

# **HIV-Associated Disease In The Era Of Combination ART**

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# Learning Aims

To enable the non-expert ID doctor and microbiologist to

- Recognise signs & symptoms of (undiagnosed) HIV disease
- Recognise, and deal with obstacles to testing
- Manage HIV testing for symptomatic patients
- Start managing some of the presenting diseases

# Outline

- The case of Li X
- The problem of late HIV diagnosis
- Prognostic impact of combination ART
- Case studies
- Whom and when to test

# The story of Li X

- **January 2008**

45 yr old Chinese man, does not speak English

Admitted via A&E, North Middlesex Hospital (London)

History of cough, fever, nausea

Anaemia, Lymphopenia

Oral candidiasis

Sent home with co-amoxiclav

Letter to General Practitioner

“consider HIV test”

# The story of Li X

- **March 2008**

Seen once by General Practitioner

Returning cough, fever, nausea

General Practice nurse:

- calls in patient for HIV test
- No Mandarin interpreter available
- Patient does not respond to letters
- Informs our HIV nurse practitioner

# The story of Li X

- **June 2008**

Admitted via A&E

Further weight loss, dry cough, fever

HIV test positive

CD4 20/ $\mu$ L

Viral Load 300.000/mL

Arterial pO<sub>2</sub> 5.2 kPa (39 mmHg)

# Interstitial lung infiltrates in HIV+ patients

Pneumocystis jirovecii (carinii) pneumonia

Miliary tuberculosis

Cytomegalovirus pneumonitis

Pulmonary cryptococcosis

Pulmonary Kaposi's Sarcoma

# The story of Li X

- **June 2008**

Admitted via A&E

Further weight loss, dry cough, fever

HIV test positive

CD4 20/ $\mu$ L

Viral Load 300.000/mL

Arterial pO<sub>2</sub> 5.2 kPa (39 mmHg)

No hepatosplenomegaly

Bronchial secretions negative

To hypoxic for bronchoscopy

Cryptococcal Antigen positive 1:32

CMV PCR negative

# The story of Li X

- **June 2008**

CPAP ventilation

Co-trimoxazole

Corticosteroids

Liposomal Amphotericin B

- **July 2008**

Further deterioration

intubated & sedated

# The story of Li X

- **June 2008**

Discussed with Mandarin interpreter:

Patient had received & understood letter from GP

Did not attend because of fear

Illegal immigrant since 10 years

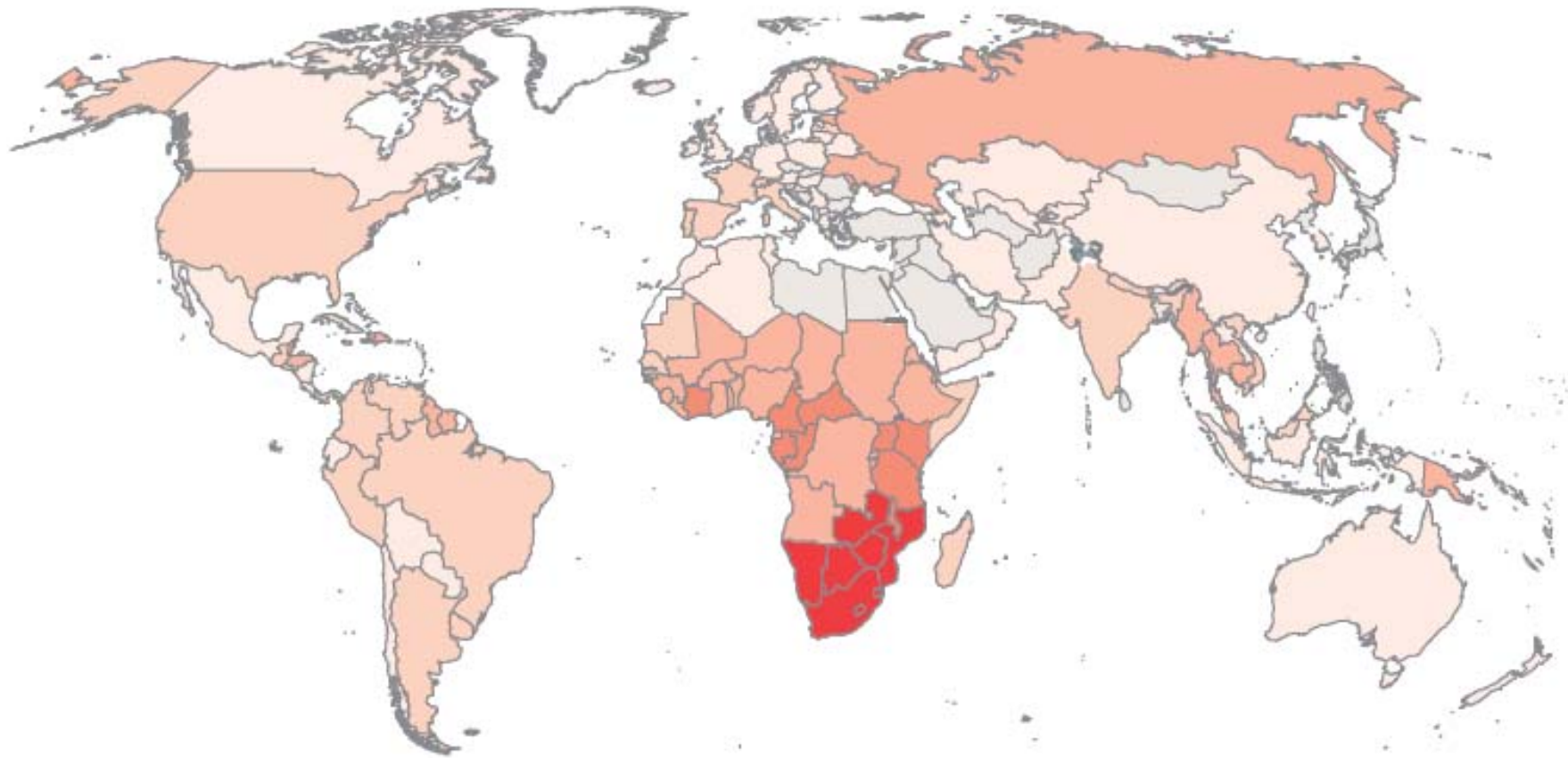
Restaurant worker

Sends money to family in China

# Outline

- The case of Li X
- **The problem of late HIV diagnosis**
  - **Epidemiology**
  - **Causes**
  - **What to do**
- Prognostic impact of combination ART
- Case studies
- Whom and when to test

# Adult Prevalence Rate of HIV (2005)



## Adult prevalence rate

■ 15.0%–34.0%

■ 1.0%–<5.0%

□ 0.1%–<0.5%

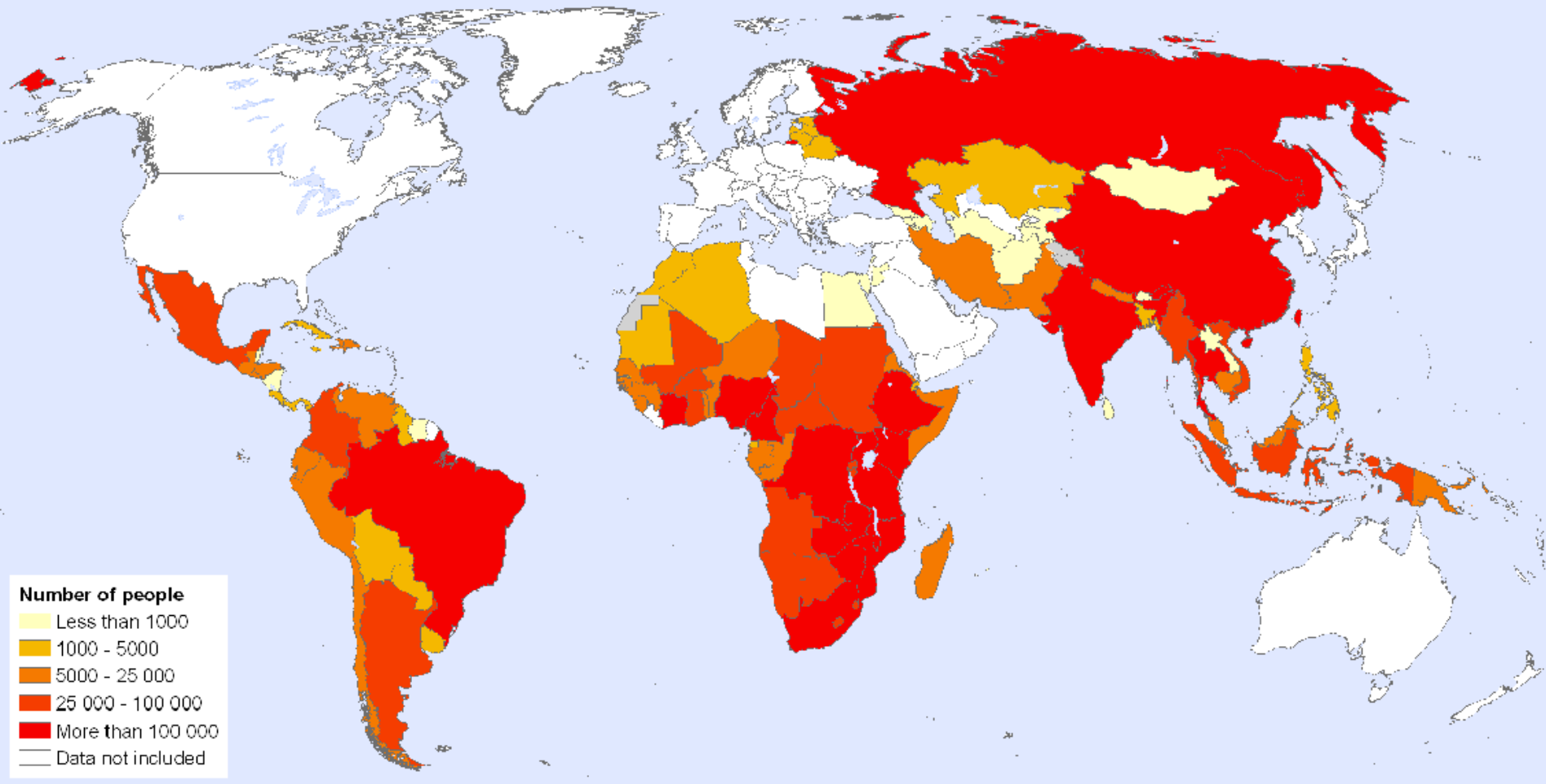
■ 5.0%–<15.0%

■ 0.5%–<1.0%

□ <0.1%

# Epidemiology of HIV

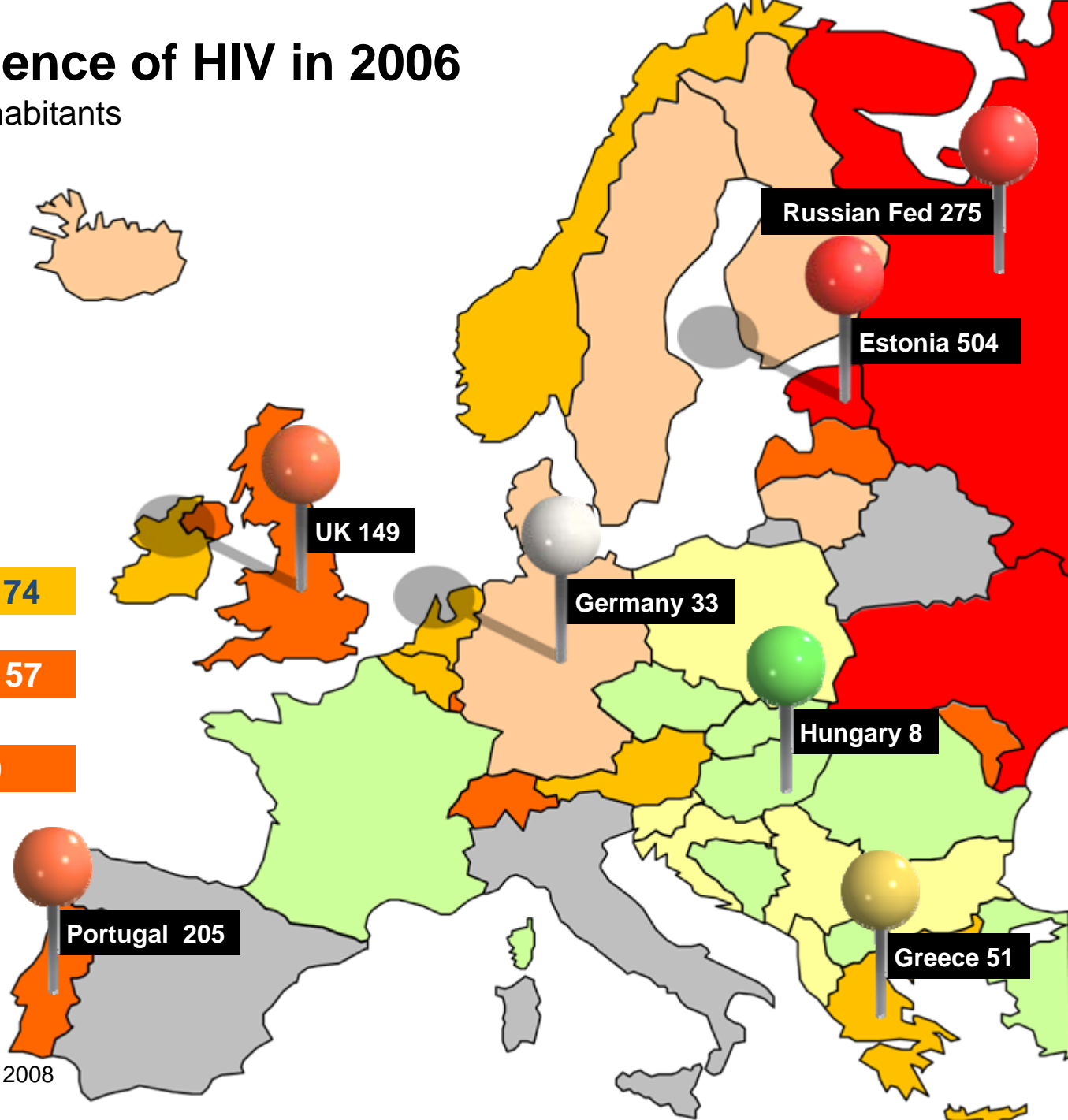
Estimated number of people in need of antiretroviral therapy in low and middle income countries, as of December 2006



UNAIDS December 2007

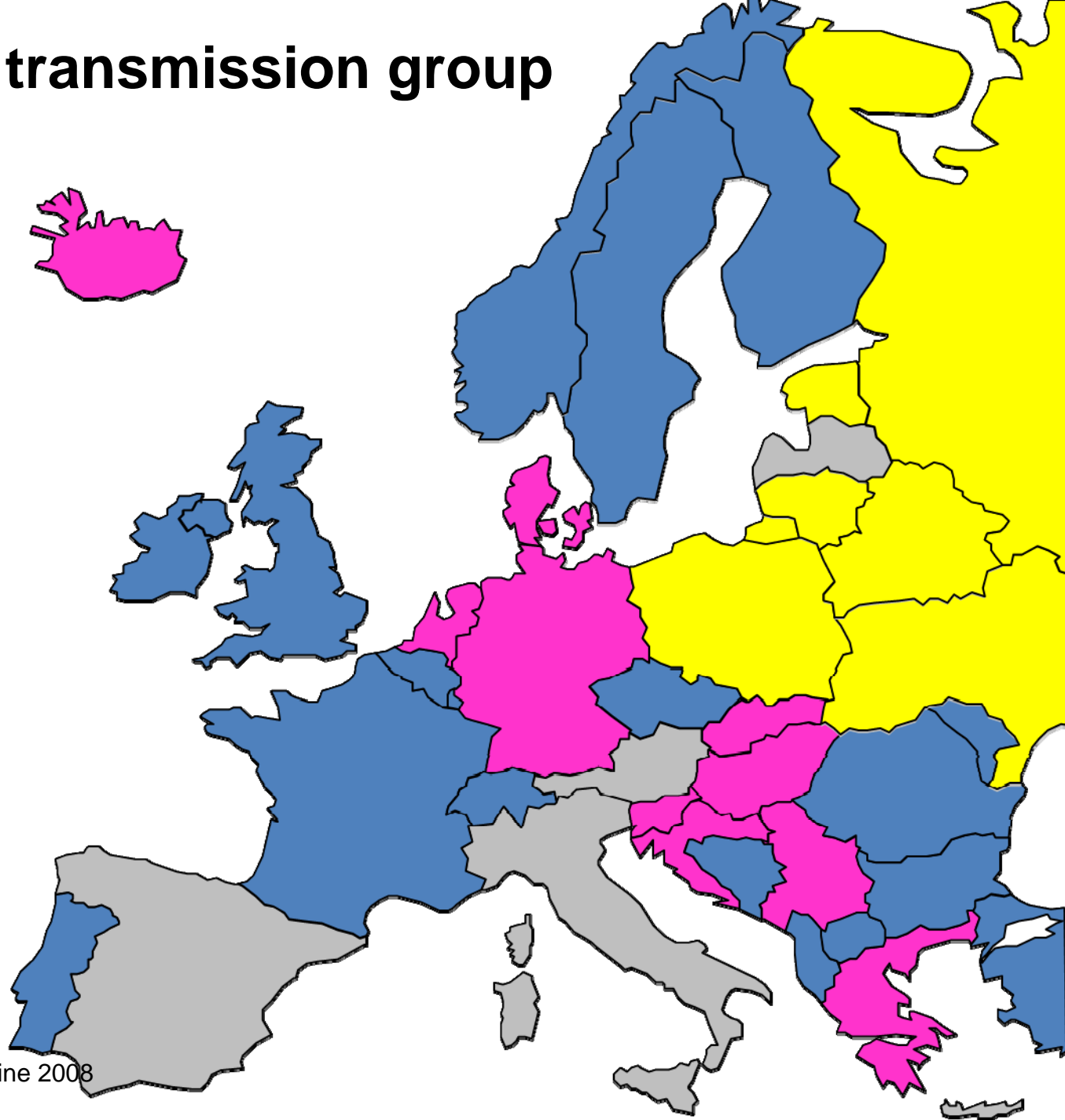
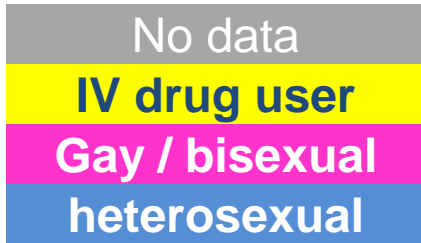
# Estimated incidence of HIV in 2006

new cases per million inhabitants

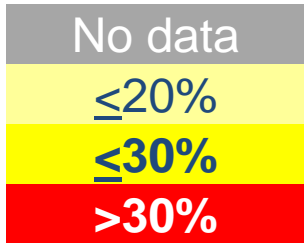


# Predominant transmission group

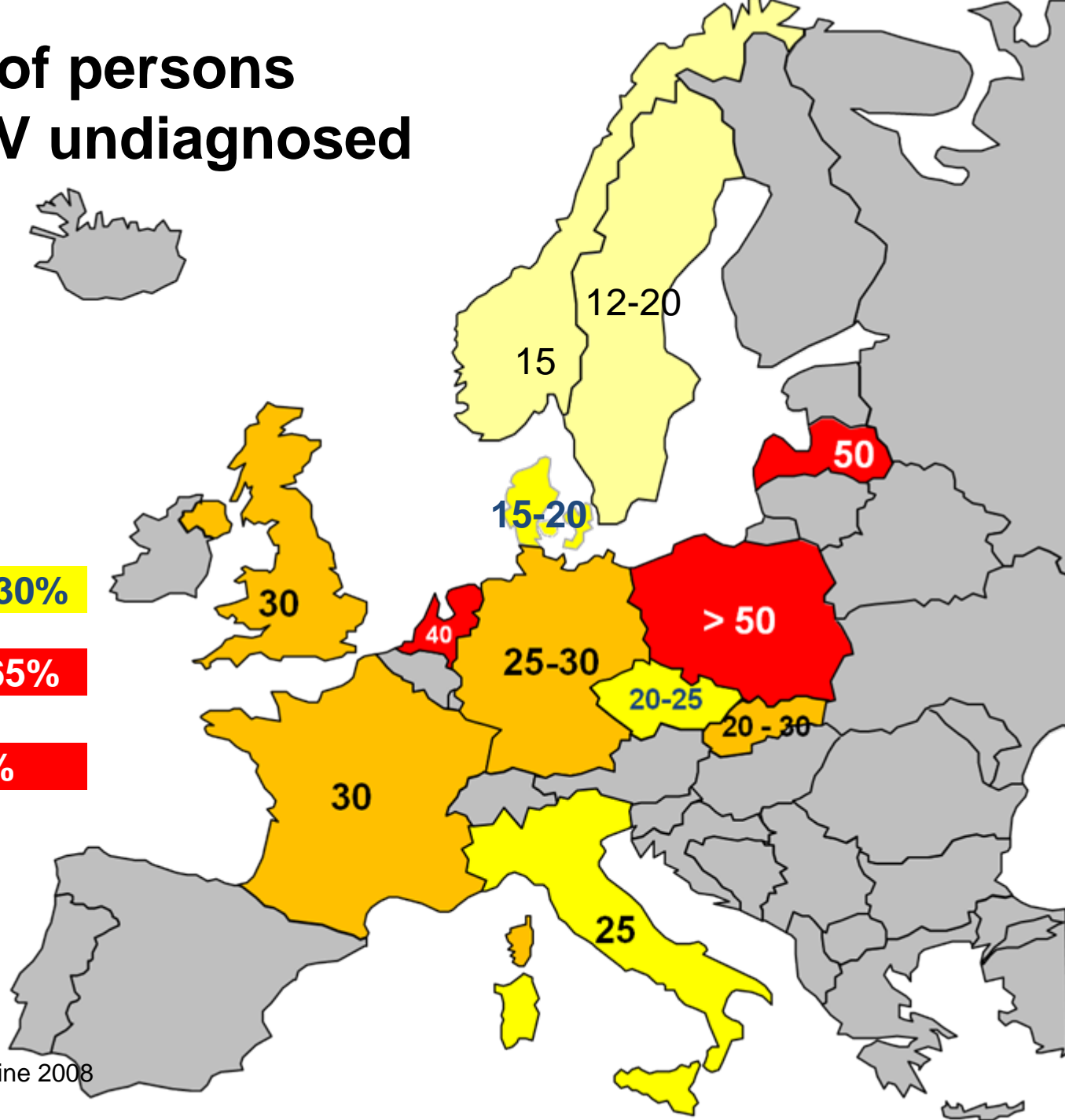
For new cases



# Estimated % of persons living with HIV undiagnosed

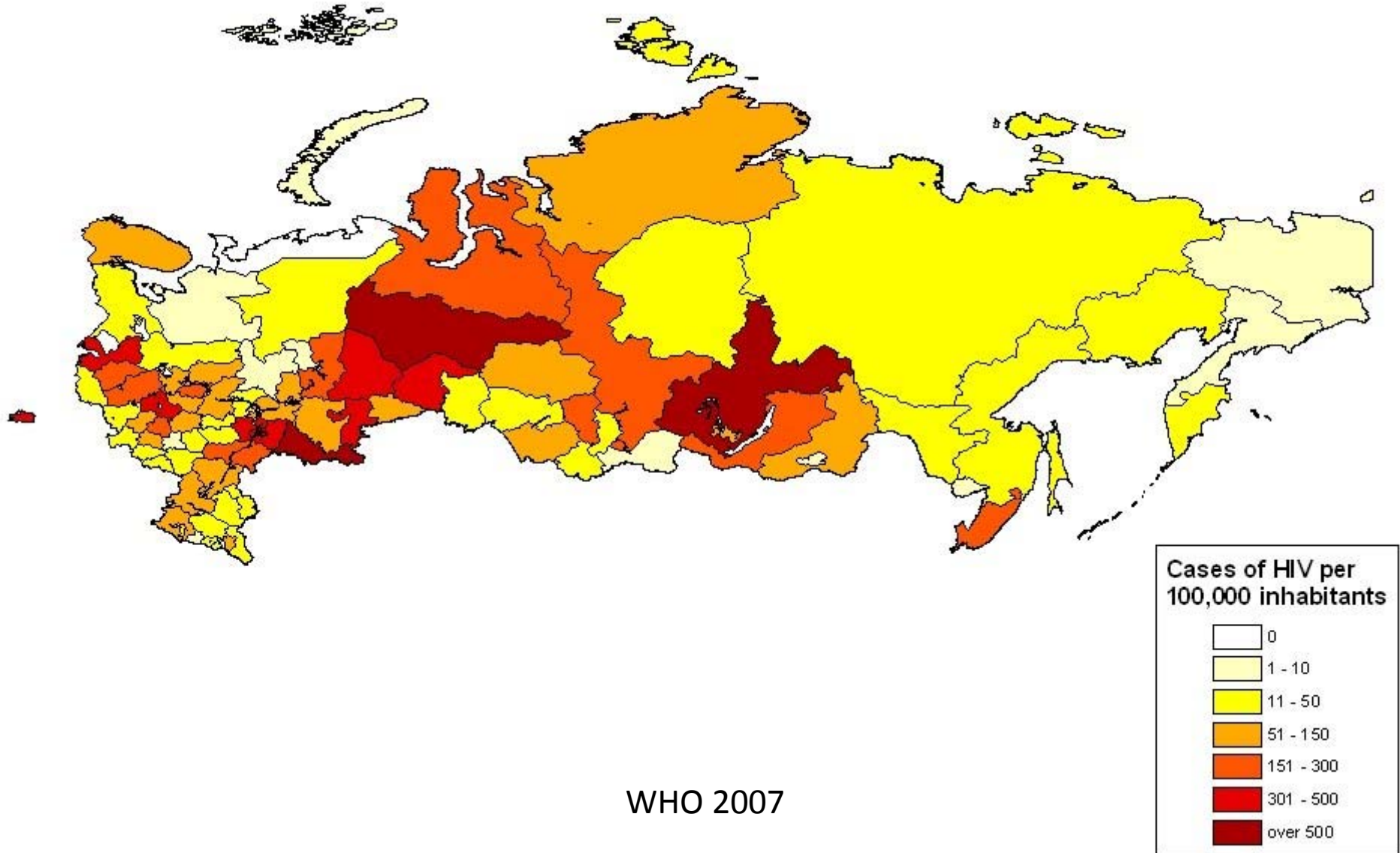


**Total EU+EEA/EFTA 30%**  
+  
**Other WHO Europe 65%**  
=  
**Whole Europe 50%**

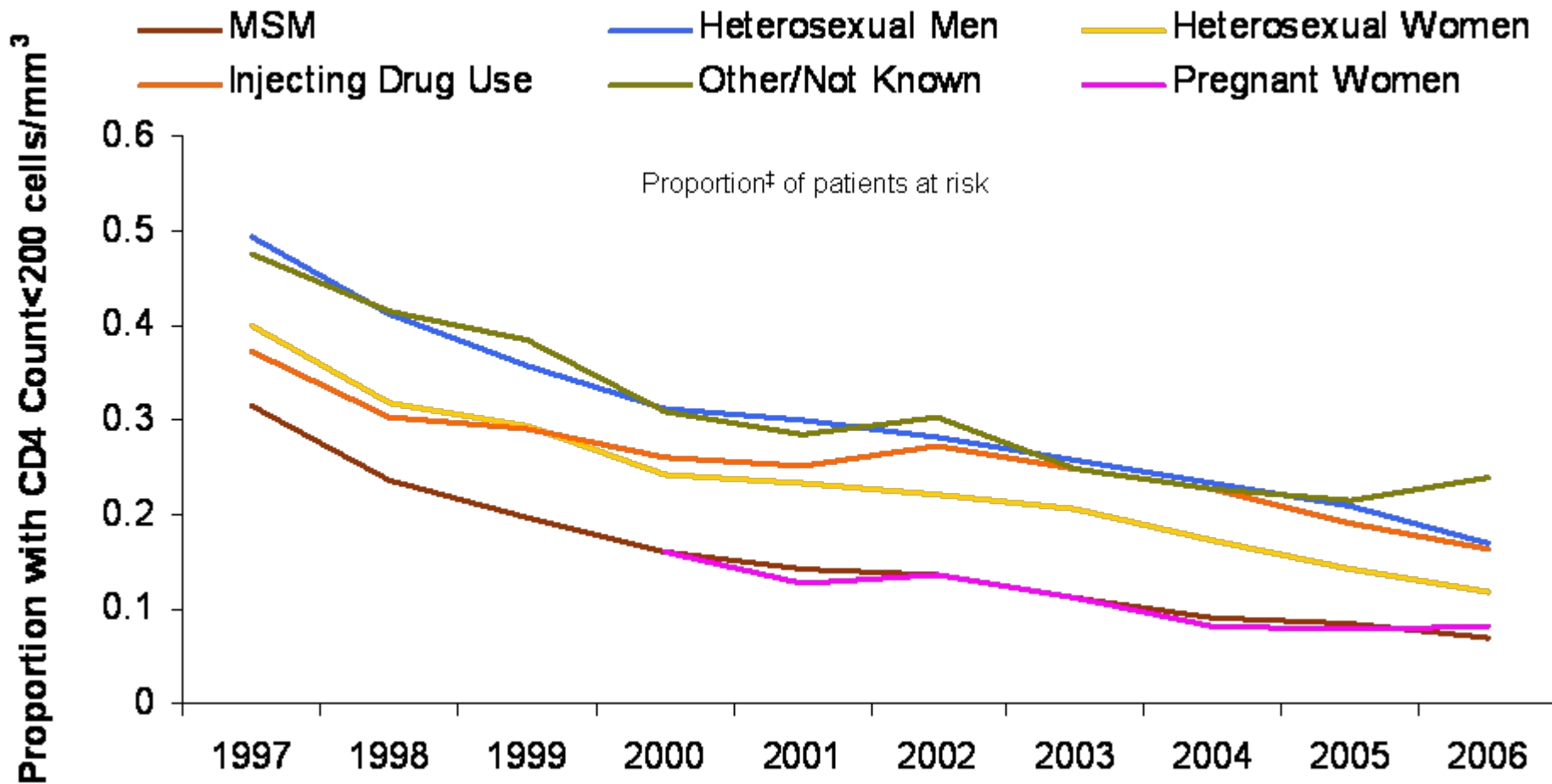


# Regional Differences

Prevalence of HIV in the Russian Federation - 31 December 2003



# Patients at high risk of opportunistic infections by prevention group



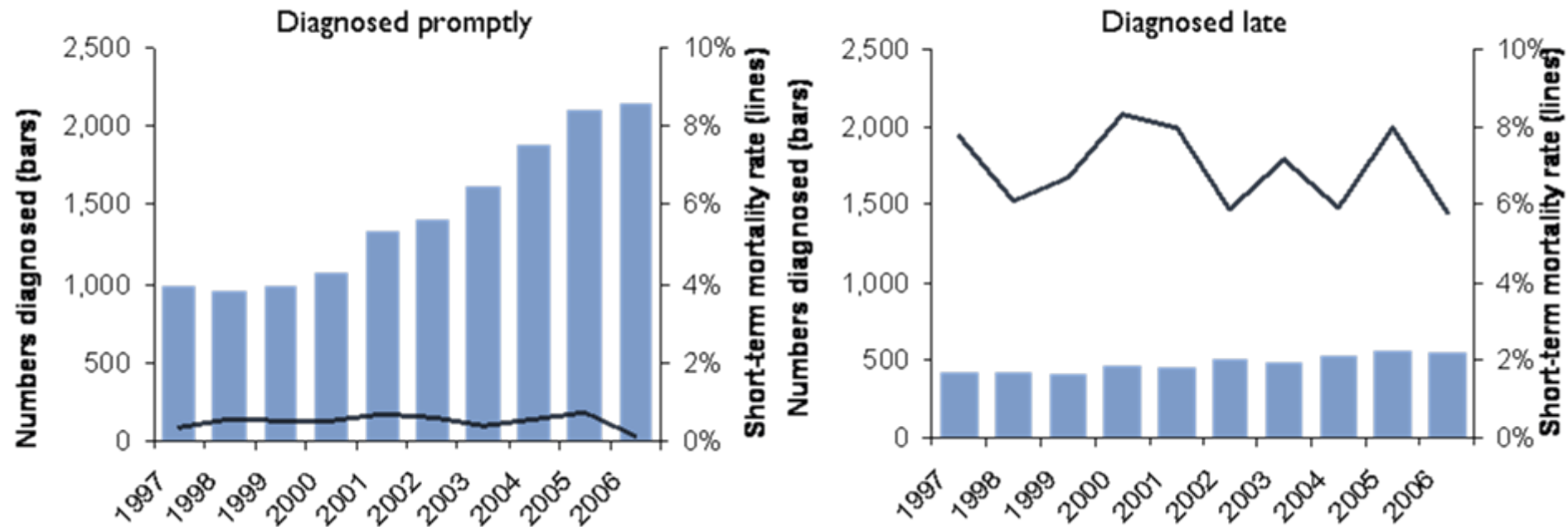
‡ Proportion of patients in each prevention group who had average CD4 counts per year less than 200 cells/mm<sup>3</sup>

England, Wales and Northern Ireland (1997-2006)

HPA 2007

# Late HIV diagnosis and mortality in Men who have sex with men

■ Number diagnosed  
— Short-term mortality



<sup>1</sup>Prompt diagnosis: CD4 count  $\geq 200$  cells/mm<sup>3</sup> within 30 days of diagnosis

<sup>2</sup>Late diagnosis: CD4 count  $< 200$  cells/mm<sup>3</sup> within 30 days of diagnosis

<sup>3</sup>Numbers of new HIV diagnoses from 2003 onwards are adjusted for reporting delays

<sup>4</sup>Percentage of patients known to have died within a year of diagnosis - further reports to be received for 2006.

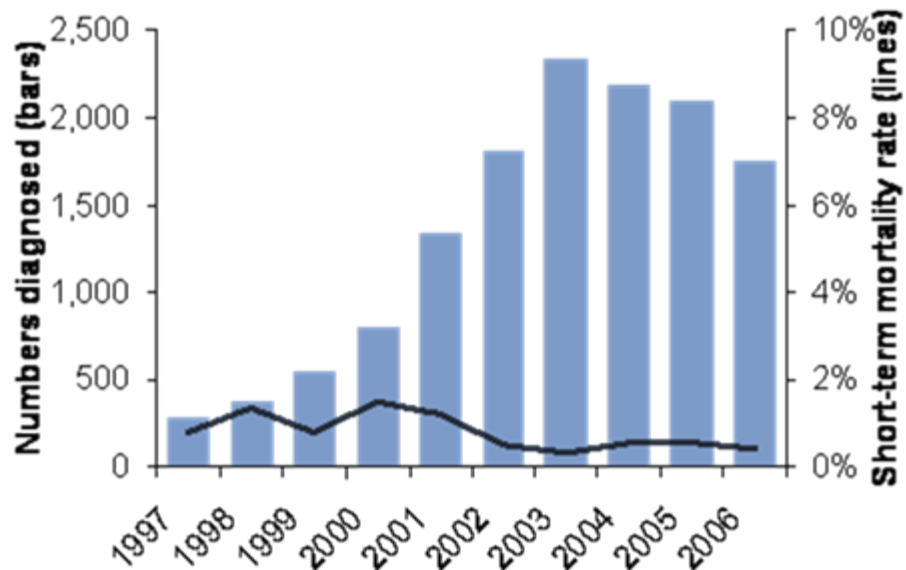
United Kingdom (1997-2006)

HPA 2007

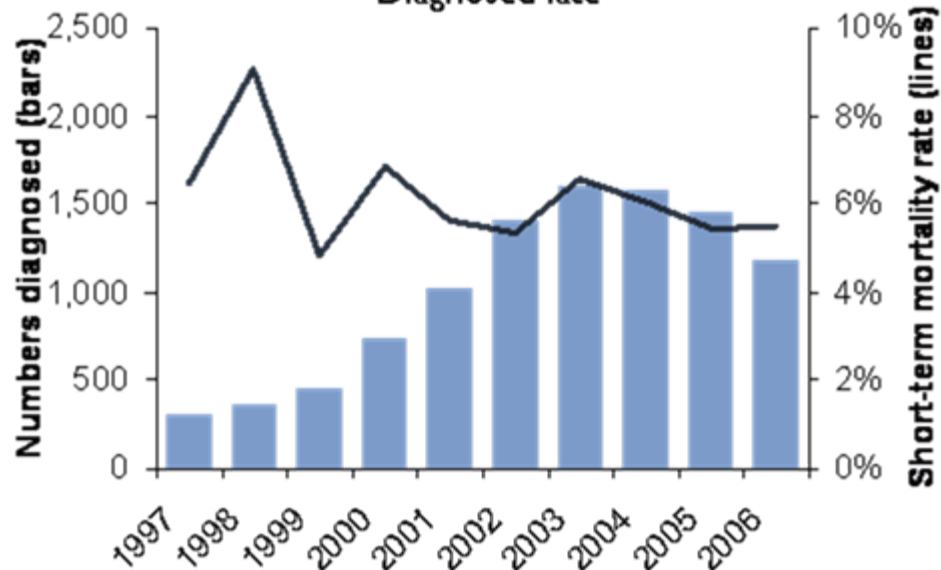
# Late HIV diagnosis and mortality in Black Africans/Caribbeans

Number diagnosed  
 Short-term mortality

**Diagnosed promptly**



**Diagnosed late**



<sup>1</sup> Prompt diagnosis: CD4 count  $\geq 200$  cells/mm<sup>3</sup> within 30 days of diagnosis

<sup>2</sup> Late diagnosis: CD4 count  $< 200$  cells/mm<sup>3</sup> within 30 days of diagnosis

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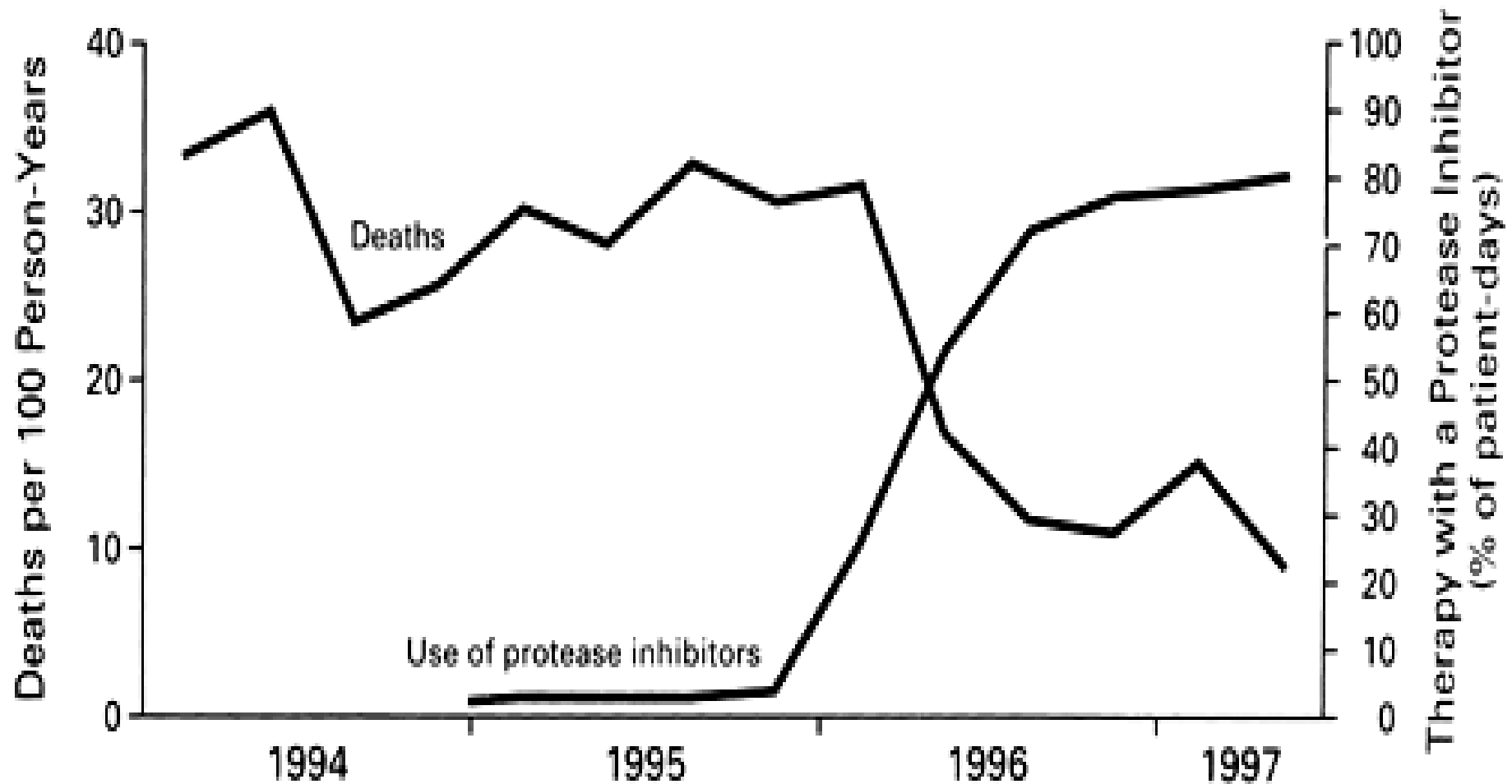
United Kingdom (1997-2006)

HPA 2007

# Outline

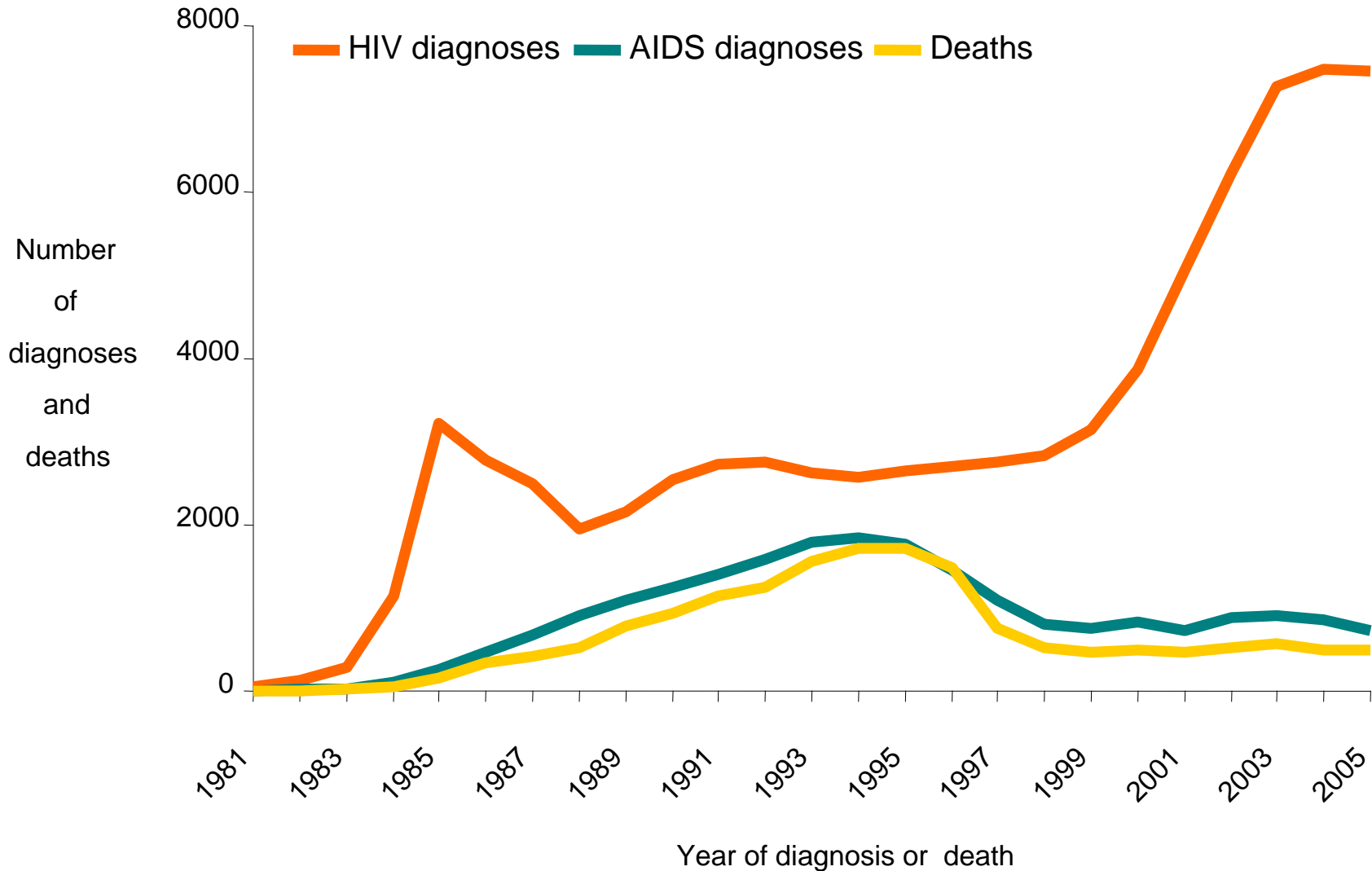
- The case of Li X
- The problem of late HIV diagnosis
- **Prognostic impact of combination ART**
- Case studies
- Whom and when to test

# Mortality in the era of combination ART



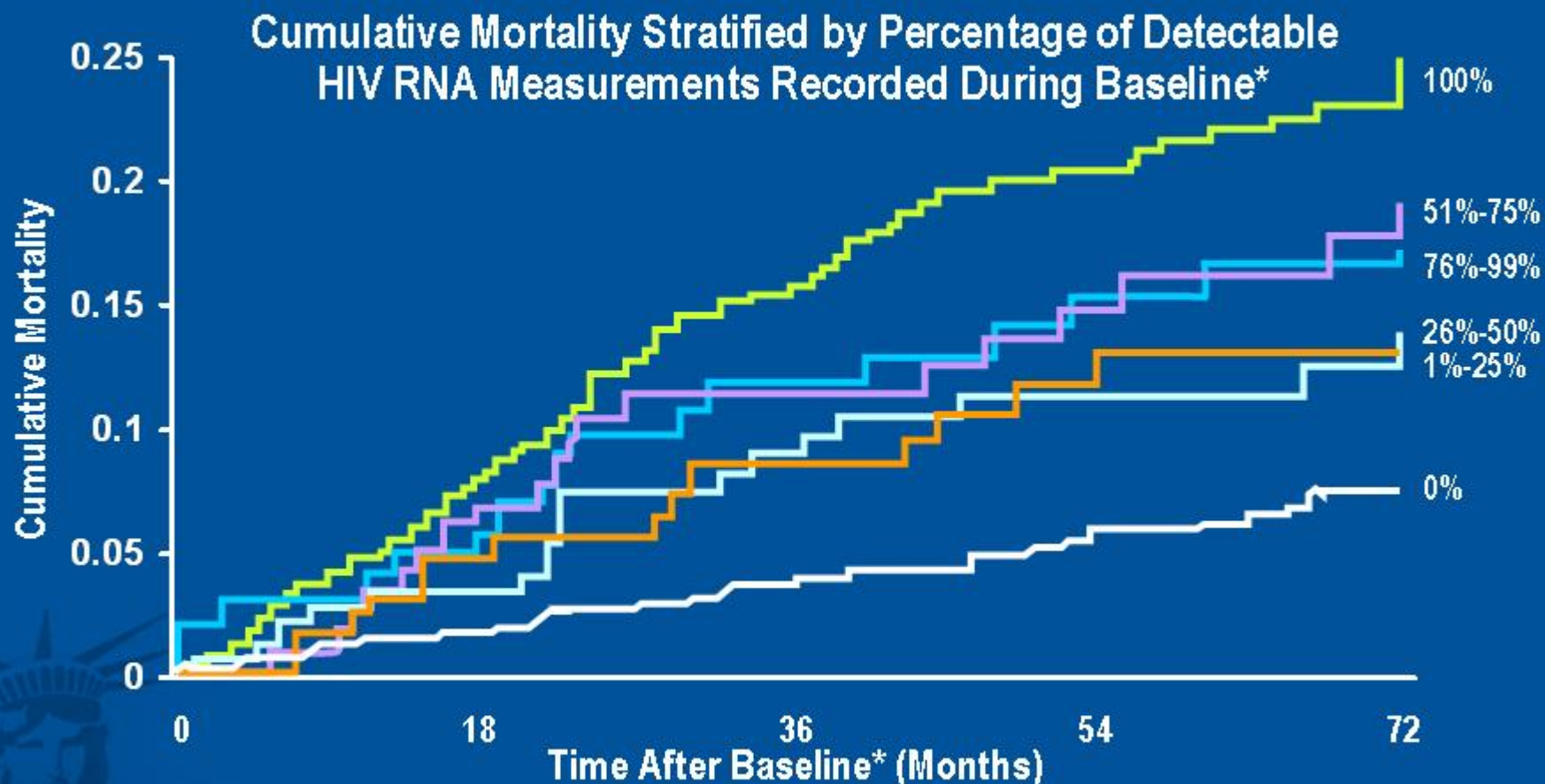
Multicenter AIDS Cohort Study, USA  
Palella N Engl J Med. 1998

# Mortality in the era of combination ART



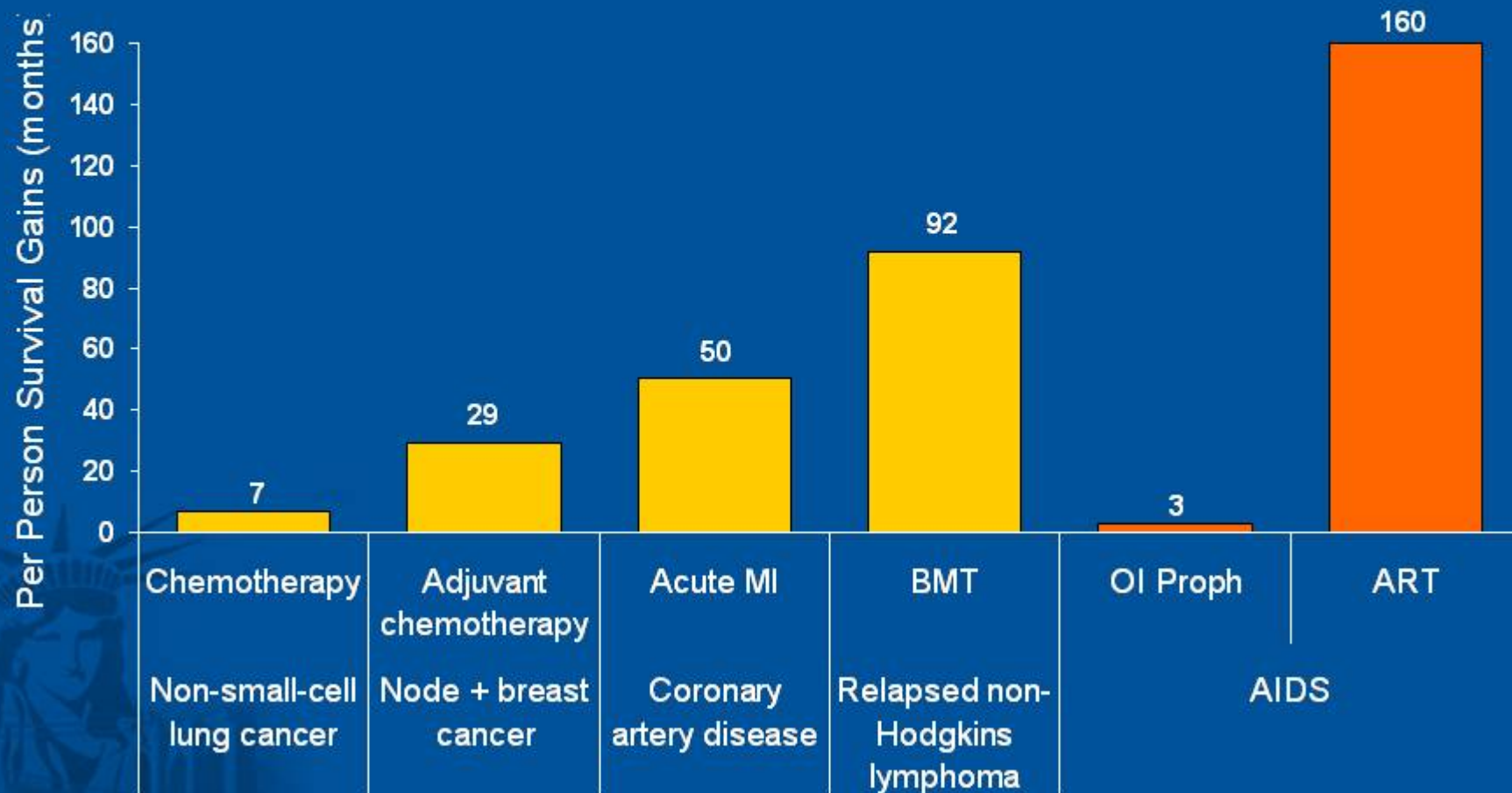
# Viral Suppression and Survival

## Danish HIV Cohort Study



\*Baseline: 18 months after initiation of HAART; n = 2046 patients who started HAART before 2002. Follow-up: 8898 patient-years after 18 months on HAART. Detectable: HIV RNA  $\geq$  400 copies/mL by proportion of time viral load detectable.

# Survival Gains With Various Disease Interventions



# Outline

- The case of Li X
- The problem of late HIV diagnosis
- Prognostic impact of combination ART
- **Case studies**
  - **Ricardo**
  - **Anna**
  - **Paul**
  - **Sanjay**
- Whom and when to test

# Ricardo

- You are on call for microbiology
- Phone call from a general practitioner
- 24 yr man, Italian origin, previously fit & well
- Wife is pregnant 36 weeks, well
- 2 weeks “bad flu”: fever, malaise
- Generalised lymph node swelling
- Splenomegaly
- Discrete maculopapular rash
- Pharyngitis
- Mononucleosis test negative

# Symptoms of Primary HIV Infection

- Fever
- Rash
- Oral ulcers
- Arthralgias
- Pharyngitis
- Loss of appetite
- Malaise
- Myalgia
- Nausea
- Headache
- Photophobia
- Night sweat
- Confusion
- Gingivitis
- Genital/anal ulcers
- Vomiting
- Meningism

# Symptoms of Primary HIV Infection

- **Fever**
- **Rash**
- **Oral ulcers**
- Arthralgias
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- Vomiting
- Meningism

# Suspected HIV Primary Infection

- HIV antibody test
- Detuned test

	Standard Test	Less sensitive “detuned” test
No HIV infection	Negative	Negative
Very early HIV infection	Negative	Negative
Primary HIV infection	<b>Positive</b>	Negative
Established HIV infection	<b>Positive</b>	<b>Positive</b>

- HIV Viral load
  - Viral load 50 to 500 ? False positive
  - >500

# Primary HIV infection

- Systemic illness <2 to >6 weeks
- “Mononucleosis – like”
- Accounts for 50% of HIV transmission
- Severity is prognostic marker
- AIDS-defining illness possible
- Ongoing trials for early intervention

## Ricardo

- Had recent unprotected male/male intercourse
- HIV antibody test negative
- HIV viral load 100.000/ $\mu$ L
- 2 weeks later antibody positive
- detuned assay positive
- Wife remained negative
- Newborn girl well

# Anna

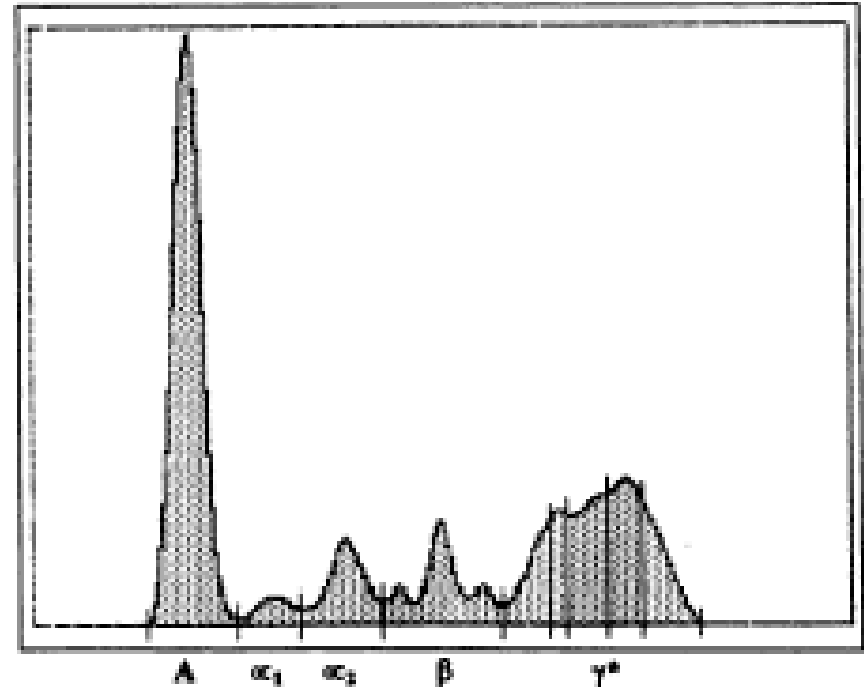
- 32 yr housewife
- Community-acquired pneumonia
- *S pneumoniae* in sputum

# Anna's routine laboratory

1 - HARPATH		File Edit Transmit Transfer Fonts Options Macro View Window Help	
NM784423	SMITH, ANNA	M U	Rec'd 05/04/2008
T1 Ward	T. 3218	Dr A Schwenk	
C, EGFR, ELB, MG			FN
Specimen No : JJ823705D	(Haematology)	<PgUp/PgDn> for more samples	
05/04/2008 09:30 Blood			
Haemoglobin	9.3	g/dl	( 11 to 17.5 ) Auth
White Cell Count	4.8	x10 <sup>9</sup> /l	( 4.0 to 11.0 ) Auth
Platelets	292	x10 <sup>9</sup> /l	( 135 to 420 ) Auth
Red Cell Count	2.91	x10 <sup>12</sup> /l	( 3.8 to 6.0 ) Auth
Packed Cell Volume	0.27	l/l	( 0.37 to 0.52 ) Auth
Mean Cell Volume	91.8	fl	( 76.0 to 96.0 ) Auth
Mean Cell Haemoglobin	31.9	pg	( 27.0 to 32.0 ) Auth
Mean Cell Haemoglobin Con	34.8	g/dl	( 31.5 to 36.5 ) Auth
Neutrophils	3.6(75.0%)	x10 <sup>9</sup> /l	( 2.0 to 7.5 ) Auth
Lymphocytes	0.7(14.6%)	x10 <sup>9</sup> /l	( 1.0 to 4.0 ) Auth
Monocytes	0.4(8.3%)	x10 <sup>9</sup> /l	( 0.2 to 1.2 ) Auth
Eosinophils	0.1(2.1%)	x10 <sup>9</sup> /l	( 0.04 to 0.4 ) Auth
Basophils	0.0(0.0%)	x10 <sup>9</sup> /l	( 0.02 to 0.1 ) Auth
Urea	4.9	mmol/l	( 1.7 to 8.3 ) Auth
Creatinine	66	umol/l	( 60 to 120 ) Auth
Estimated GFR	Unable to calculate. Patient <18y or missing data		Auth
Corrected Calcium	2.29	mmol/l	( 2.10 to 2.60 ) Auth
Calcium	1.96	mmol/l	( 2.10 to 2.60 ) Auth
Phosphate	1.07	mmol/l	Auth
Aspartate Transaminase	34	u/l	Auth
Alkaline Phosphatase	94	u/l	Auth
Total Bilirubin	2	umol/l	( 0 to 15 ) Auth
Total Protein	80	g/l	( 62 to 82 ) Auth
Albumin	27	g/l	( 35 to 50 ) Auth

# Chronic HIV Infection: Laboratory Clues

- **Pancytopenia (mild to moderate)**
  - Normocytic anaemia
  - Lymphocytopenia
  - Thrombocytopenia
- 
- **ESR ↑**
  - CRP normal or ↑
- 
- **Dysproteinaemia**
  - Total protein ↑
  - Albumin normal or ↓



# Anna

- No known risk factors for HIV infection
- Past history: shingles 2007
- HIV test positive
- CD4 cell count  $120/\mu\text{L}$

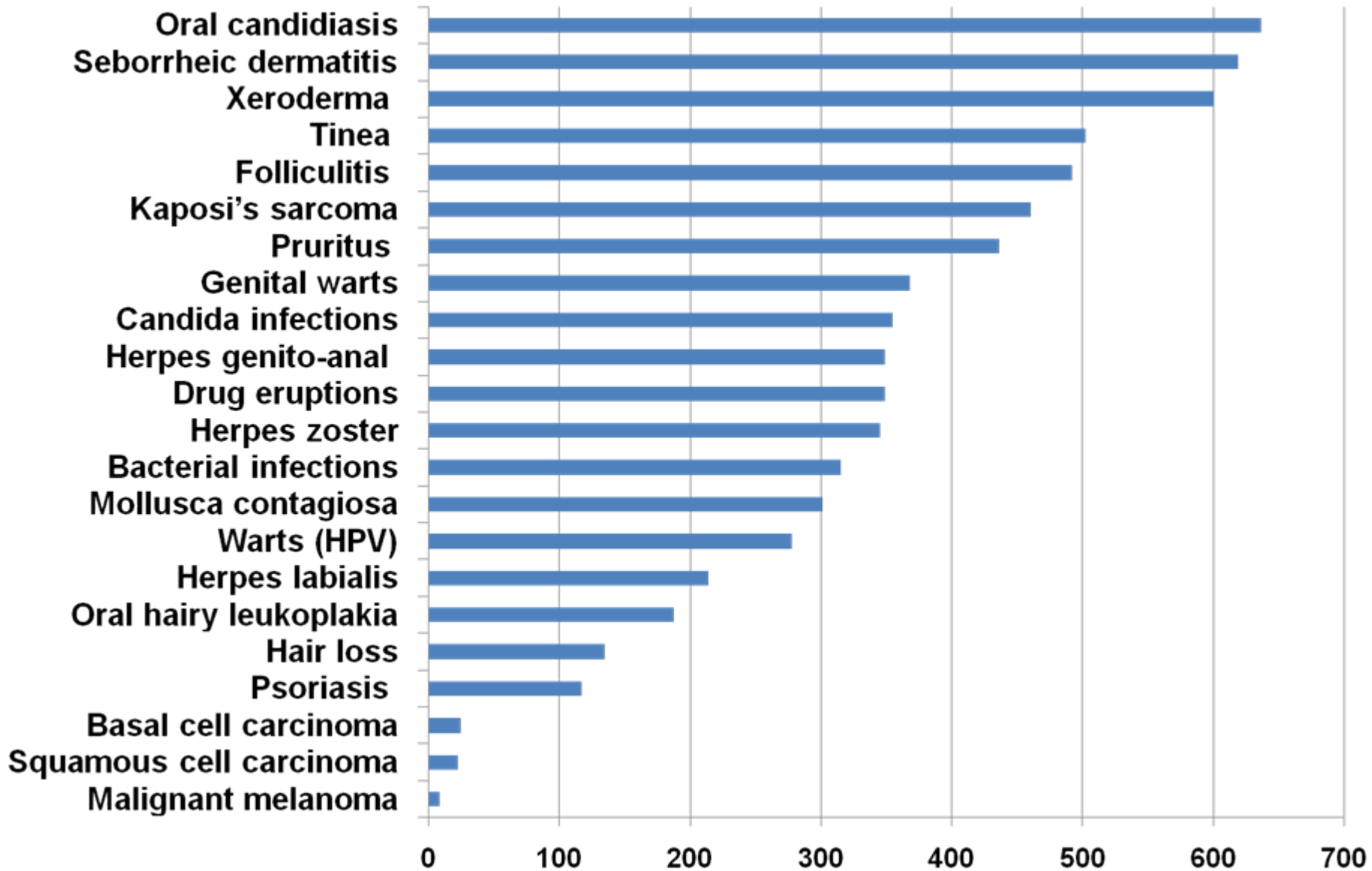
# Paul

- Received 4 requests for skin scrapings and biopsies over 2 years from general practitioner and dermatologist
- 49 year old male patient
- No significant medical history apart from
- “lumps and bumps”
- Itchy follicular lesions all over body
- Recent psoriasiform plaques
- Cold sores

- Pictures:

- Eosinophilic folliculitis
- Lichen planus
- Seborrhoeic dermatitis
- Herpes
- Oral candidiasis
- Oral hairy Leukoplakia

# Problems in a HIV Dermatology Clinic



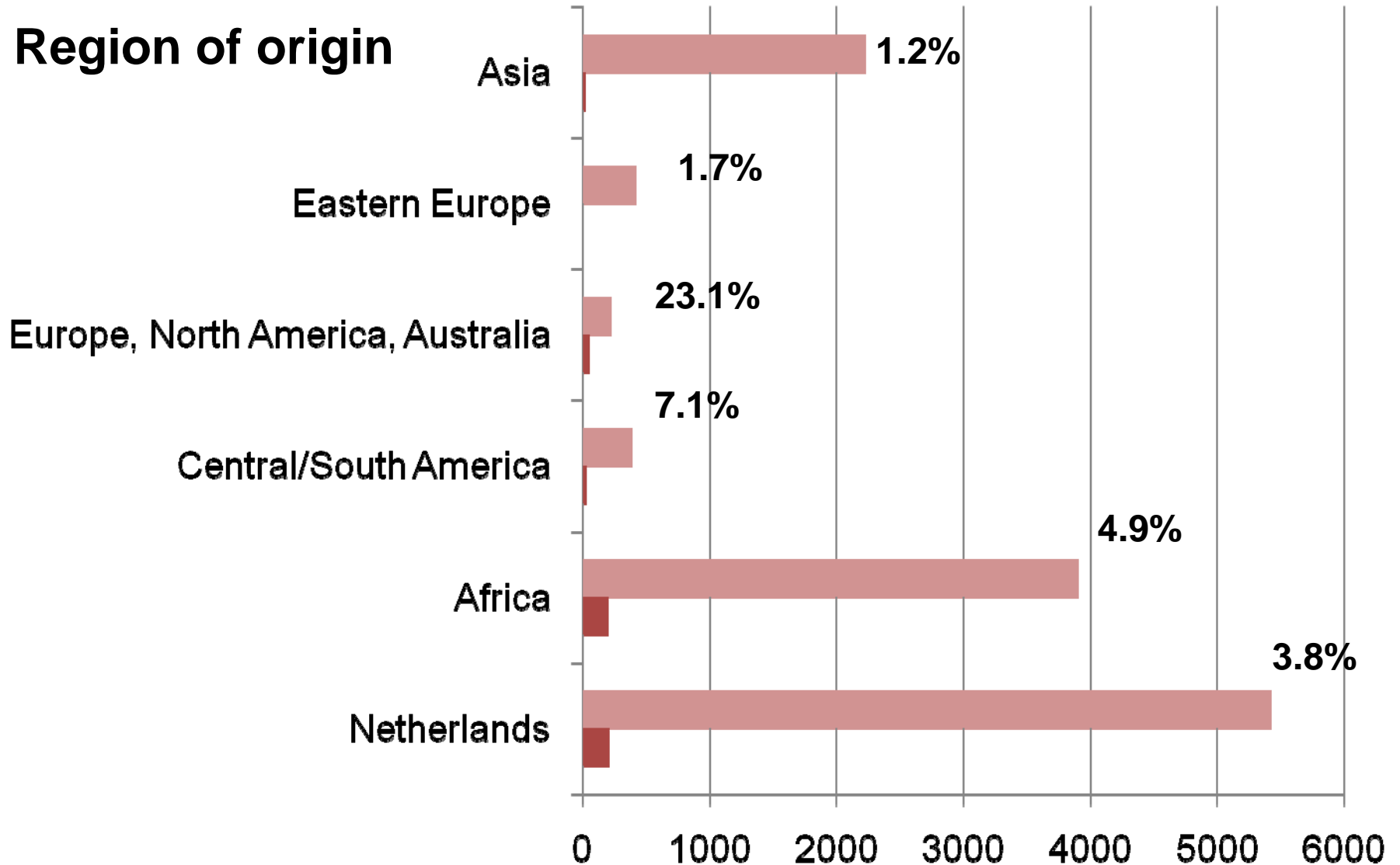
Total number of patients 1982 - 2000 = 2149

Schoefer, Sacks, Ochsendorf, HIV Medicine 2007, p582 ([www.hivmedicine.com](http://www.hivmedicine.com))

# Sanjay

- 78 year old Indian gentleman
- 2 months history of cough
- Married, 5 children, 3 grandchildren
- Sputum: acid fast bacilli +

# HIV prevalence in TB patients, Netherlands 1993–2001



# HIV prevalence in TB patients, London 1998 - 1999

<b>Ethnic origin</b>	<b>n/total</b>
African	8/57 (14%)
Indian	14/97 (12%)
White	2/38 (5%)
Other	1/10 (10%)
Total	23/202 (11.4%)

Anonymous unlinked testing in a South London TB clinic  
Bowen et al, Lancet 2000

# Sanjay

- Gujarati origin
- Immigrated to UK from Uganda 1972
- Frequent travel to East Africa for business
- HIV positive
- CD4 cell count  $20/\mu\text{L}$
- Starts ARV after 2 months TB treatment
- Viral load undetectable, CD4  $230/\mu\text{L}$

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- **Whom and when to test**

# Prevalence of HIV in Indicator Diseases

Disease	HIV Prevalence (%)
Candidiasis	6 – 23
Zoster	?
Cryptococcosis, skin	77
Oral manifestations of HIV disease	?
Hepatitis B	?
Hepatitis C	8 – 59
Lymphogranuloma venereum	74
Tuberculosis	10 – 25
Community acquired pneumonia	19 – 24
Meningitis	?
Nosocomial diarrhoea	10 – 12
Unexplained fever	3
Mononucleosis	7
Laboratory indicators	?
Kaposi's Sarcoma	45

Gazzard B et al  
HIV Med 2008

# Missed Opportunities For HIV Testing

**3054** (72%) had attended healthcare in last 3 years without HIV test

=

19.296 attendances (4 per patient)

=

**3888** suggestive symptoms

**2734** suggestive of seroconversion illness

**4242** new HIV cases  
South Carolina  
2001 – 2006

**1286** (42%)  
AIDS within 1 year

# HIV Testing, the US Way

- For patients in all health-care settings
- HIV screening for patients in all health-care settings with **implied consent** and opt-out.
- Persons at high risk annual re-test.
- No prevention counseling required.

Revised Recommendations for HIV Testing of Adults,  
Adolescents, and Pregnant Women in Health-Care Settings  
CDC  
MMWR Sept 22, 2006 / 55(RR14)

# European Recommendations (Draft)

- All healthcare professionals to know indicator diseases and promote HIV testing
- Focus on general practitioners, dentists, dermatologists, gynaecologists, STD clinicians and emergency physicians
- All individuals with TB and other indicator diseases should be tested for HIV.
- All STD clinic patients offered annual HIV test
- Consider opt-out testing for all pregnant women.
- Laboratory abnormalities associated with HIV infection should lead to HIV testing.
- Routine HIV testing with certain malignancies
- EACS to audit predictive value of indicator diseases

# Take Home Messages and Questions

- **The problem of late HIV diagnosis**
- 
- **Prognostic impact of combination ART**
- **Case studies**
- 
- **Whom and when to test**
- Society-related delay (denial, exclusion)
- Lack of recognition by doctors
- One of the most cost-efficient healthcare interventions
- Primary HIV infection
- Laboratory indicators
- Indicator disease
- Epidemiological risk can be misleading
- General testing (Opt-out vs opt-in)
- Symptom-driven testing