- Despite attempts to increase HIV testing, a substantial proportion of individuals with HIV are diagnosed late
- Risk factors include older age, low socio-economic status and logistical barriers for testing, but may vary by setting and patient group
- Late presentation is associated with a high risk of clinical progression, is costly to treat and may contribute to the ongoing HIV epidemic
- The only way to reduce late presentation is to increase HIV testing by increasing patient/clinician awareness, increasing access to testing and reducing stigma

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