Advanced Course in Clinical Parasitology (ACCP)

Barcelona, September 6th 2011

Overview of Opportunistic Infections in the HAART Era

Dr. José M. Miró

Infectious Diseases Service

Hospital Clinic – IDIBAPS

University of Barcelona

Barcelona (Spain)

E-mail address: jmmiro@ub.edu

Global estimates for adults and children, 2009

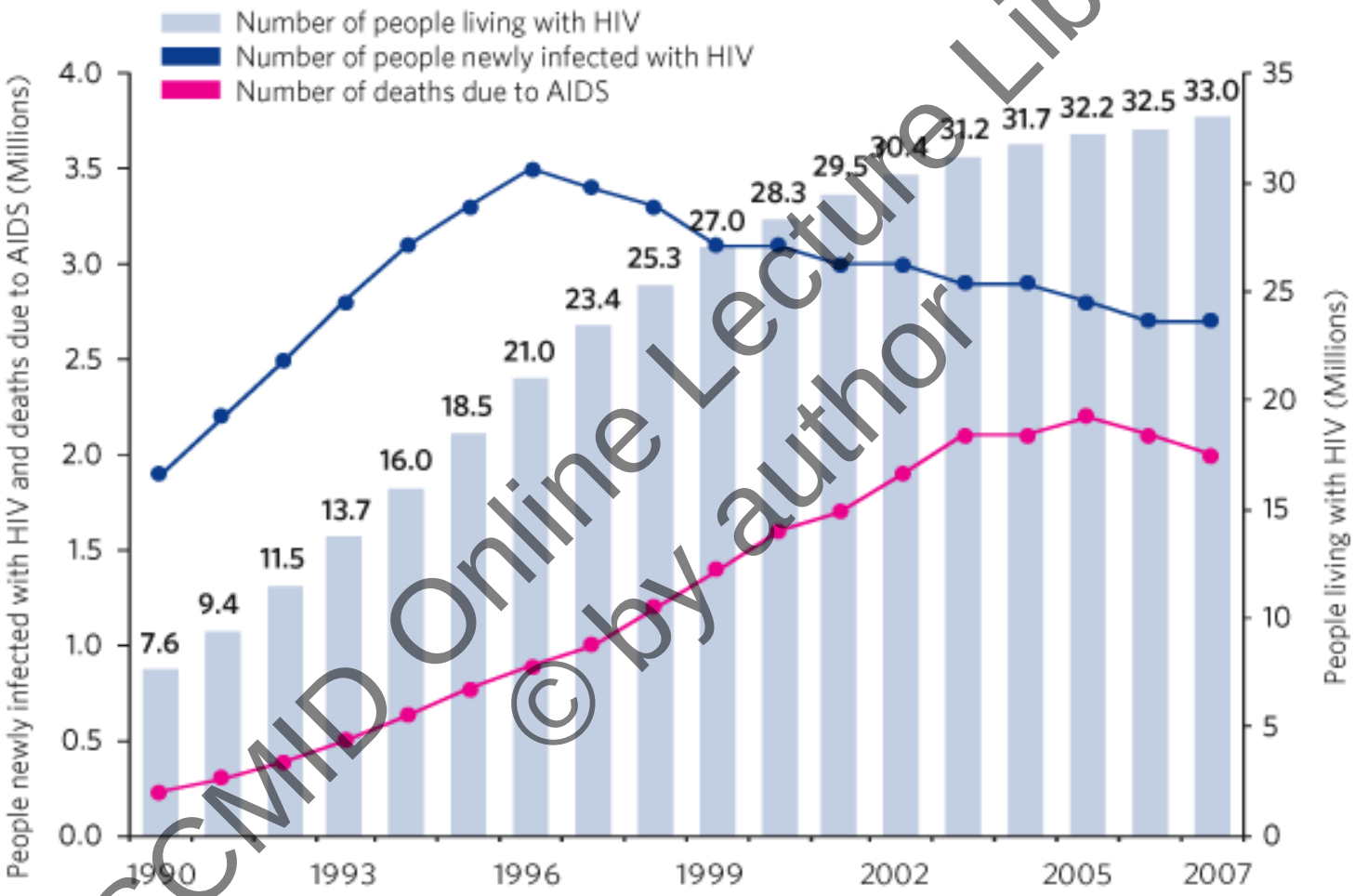
People living with HIV	33.4 million [31.1–35.8 million]
New HIV infections in 2008	2.7 million [2.4–3.0 million]
Deaths due to AIDS in 2008	2.0 million [1.7–2.4 million]

The ranges around the estimates in this table define the boundaries within which the actual numbers lie, based on the best available information.

UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

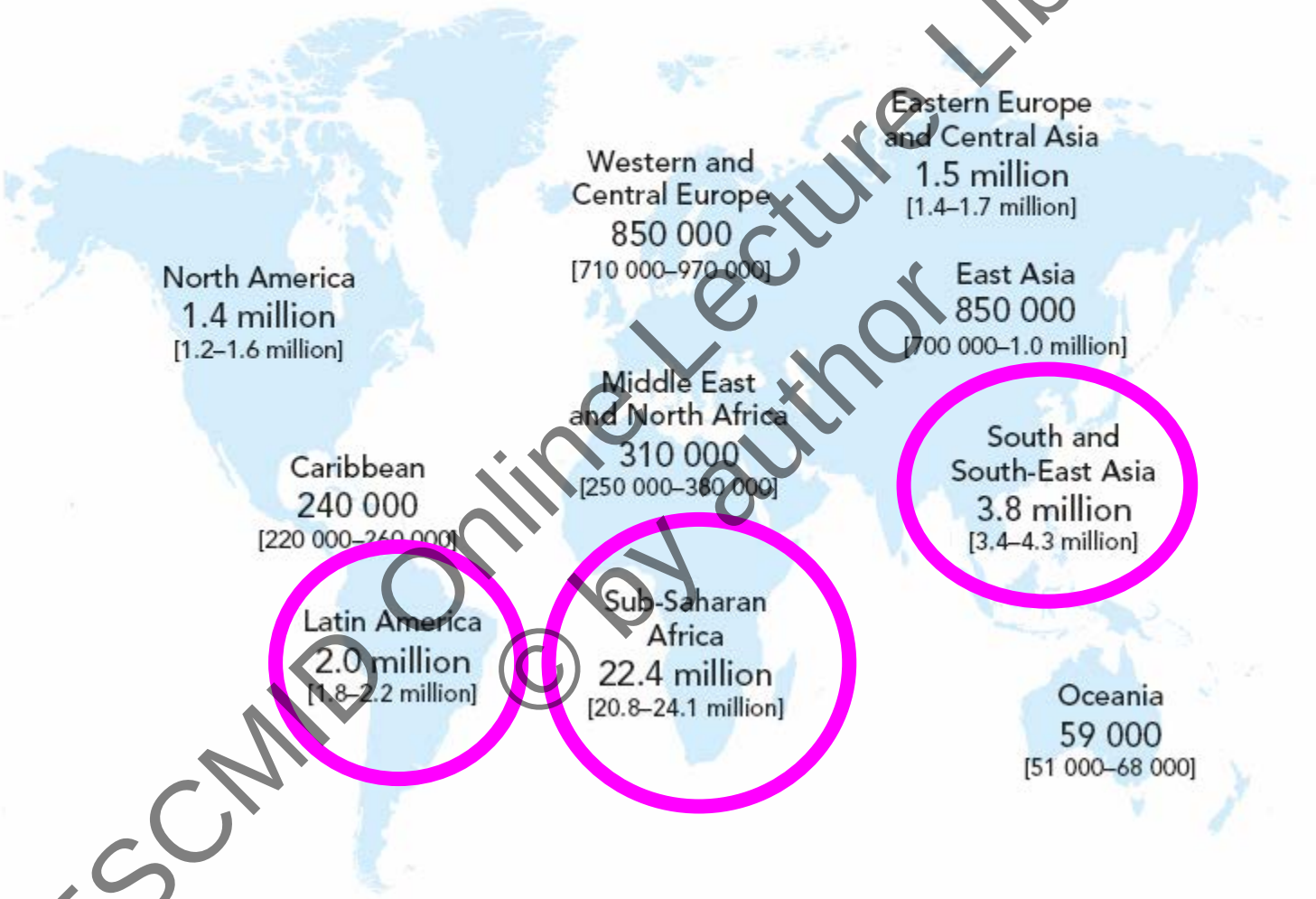
World Health Organization

Global estimates for adults and children over time



Total: 33.4 million (31.1–35.8 million)

Adults and children estimated to be living with HIV, 2008

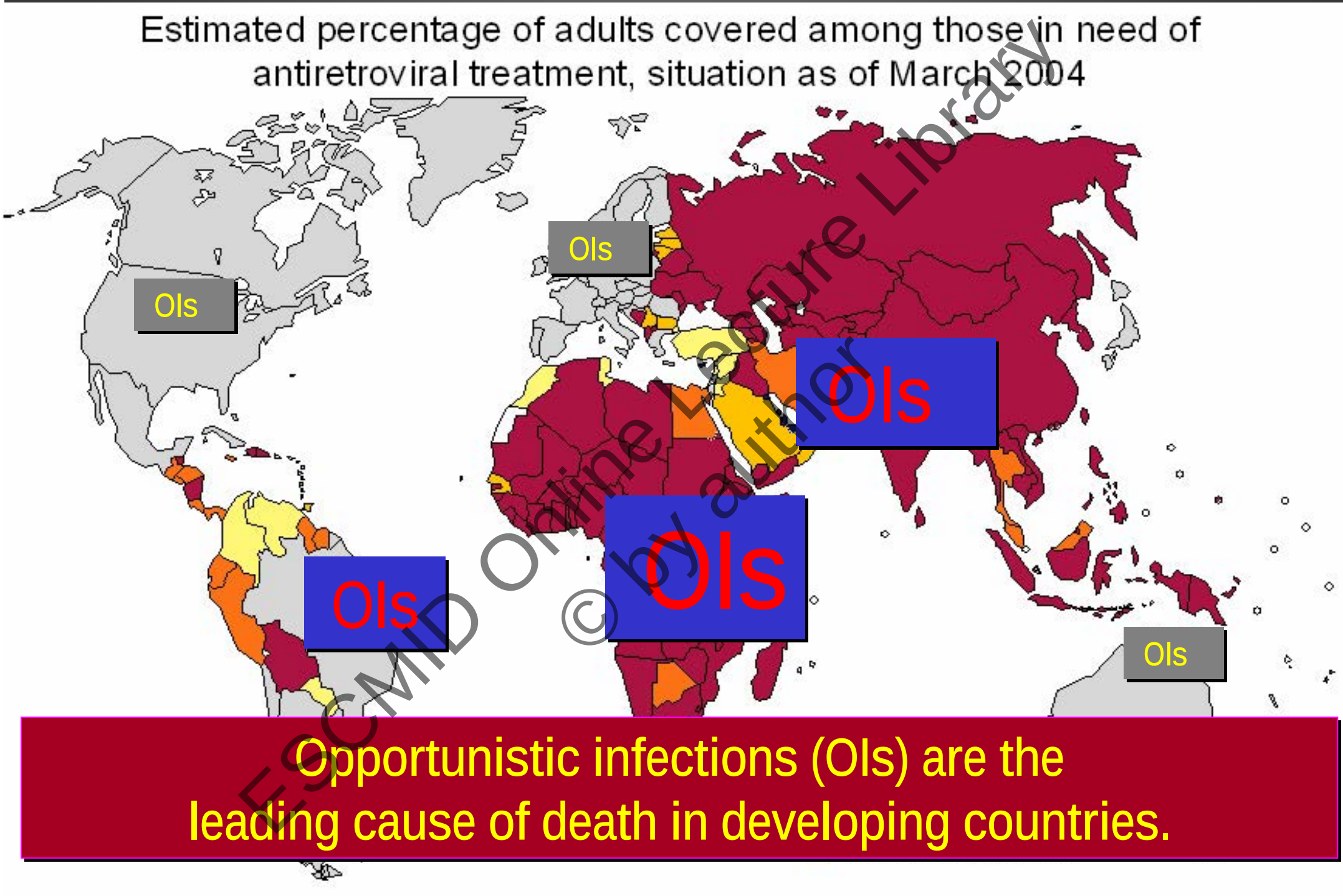


Total: 33.4 million (31.1–35.8 million)

Magnitude of the HIV-Infection in Spain

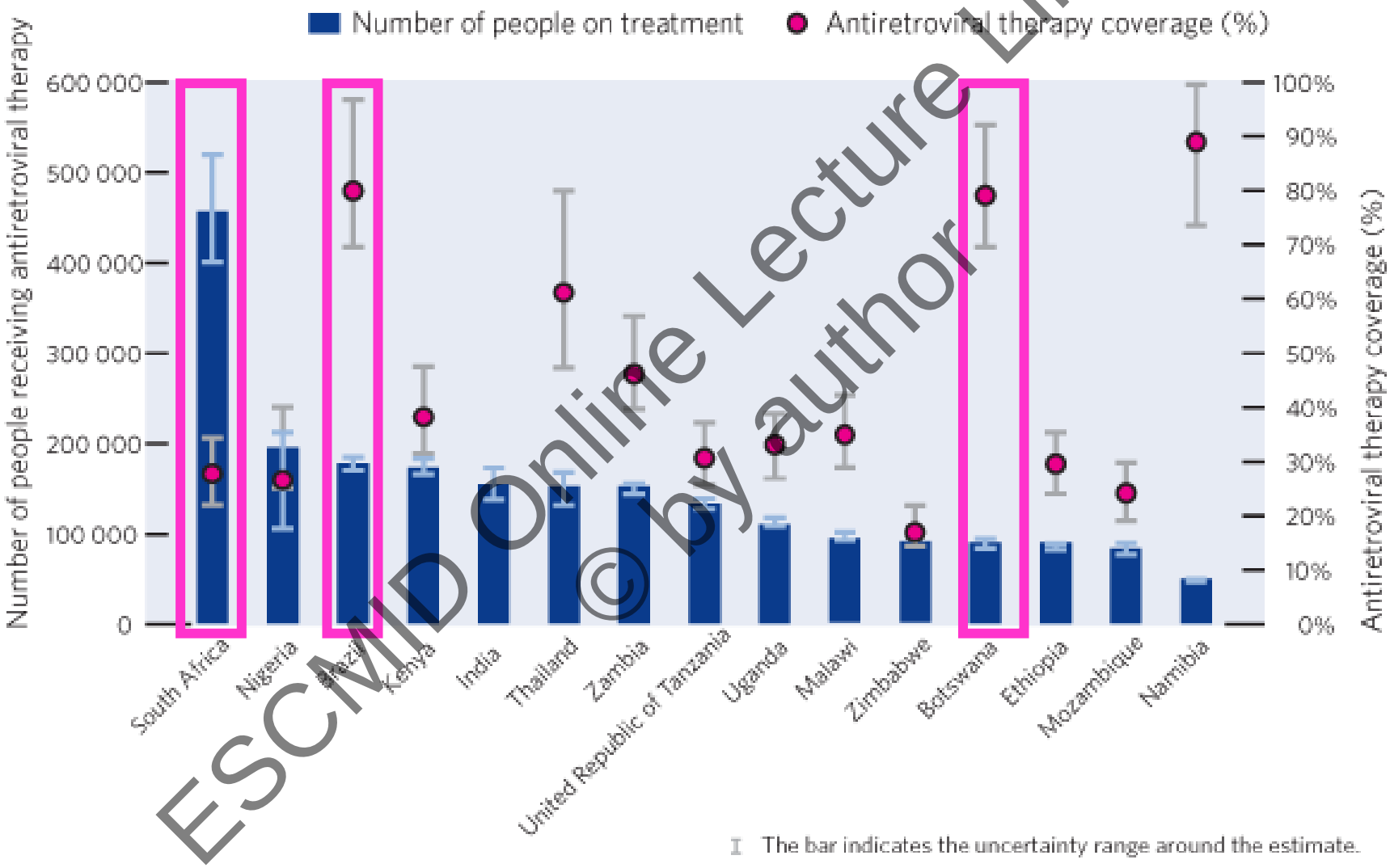
Estimated No. Patients		No. cases
• HIV-infected patients*	-	150,000
• HCV coinfection**	50%	75,000
• HBV coinfection**	5%	7,500
• Unkown HIV-1 infection	30%	50,000
• Late presenters	50%	

* Hamers FF. Lancet. 2004; 364:83; **GESIDA/FIPSE. EIMC. 2005;23:340.



Opportunistic infections (OIs) are the leading cause of death in developing countries.

cART access in low- and middle-income countries



CD4 count at start of ART, 2003-2005

42 countries, 176 sites, 33,008 patients

Numbers are median CD4 counts

First line regimens, 2003-2005

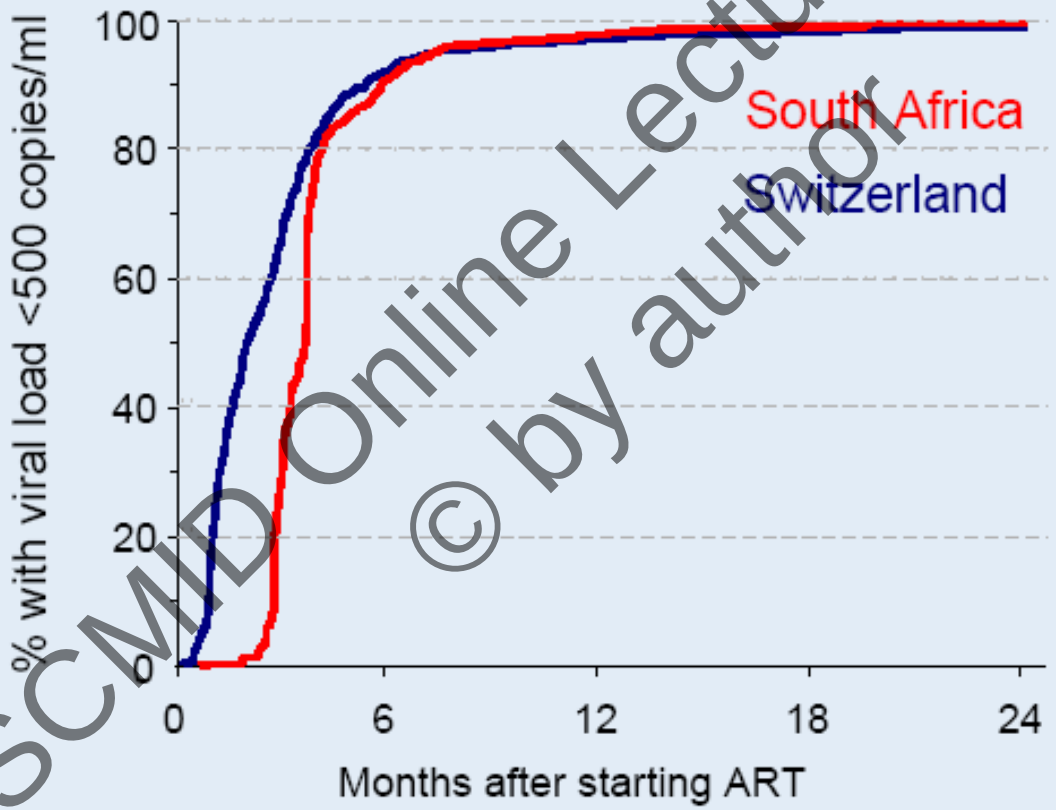
No. of regimens used to treat 90% of patients

North America	South America	West, Central & East Africa
59	11	3

Western Europe	Asia	Southern Africa
47	3	3

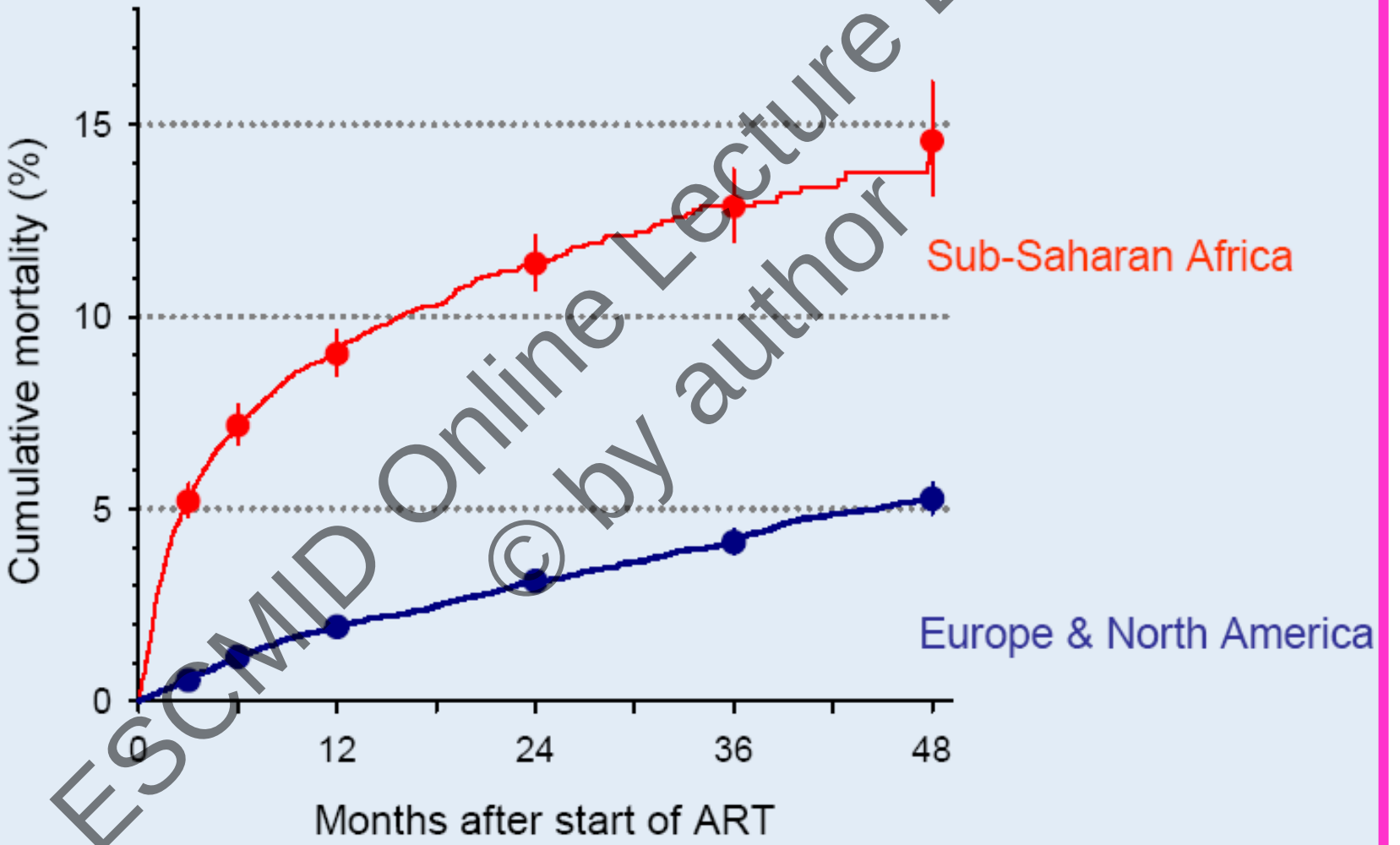
Egger M, *et al. 14th CROI*, Los Angeles 2007, #62

Initial virologic response (<500 copies/ml)



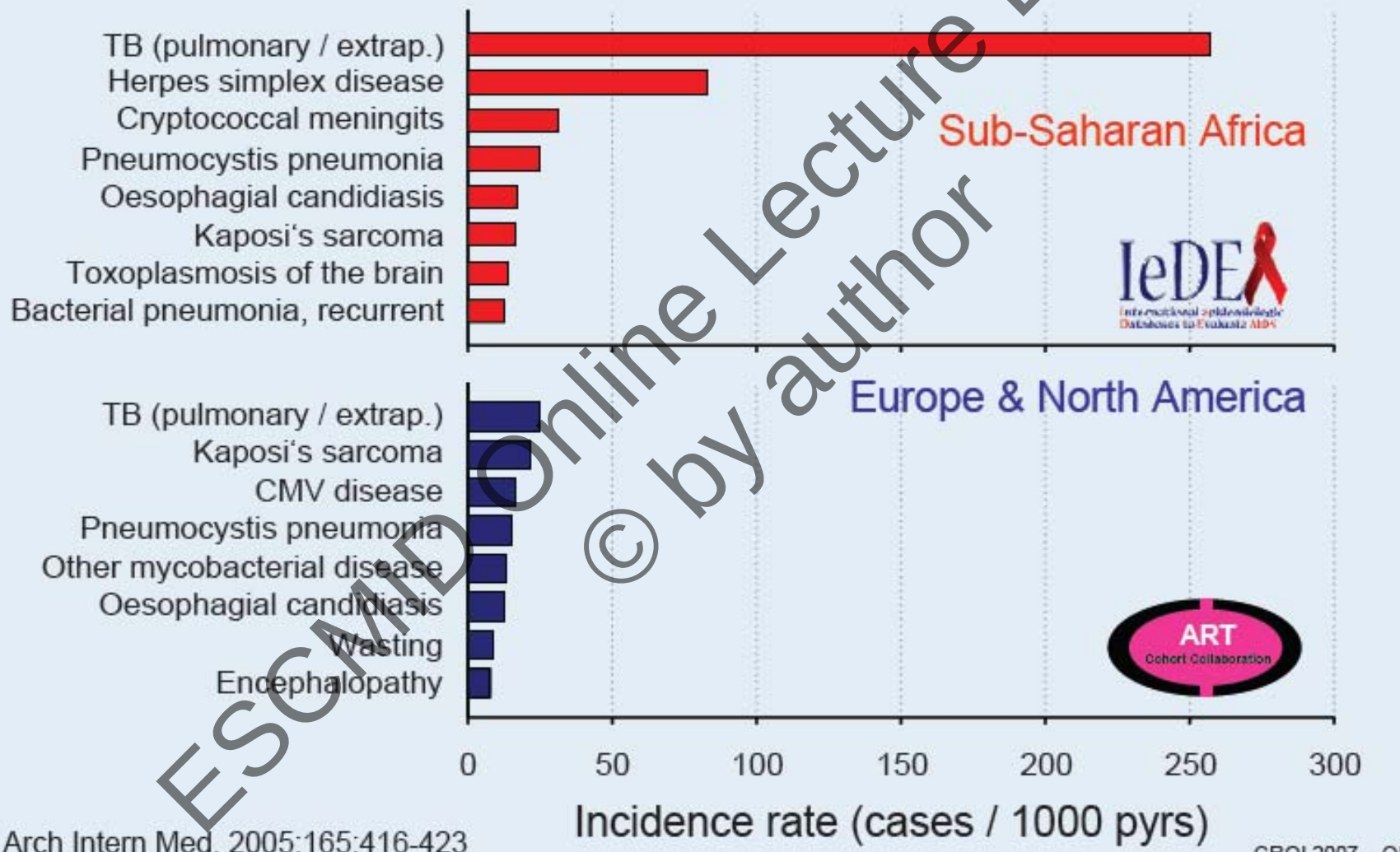
Egger M, *et al. 14th CROI*, Los Angeles 2007, #62

Mortality over four years

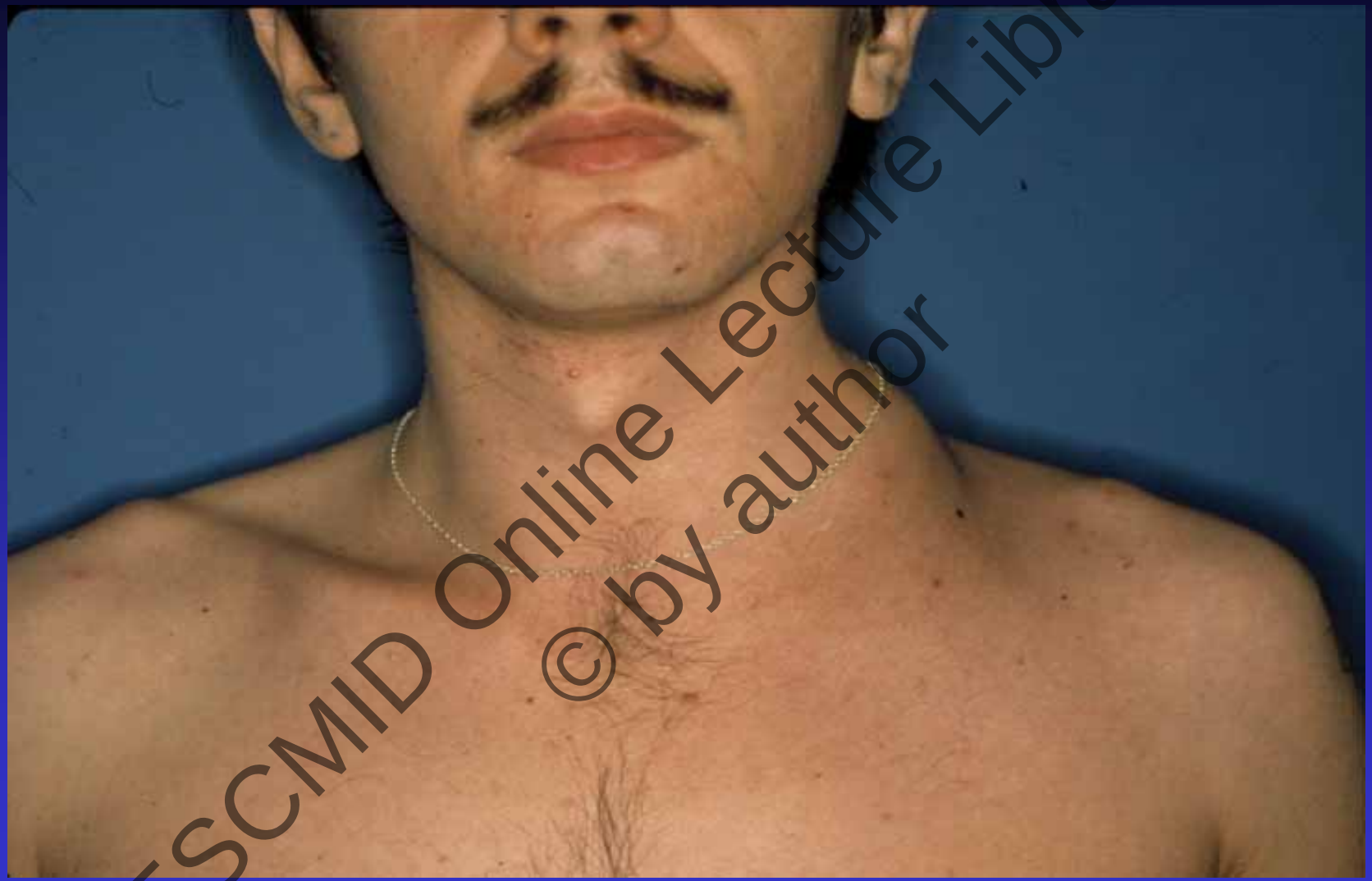


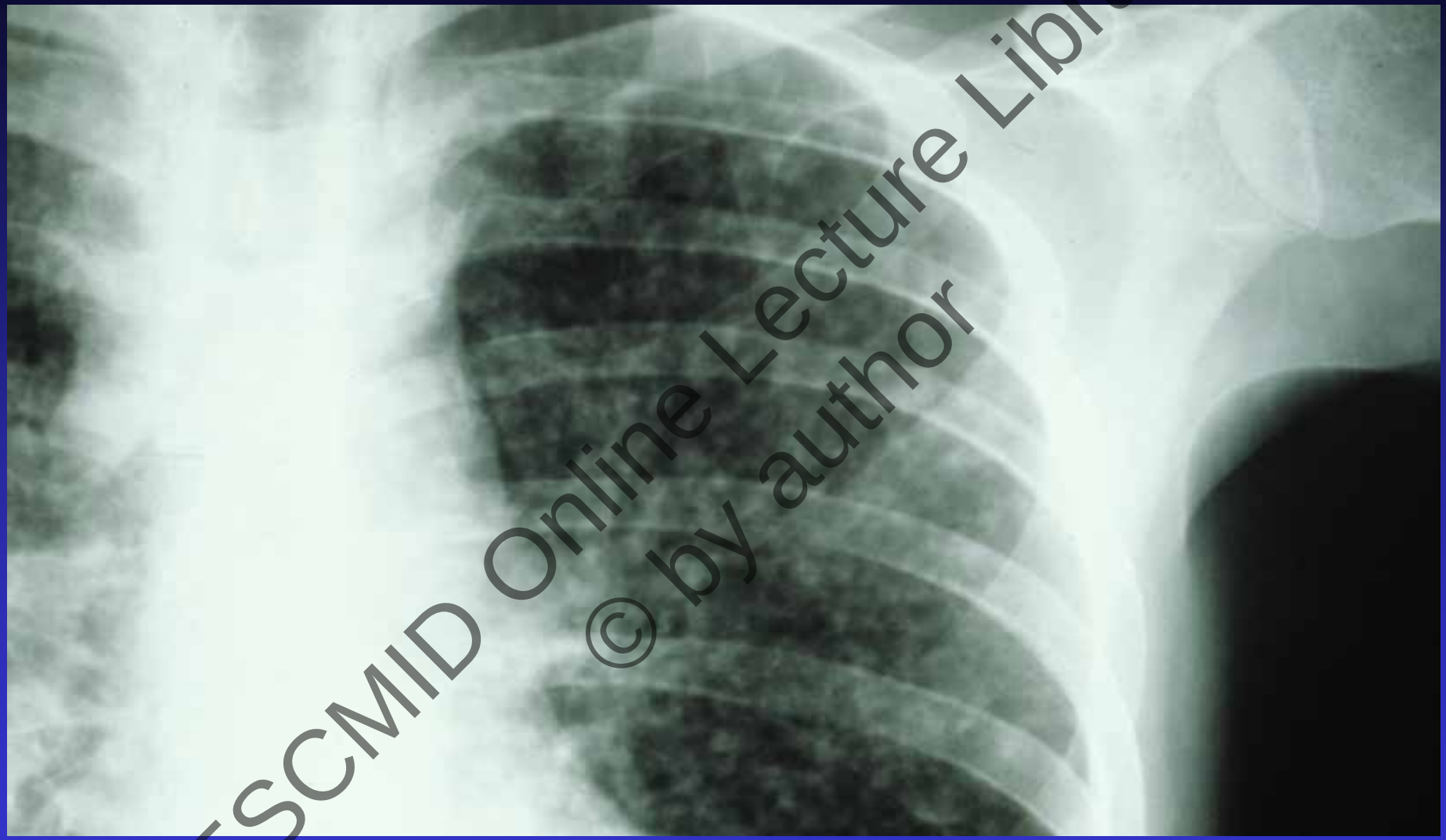
Egger M, *et al. 14th CROI*, Los Angeles 2007, #62

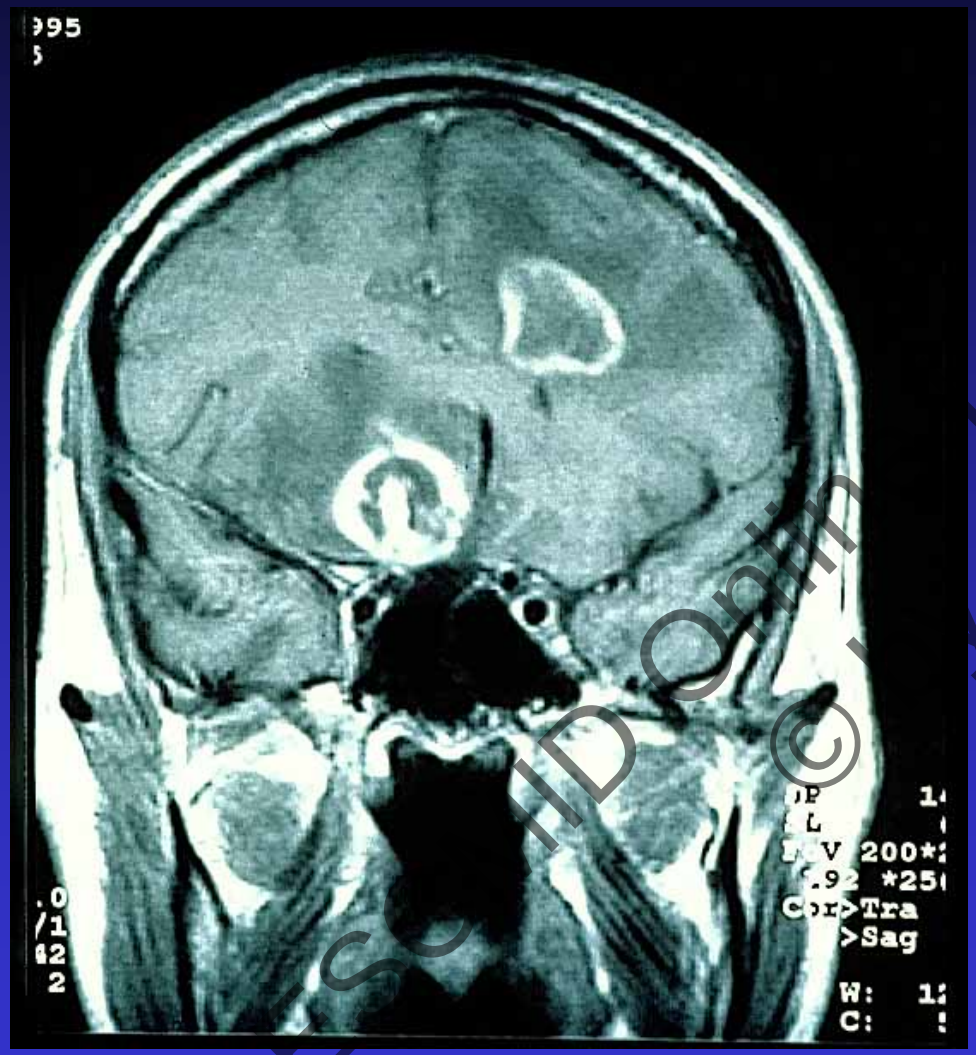
Most common OIs in first 3 months

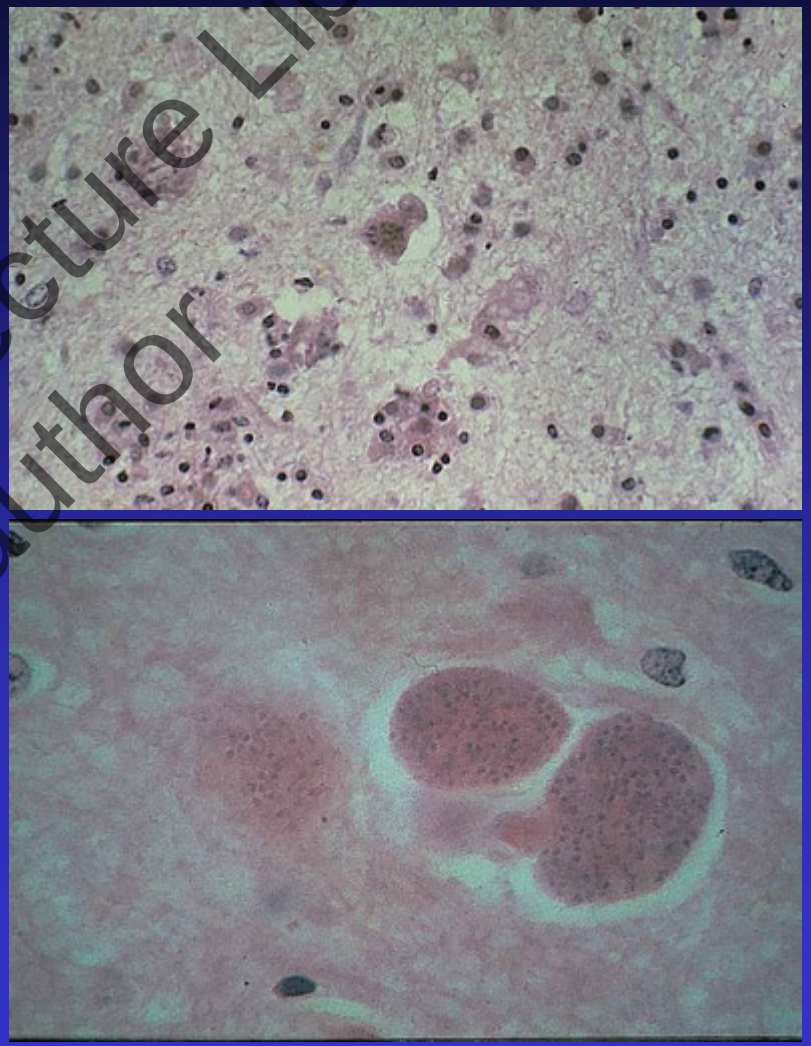


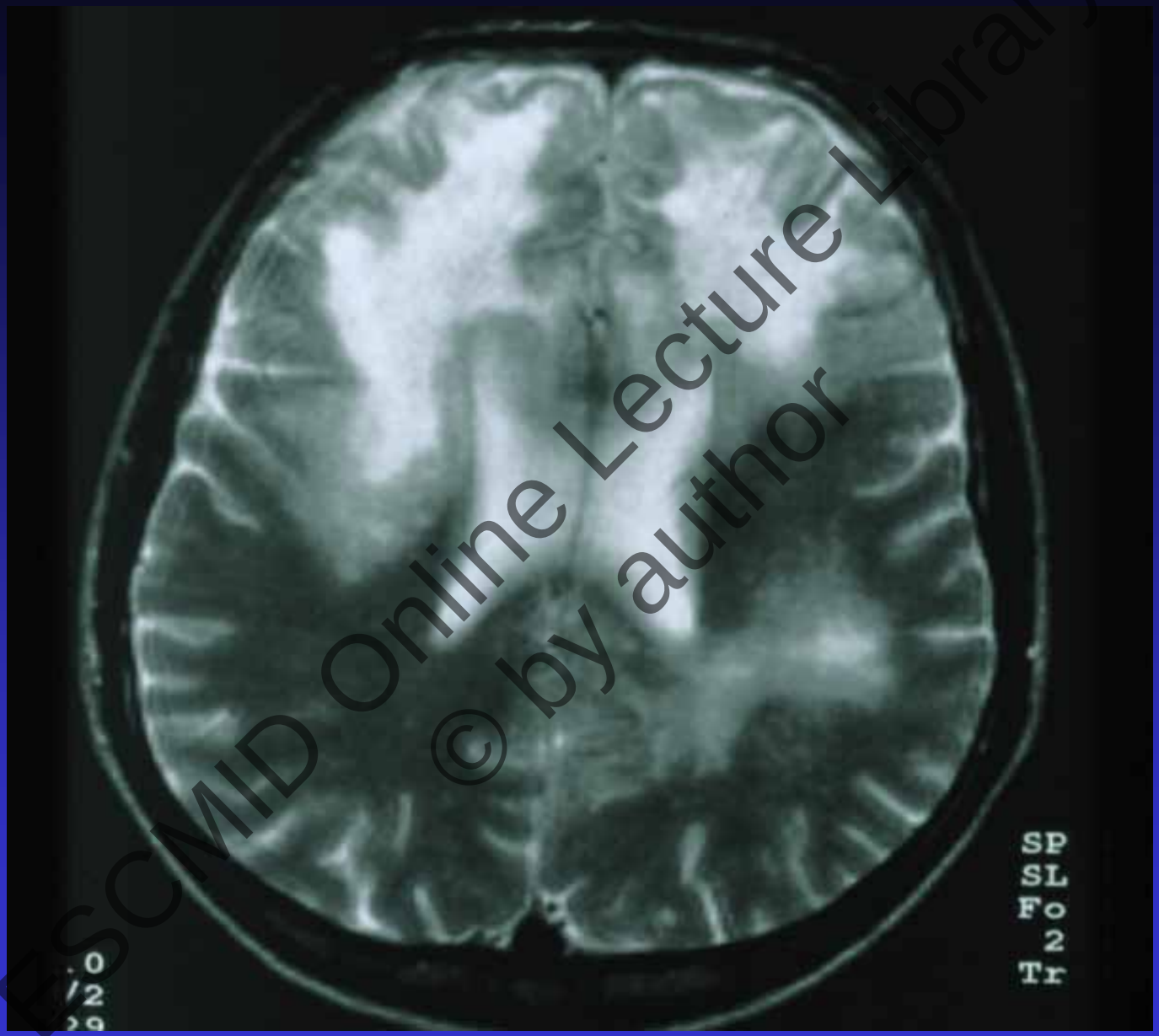
Arch Intern Med. 2005;165:416-423

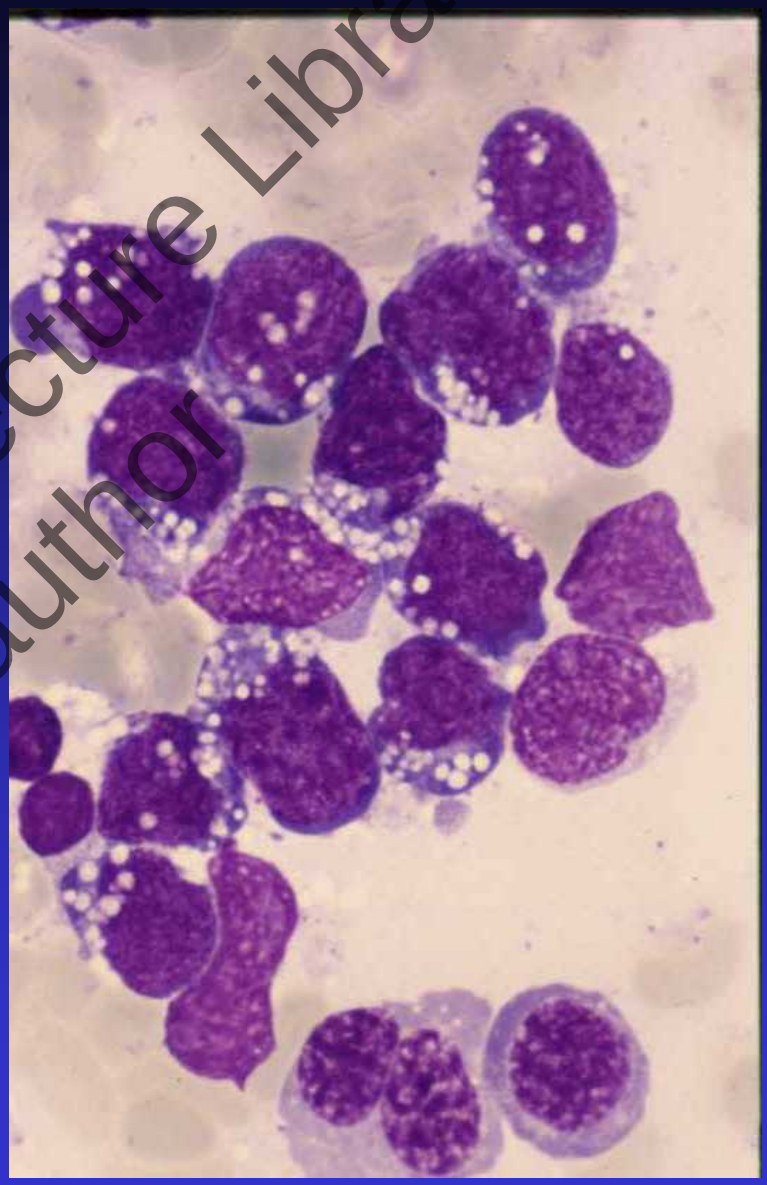












C Events at HIV Diagnosis in Late Presenters From Italy, Spain, UK & Canada

Mussini C et al. AIDS 2008, 22:2461–2469

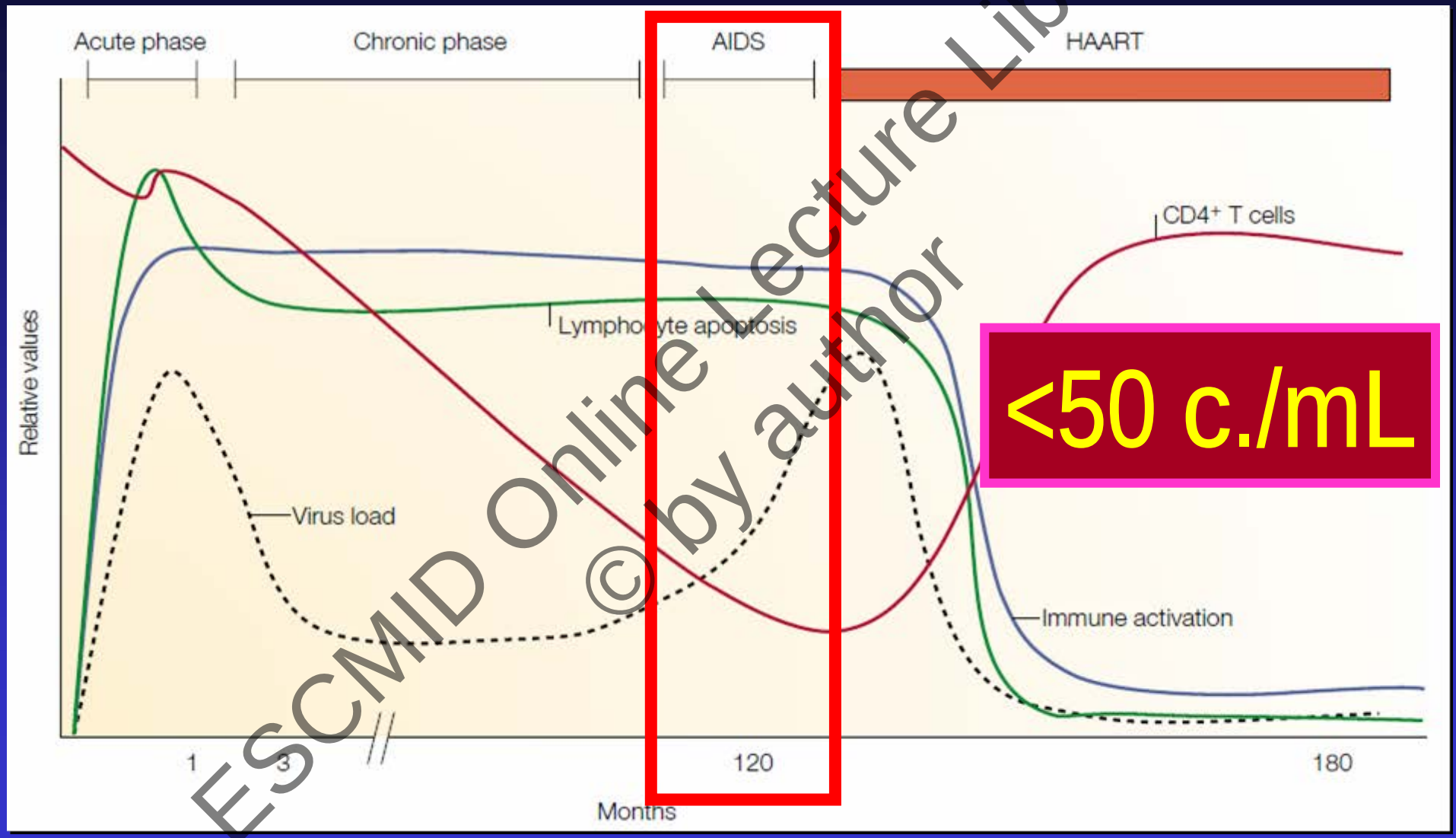
• *P. jirovecii* pneumonia (PCP)	268 (35%)
• Tuberculosis	168 (22%)
• Esophageal candidiasis	94 (12%)
• CNS toxoplasmosis	65 (9%)
• CMV disease	51 (7%)
• Kaposi's sarcoma	65 (9%)
• NHL	28 (4%)
• Other Opportunistic Infections	115 (15%)

CD4 lymphocytes & C Events

CoRIS (N= 477; 2004-07)

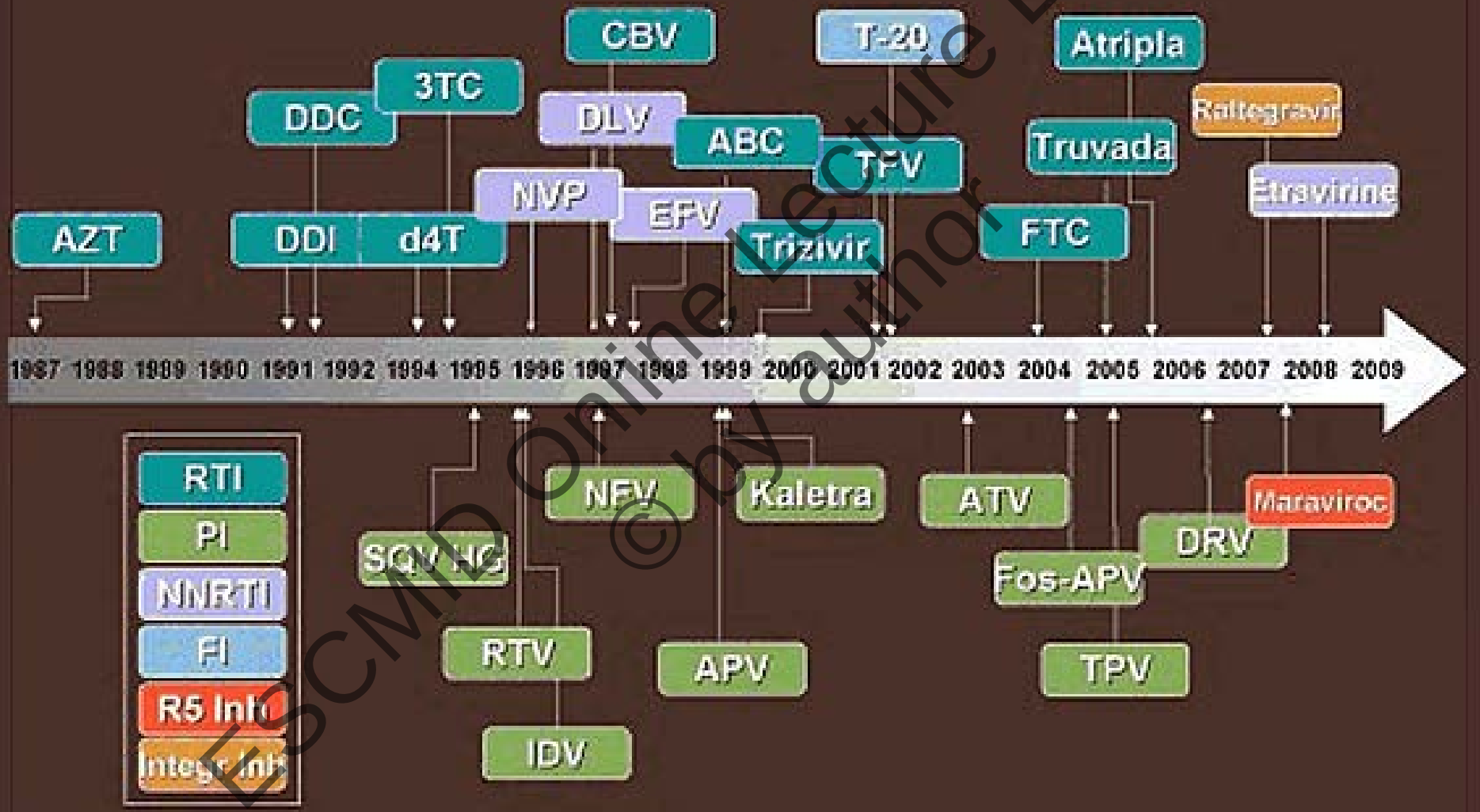
C event	Median	IQR
Pulmonary tuberculosis	221	95; 385
Extrapulmonary tuberculosis	80	24;135
P. jirovecii pneumonia	29	11;61
Esophageal candidiasis	35	12;111
CNS toxcoplasmosis	49	20;138
Meningeal cryptococcosis	22	8;53
PML	100	61;151
Kaposi sarcoma (KS)	130	69;276
Non-Hodgkin lymphoma (NHL)	128	59;260

Natural history of HIV infection

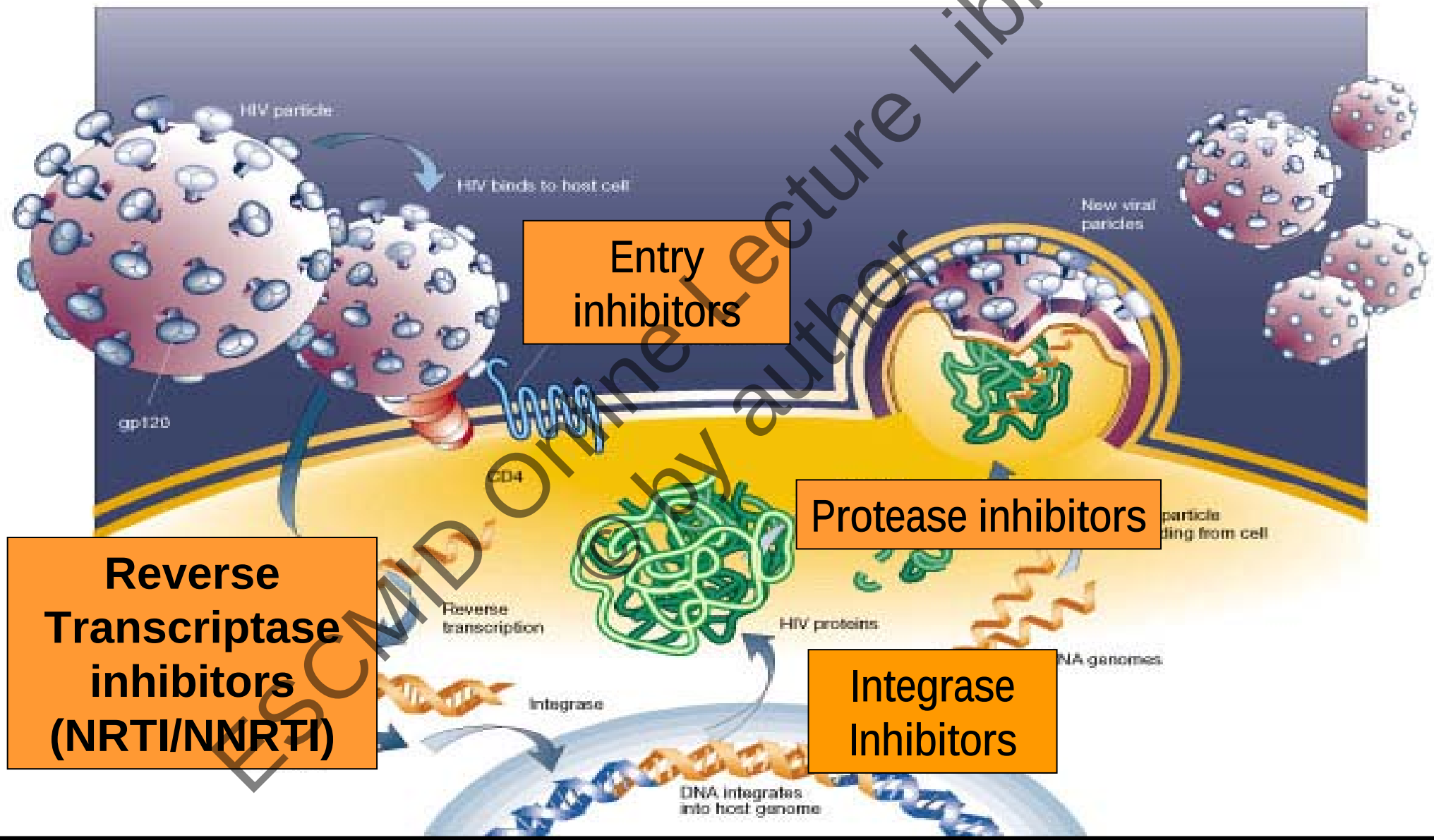


Gougeon ML. Nature Immunol. 2003.

CONTINUING EVOLUTION OF HAART



Mechanism of action of ARV drugs



Marketed Antiretrovirals in Spain (2011)

- **NRTI***
  - Zidovudine (AZT)
  - Didanosine (ddI)
  - Zalcitabine (ddC)
  - Lamivudine (3TC)
  - Stavudine (d4T)
  - Abacavir (ABV)
  - Emtricitavine (FTC)
- **NtRTI***
  - Tenofovir (TDF)
- **NNRTI**
  - Efavirenz
  - Nevirapine
  - Etravirine
- **ENTRY INHIBITORS**
  - - Fusion inhibitors: Enfuvirtide (T-20)
  - - CCR5 inhibitors: Maraviroc; Vicriviroc (viral phenotype)
- **PROTEASE INHIBITORS (IP)**
  - Saquinavir / Indinavir / Nelfinavir
  - Ritonavir (rtv)
  - Fosamprenavir/rtv
  - Lopinavir/rtv (Kaletra®)
  - Atazanavir/rtv
  - Tipranavir/rtv
  - Darunavir/rtv
- **INTEGRASE INHIBITORS**
  - Raltegravir
  - Elvitigravir

*Combos: Combivir®; Kivexa®; Truvada®; Trizivir®, Atripla®

2011 Spanish Recommendations for cART in HIV-1-Infected Antiretroviral Naïve Patients

¿When to start?

1.- Symptomatic patients (B/C events): all cases

2.- Asymptomatic patients

- CD4 < 350 cels/mm3: Recommended in all cases (A)
- CD4 350-500 cels/mm3: Recommended in most cases (B)*
- CD4 > 500 cels/mm3: Delayed in general. Recommended in some situations (B)**.

* Exceptions: Stable CD4 T-cell count, Low plasma HIV-1 RNA viral load, unwillingness.

** Liver cirrhosis, chronic C/B hepatitis, Plasma HIV-1 RNA Viral Load > 10^5 copies/ml; CD4 <14%; Age >55 years; High cardiovascular risk; HIV-related nephropathy; and, serodiscordant couples with high risk of transmission

2011 Spanish Recommendations for cART in HIV-1-Infected Antiretroviral Naïve Patients

First Line Regimens

NNRTI-based regimens:	EFV + 2 NRTIs* QD
PI/r-based regimens:	LPV/r (Kaletra®)+ 2 NRTIs* BID/QD
	DRV/r + 2 NRTIs* QD
	ATV/r + 2 NRTIs* QD
Raltegravir-based regimens:	RAL BID + 2 NRTIs* QD

Triple NRTI Regimen	Not recommended as first line Rx. Only alternative: Trizivir® ± TDF.
Alternatives	Maraviroc (R5)+ 2 NRTIs*.

*NRTIs: Truvada® Atripla®; Kivexa® if HLA-B*5701 Neg.; Alternative: Combivir®; ddI+FTC/3TC.

Combined Antiretroviral Therapy

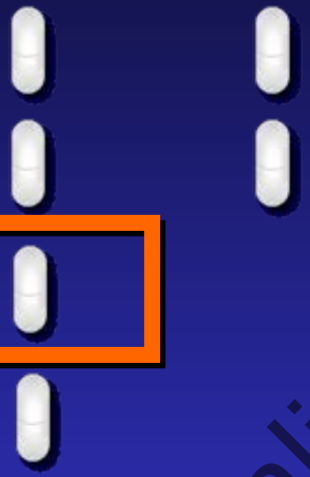
NRTIs/NtRTI

Combivir®

Trizivir®

Truvada®

Kivexa®*



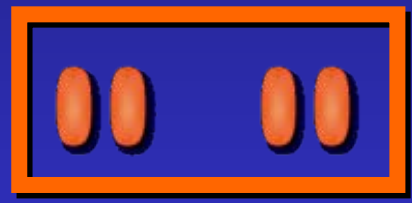
NNRTIs

Efavirenz

At night

Boosted PIs

Lopinavir
+ Ritonavir (Kaletra®)



NRTIs/NtRTI+NNRTI

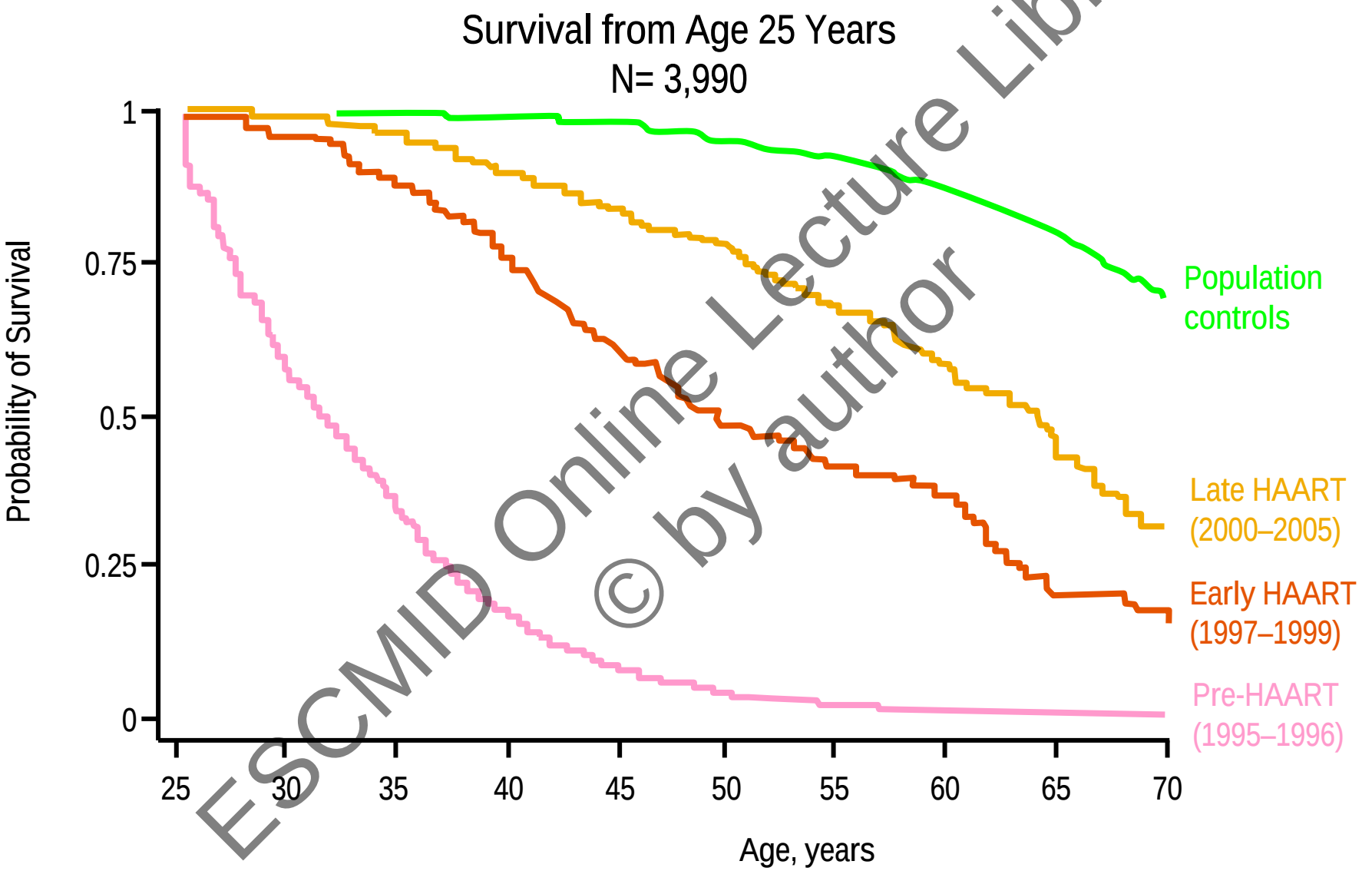
Atripla®

Integrase Inhibitors

Raltegravir

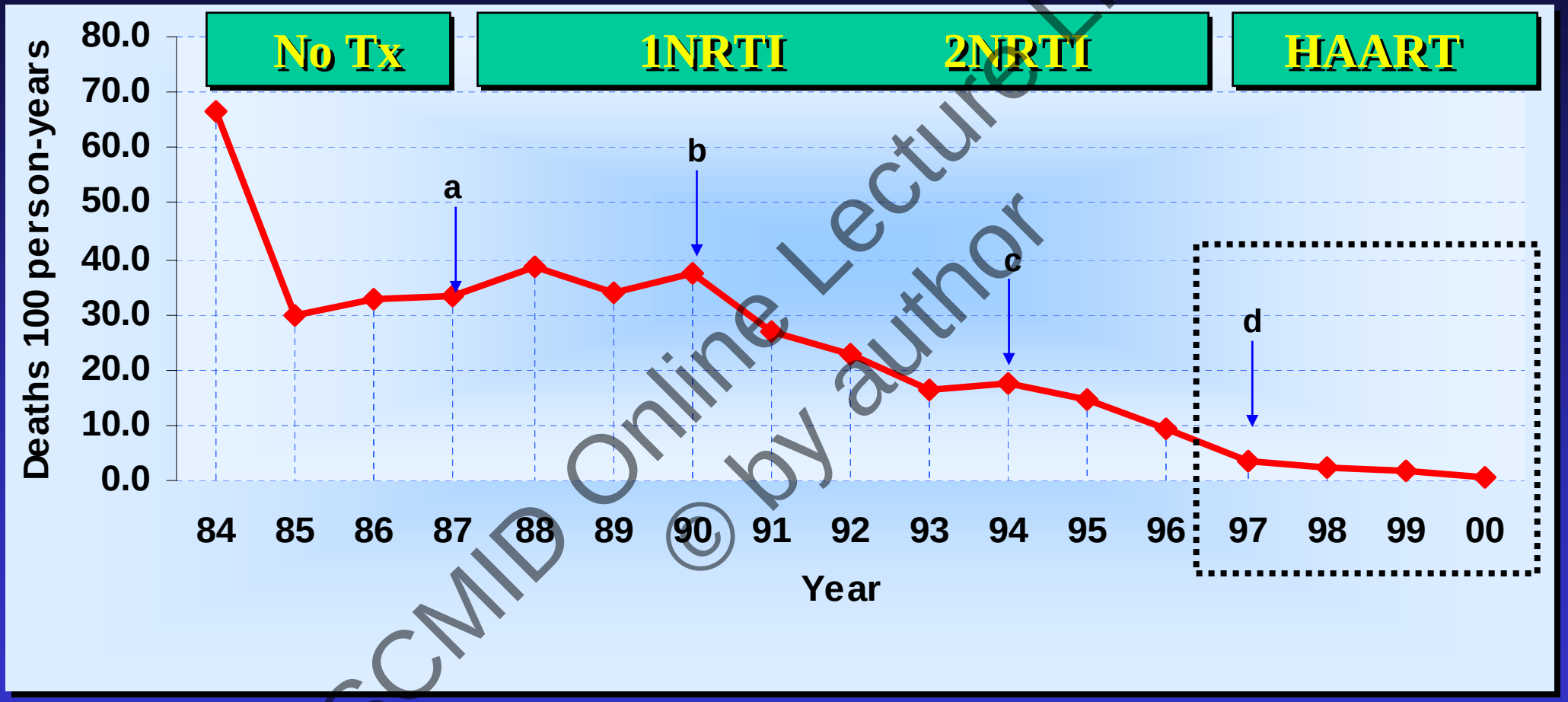
* HLA-B5701 negative

Late HAART Era Patients Still Have a 10y Shorter Life Expectancy than HIV- Controls



Adapted from Lohse N, et al. Ann Intern Med 2007;146:87–95

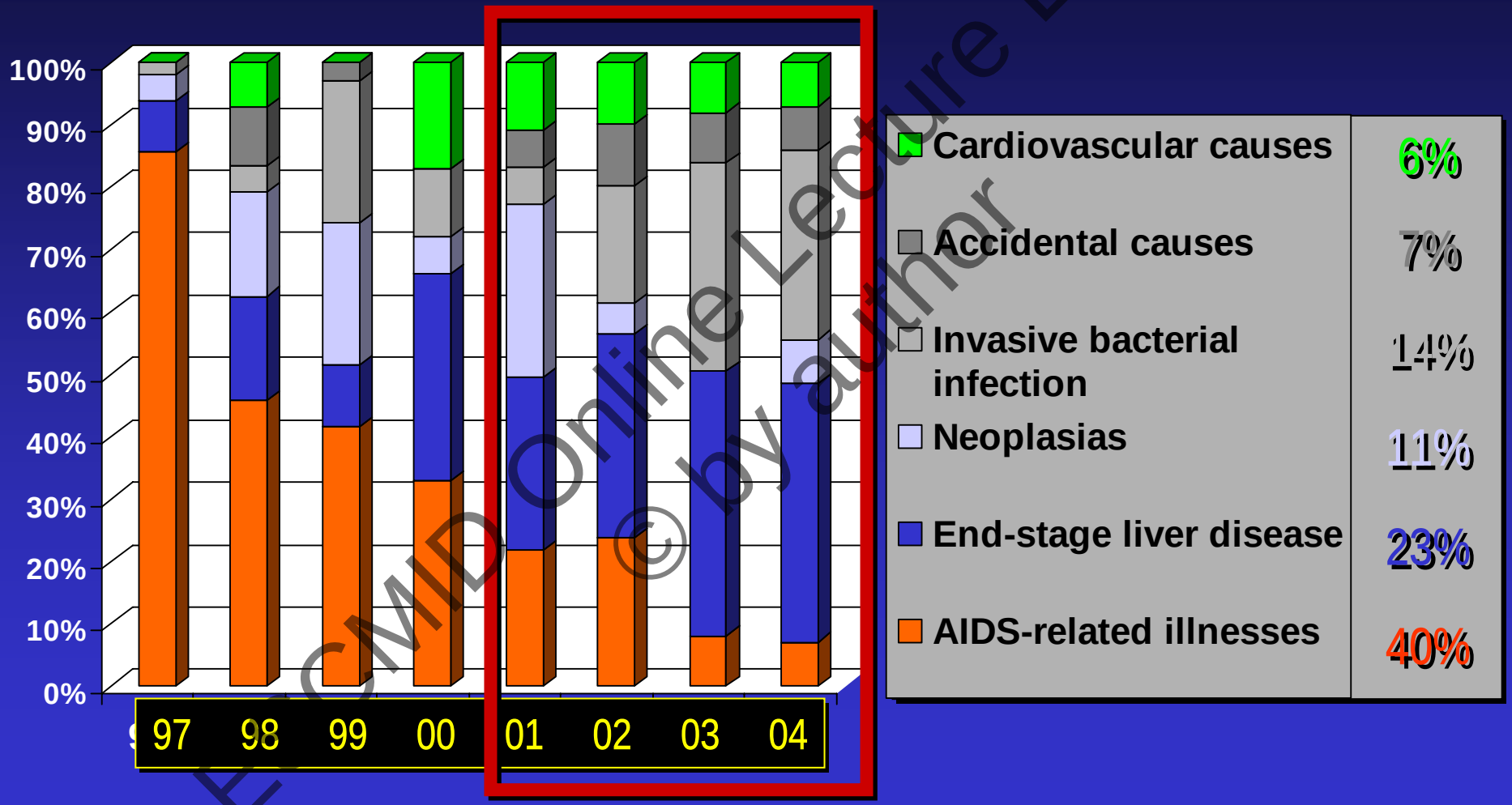
Mortality in HIV-1-Infected Patients (1984-2000). H. Clinic Cohort (No.=4,500). Barcelona, Spain.



a: AZT; b: OI´s Prophylaxis; c: 2 NRTI; d: HAART (≥2NRTI + ≥1PI or NNRTI)

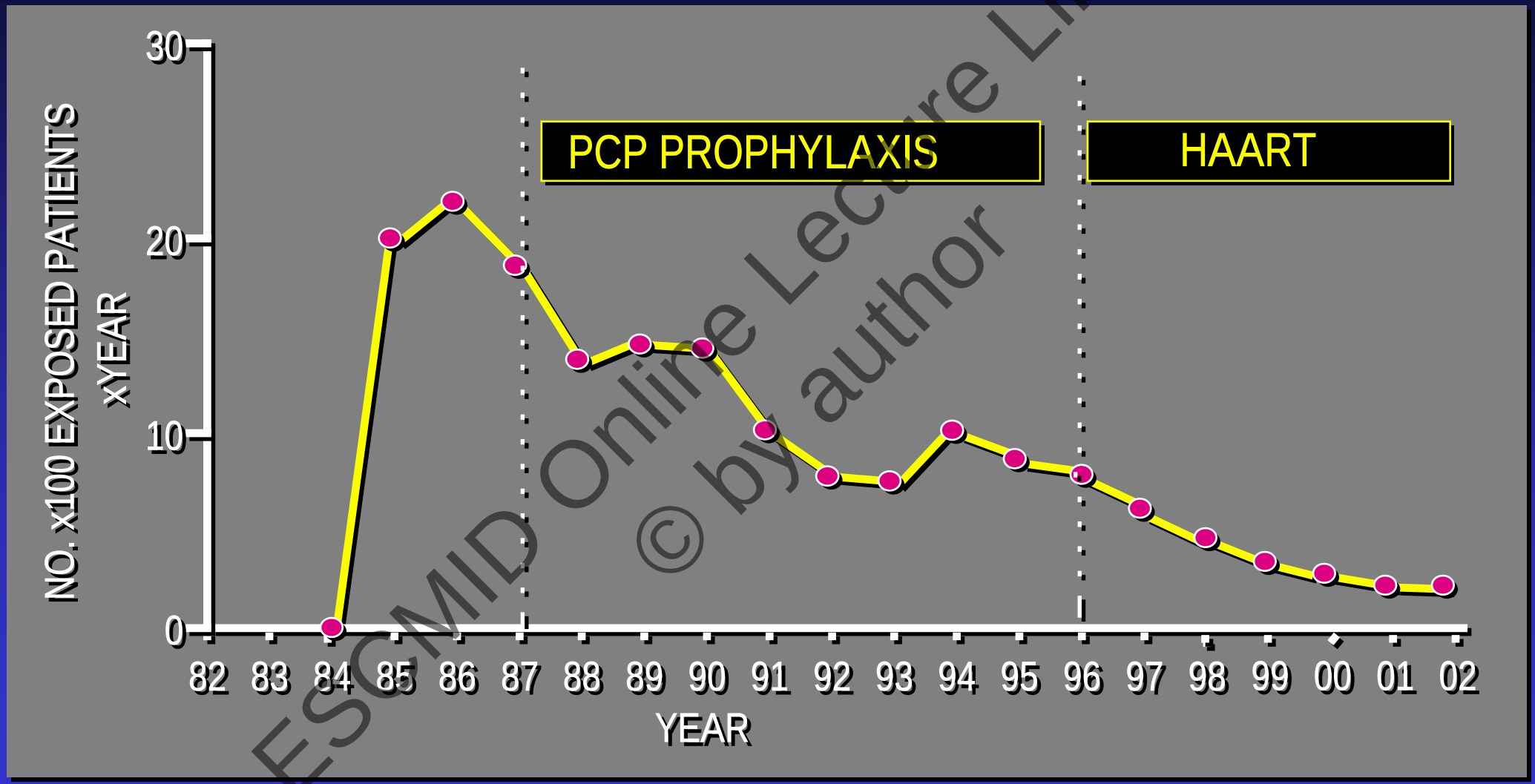
Pérez-Cuevas JB. Doctoral Thesis. University of Barcelona. 2001.

Causes of Death in 235 HIV-Infected Patients Barcelona Hosp. Clinic Cohort (N=4,471; 1997-2004)



Martinez E. et al. HIV Medicine. 2007; 8: 251–258.

Incidence of PCP in HIV-Infected Patients at the Hosp. Clinic (Barcelona, Spain) between 1984 -2002



HAART: Highly Active Antiretroviral Therapy (≥2NRTI plus ≥1PI/NNRTI)

Why will OIs continue to appear in the HAART era ?

1. No prophylaxis / No cART

- Unaware of HIV-1 infection (LATE PRESENTERS)
- No access to care
- Provider omission
- Early occurrence of OI
- Drug intolerance
- Non-compliance

2. On OI prophylaxis (breakthrough OI)

- Drug-drug PK interactions (e.g. Rifampin - TMP/SMX*)
- Immunological failure (CD4 <50/uL**)
- Drug resistance (e.g. DHPS mut.)

*Ribera E et al, AACh. 2000; ** Veenstra J et al, CID, 1997; Saah AJ et al, JAMA, 1995; Moorman A et al, IDSA, 1997; Kaplan J et al, JAMA, 2003; Morris E et al, Emerging Infec Dis, 2004.

Late Presentation of HIV-1 Infection: a Consensus Definition

Antinori A et al. HIV Med. 2011 Jan;12(1):61-4.

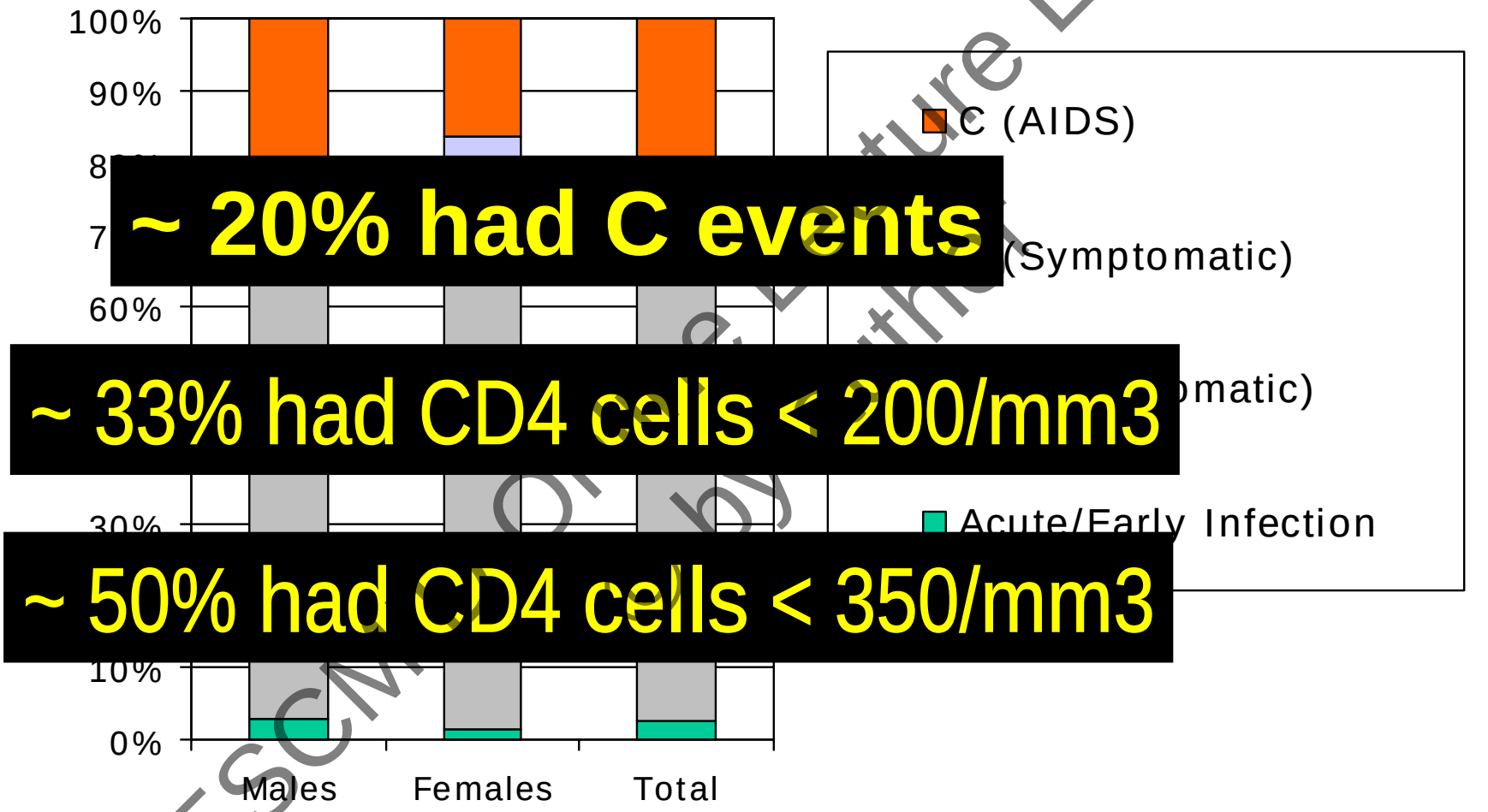
Late presentation

CD4+ T cells <350 cells/µL, or
AIDS-defining event

Presentation with advanced HIV disease

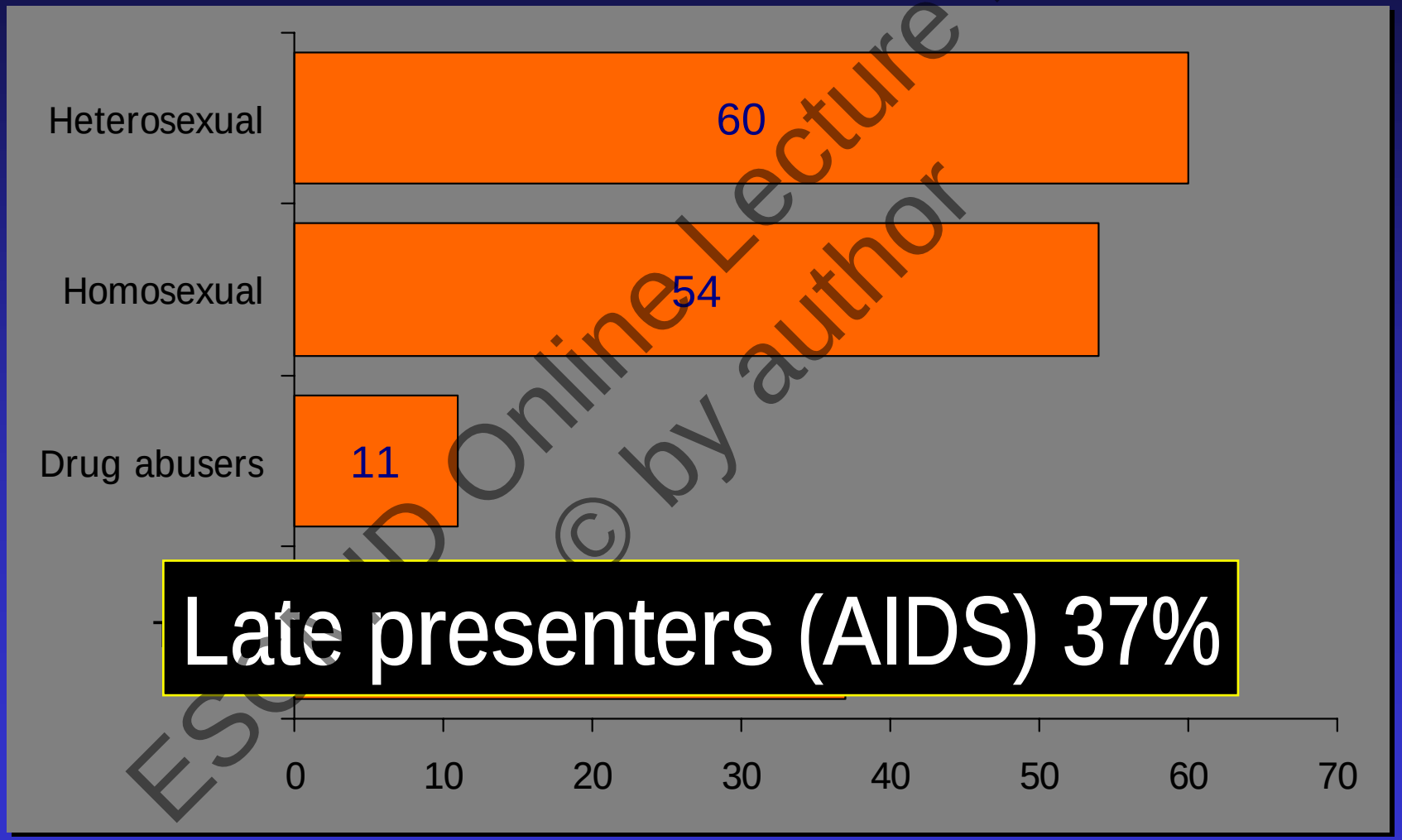
CD4+ T cells <200 cells/µL, or
AIDS-defining event

Late presenters in the HAART era in Spain
Clinical Stage at HIV Diagnosis (N=1,591)



Caro-Murillo AM et al. Enferm Infecc Microbiol Clin. 2007; 25:23-31.

Late presenters in Spain (N=2,010; 2006)



Late presenters (AIDS) 37%

Updated December2006

Factors Associated with Late Presentation in Spain

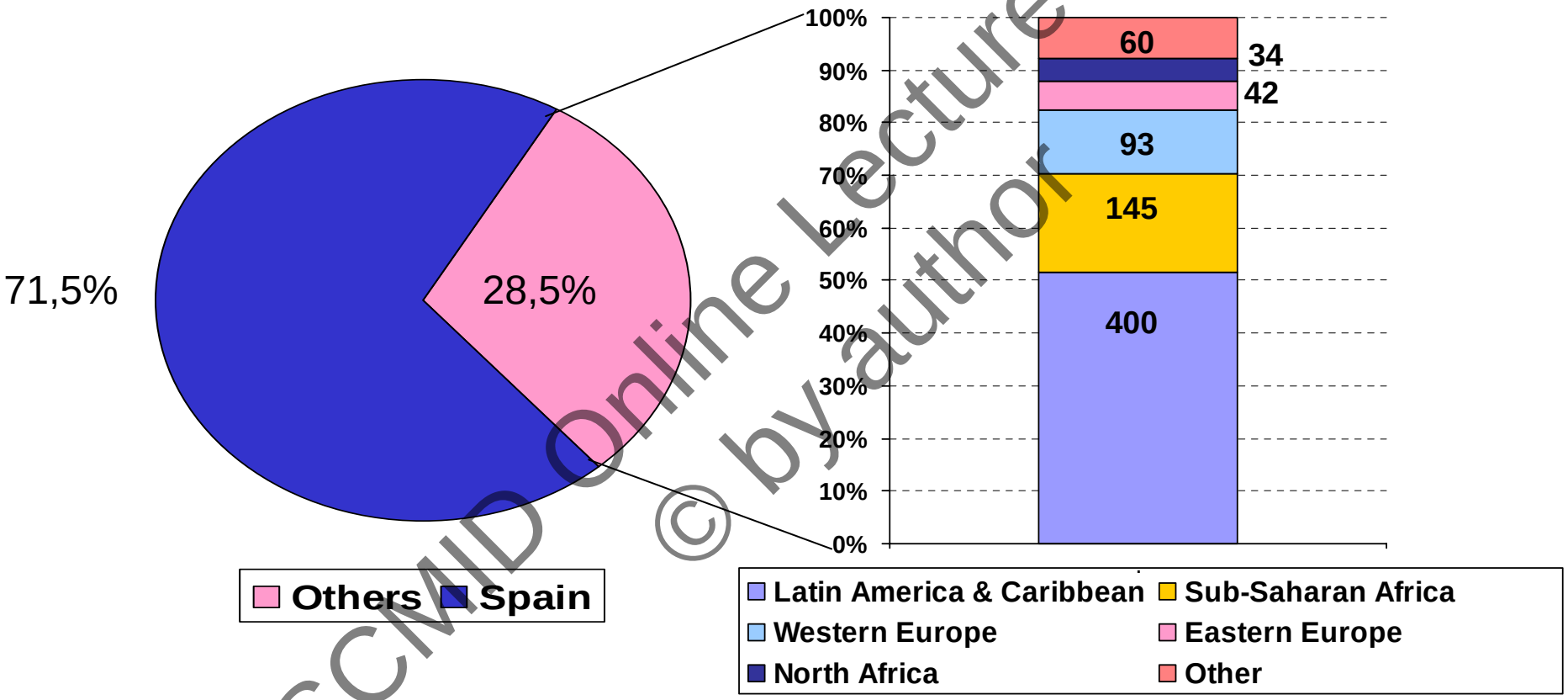
Sobrino P et al, Current HIV Research, 2009, 7: 224-230

- CoRIS: 2,564 antiretroviral naïve individuals (2004-2006).
- Prevalence 37% (C events or CD4 < 200 cells/µL).
- Risk factors: 1) Low educational level; 2) HTX and IDU (compared with MSM); 3) Old Men. Immigration was not a RF in Spain.

Mortality after starting cART			
Late Diagnosis	Death/ person-years	Rate	HR (CI 95,0%)
Yes	22 / 683	3,22	5,22 (1,88-14,5)
No	5 / 1192	0,42	1
Total	27 / 1875	1,44	

Country of Origin = 28.5% Immigrants

Endemic OI: e.g. Histoplasmosis



Caro-Murillo AM et al. Enferm Infecc Microbiol Clin. 2007; 25:23-31.

What is the Best Timing for Starting cART in AIDS Patients with Opportunistic Infections?

Acute therapy	Maintenance therapy

Immediate cART

Deferred cART

- High pill burden
- Overlapping side effects
- PK interactions
- Risk of IRIS

?

- High risk of HIV disease progression and death in patients with advanced disease (CD4<50 cells/mm^3)