EACS European AIDS Clinical Society MEETING

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

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

HIV and Tuberculosis in Western Europe

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HIV and Tuberculosis in Western Europe

- The early HIV-TB epidemic in Western Europe
- The impact of cART on the epidemic
- Can we eliminate the HIV-TB epidemic in Western Europe?

HIV and Tuberculosis in Western Europe

- **The early HIV-TB epidemic in Western Europe**
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ACQUIRED IMMUNE DEFICIENCY SYNDROME: SPECIFIC ASPECTS OF THE DISEASE IN HAITI

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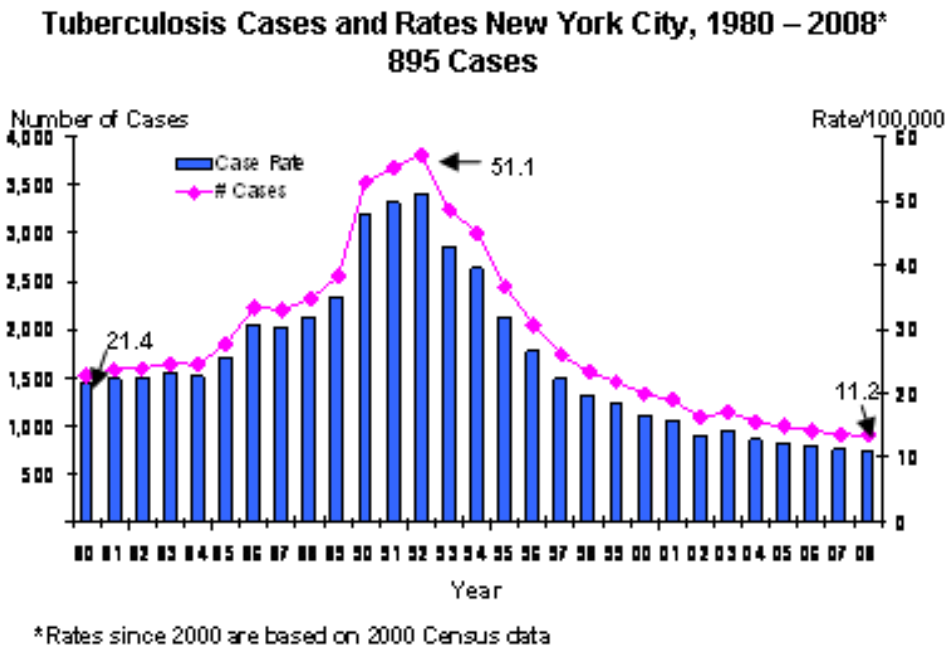
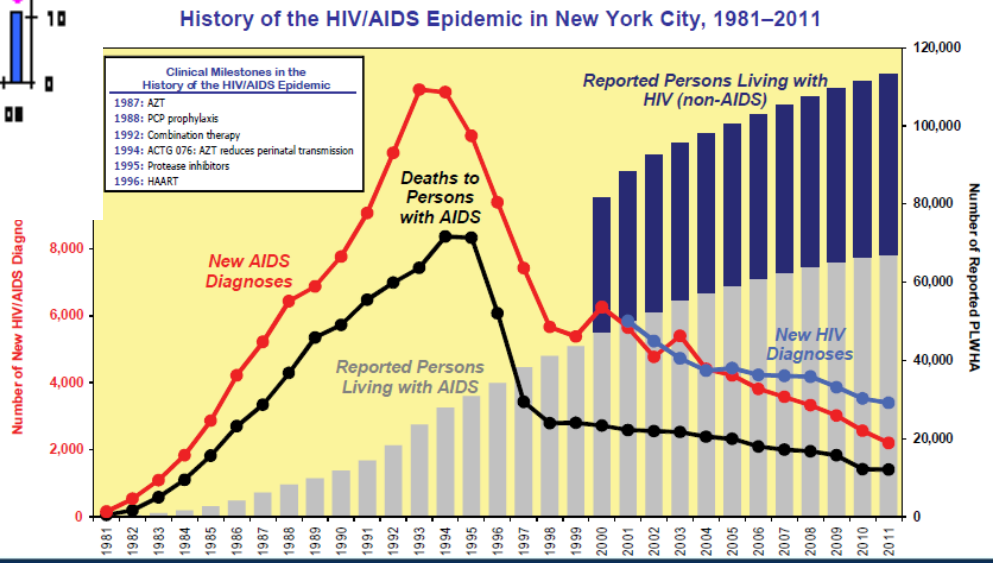
Annals New York Academy of Sciences December 1984

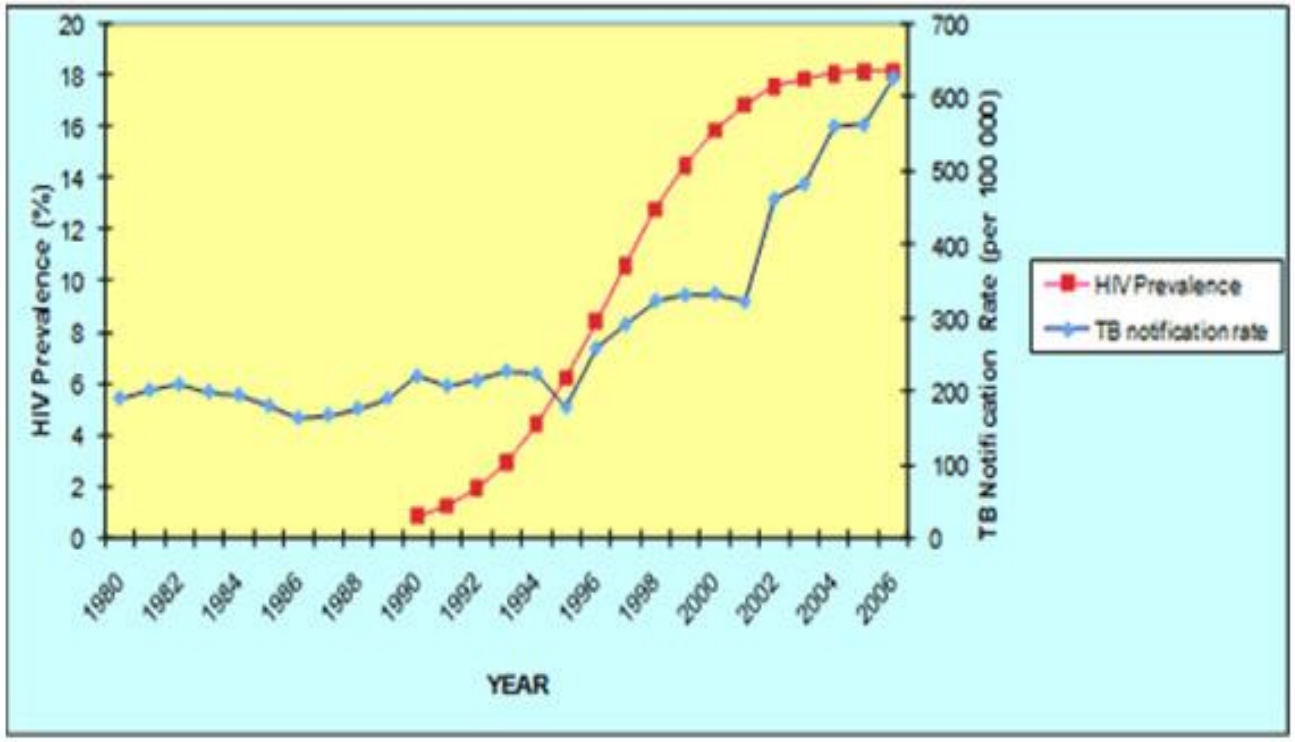
HIV epidemic and TB incidence in New York City





Source: NYC DoH

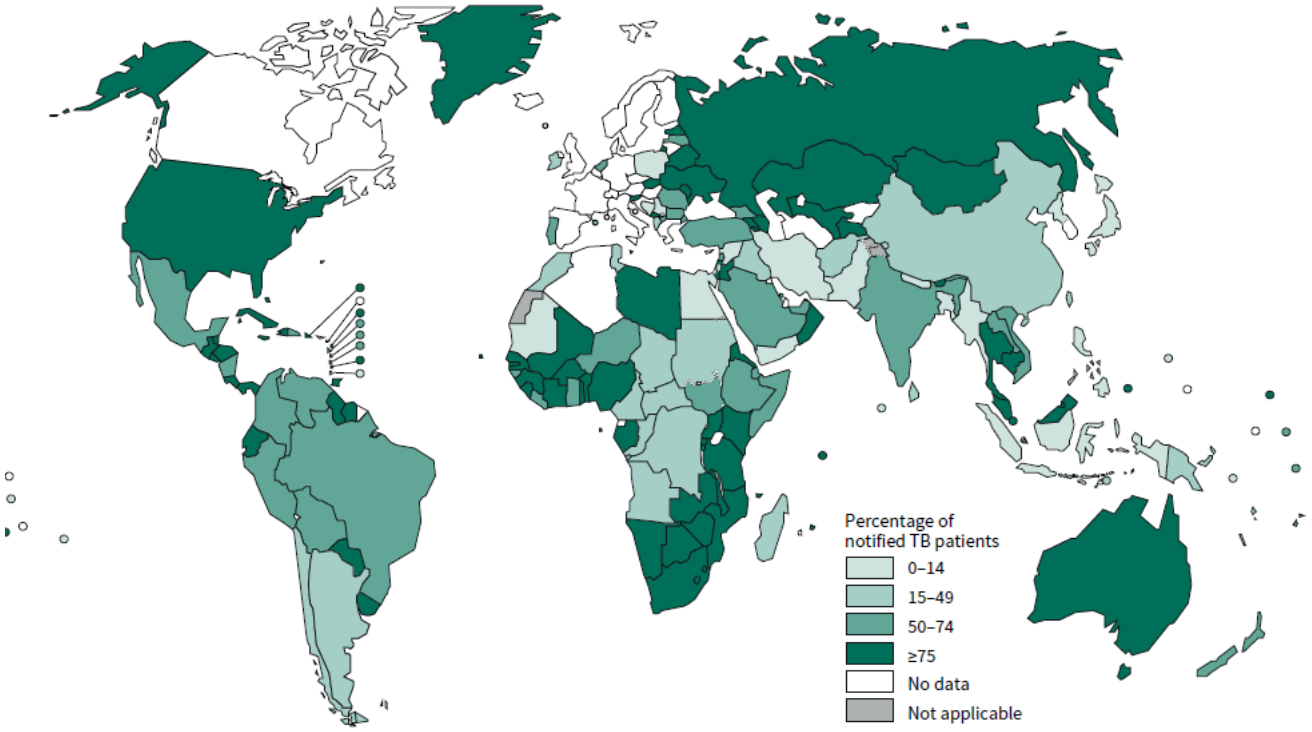
L’epidemia di HIV e di tubercolosi in Sud Africa



Fonte: SACEMA Weekly

Percentage of notified TB patients with known HIV status by country, 2013

" An estimated 1.1 million (13%) of the 9 million people who developed TB in 2013 were HIV-positive …. 360 000 of whom died ….."



[1] Data for the Russian Federation are for new TB patients in the civilian sector only.

WHO Global tuberculosis report 2014.

Journal of Infection (1994) **28**, 261–269

Tuberculosis and AIDS: a retrospective, longitudinal, multicentre study of Italian AIDS patients

Enrico Girardi,* Giorgio Antonucci,* Orlando Armignacco,* Stefania Salmaso,† Giuseppe Ippolito,* and The Italian group for the study of tuberculosis and AIDS (GISTA)‡

located in 11 of the 20 regions of Italy participated in this study. We investigated 1691 patients with AIDS diagnosed in 1988 and 1989 and reported to the National AIDS Registry by participating units before the end of December 1990. By that time *M. tuberculosis* had been cultured from 193 patients (11·4%). Compared with intravenous

conclude that in Italy the proportion of AIDS patients who develop tuberculosis is higher than in other industrialised countries and differences in the incidence of

Extrapulmonary TB as AIDS presenting illness in Europe in the pre-cART era

Table 1 Proportion of AIDS cases with extrapulmonary tuberculosis (EPTB) by country of diagnosis

	Total no. of AIDS cases	No. with EPTB	% with EPTB
Austria	642	34	5.3
Belgium	761	66	8.7
France	15613	859	5.5
Germany	6233	196	3.1
Italy	11732	428	3.6
Netherlands (Amsterdam)	945	47	5.0
Portugal	786	194	24.7
Switzerland	1959	62	3.2
United Kingdom	4527	109	2.4
Total	43198	1995	4.6

Table 2 Proportion of AIDS cases with extrapulmonary tuberculosis (EPTB) by HIV transmission category

	Total no. of AIDS cases	No. with EPTB	% with EPTB
Homo/bisexual	19517	533	2.7
IDU*	14788	863	5.8
Haemophiliac	809	19	2.3
Transfusion recipient	1185	48	4.1
Heterosexual subgroup 1†	2251	306	13.6
Heterosexual subgroup 2‡	2304	117	5.1
Other/undetermined	2344	109	4.7
Total	43198	1995	4.6

Schwoeble V. et al Tubercle Lung Dis 1995

TB in AIDS patients in Europe in the pre-cART era
The AIDS in Europe Initiative

Table 2. Characteristics of acquired immune deficiency syndrome (AIDS) patients reported with pulmonary (PTB) and extra-pulmonary (EPTB) tuberculosis; AIDS in Europe study, 1979–1989.

	AIDS patients	PTB		EPTB		Both	
		n	% [95% CI][1]	*n*	% [95% CI]	*n*	% [95% CI]
Region							
Northern Europe	2508	83	3.3 [2.7–4.1][2]	73	2.9 [2.3–3.7][3]	140	5.6 [4.7–6.6][3]
Central Europe	1948	93	4.8 [3.9–5.8]	160	8.2 [7.1–9.5]	229	11.8 [10.4–13.3]
Southern Europe	2087	104	5.0 [4.1–6.0]	462	22.1 [20.4–23.0]	521	25.0 [23.1–26.9]
Transmission category							
Homosexual	3962	153	3.9 [3.3–4.5]	218	5.5 [4.8–6.3]	340	8.9 [7.7–9.5]
IDU	1772	79	4.5 [3.6–5.6]	390	22.0 [20.1–24.0]	429	24.2 [22.3–26.3]
Others	676	39	5.8 [4.2–7.9]	72	10.7 [8.5–13.3]	99	14.6 [12.1–17.6]
Unknown	134	9	6.7 [3.3–12.7]	15	11.2 [6.6–18.1]	22	16.4 [10.8–24.0]

Northern Europe (Denmark, Ireland, Finland, North Germany, the Netherlands, Sweden, the UK), Central Europe (Belgium, France, South Germany, Hungary, Luxembourg, Switzerland) and Southern Europe (Greece, Israel, Italy, Portugal and Spain).

Sudre P- et al Tuberc Lung Dis 1996

THE LANCET, DECEMBER 23/30, 1989

Hospital Infection

NOSOCOMIAL EPIDEMIC OF ACTIVE TUBERCULOSIS AMONG HIV-INFECTED PATIENTS

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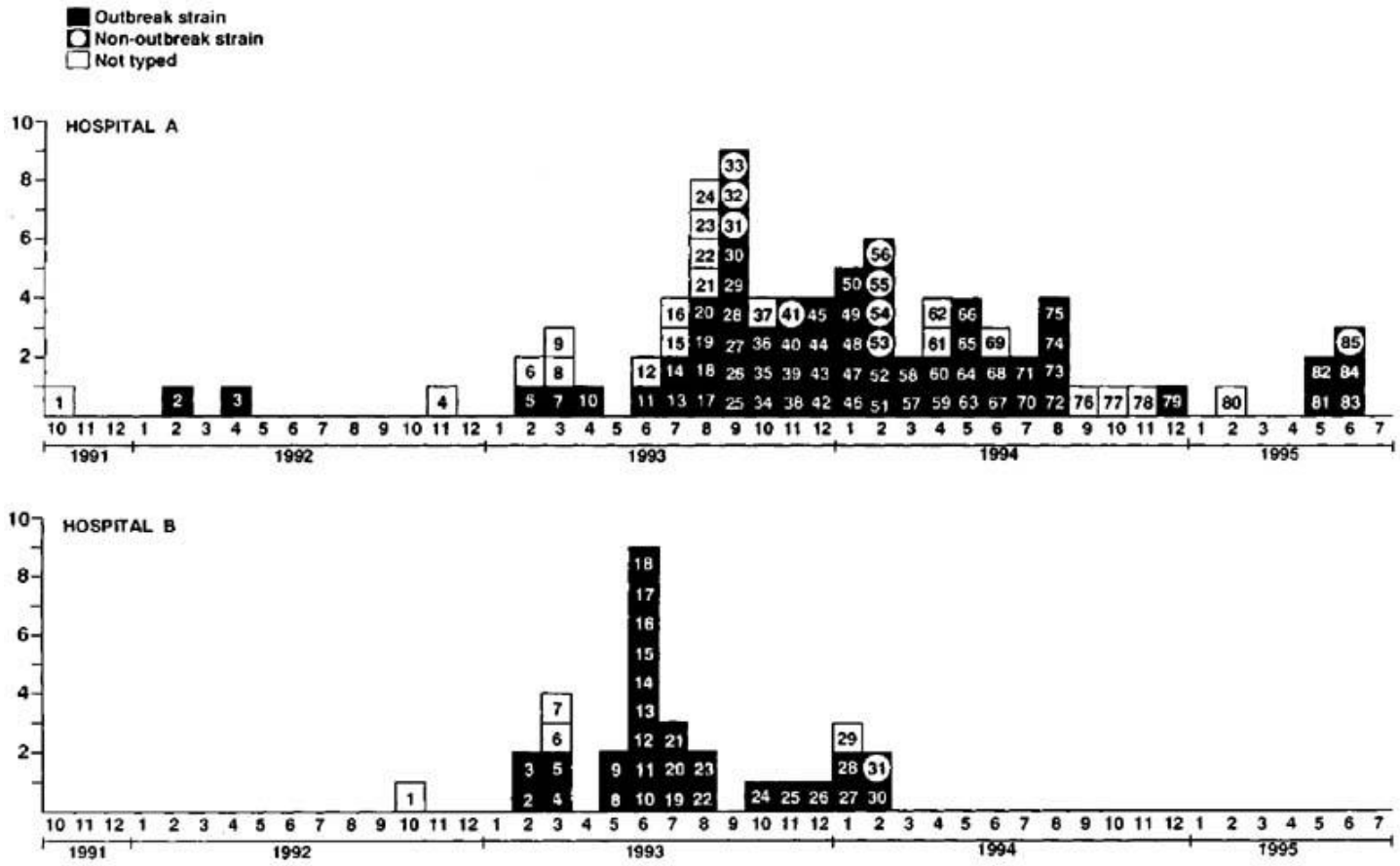
Summary In an investigation of a nosocomial outbreak of tuberculosis, 18 HIV-infected inpatients were found to have been exposed to *Mycobacterium tuberculosis*; active tuberculosis developed in 8, 7 within 60 days of diagnosis of the index case. The patients with lower total lymphocyte and CD4 lymphocyte counts were more likely to get the disease than were those with higher counts. A low score on multiple antigen skin testing was also associated with the development of active tuberculosis. 4 of the 18 patients had a positive tuberculin skin test before exposure to *M tuberculosis*; none of them subsequently got the disease.

MDR-TB emergence in nosocomial outbreaks among PLWHIV
A multi-institutional outbreak in Milan



Moro et al AIDS 1998

MDR-TB emergence in nosocomial outbreaks among PLWHIV
A multi-institutional outbreak inMilan

A multi-institutional outbreak in Milan MDR or XDR ?

"At hospital B, isolates from 30 patients were tested in 1993 for six additional drugs: all were resistant to amikacin, kanamycin, and terizidon; 24 (80.0%) patients were resistant to cycloserine, 21 (70.0%) to ofloxacin, and two (6.7%) to pyrazinamide"

Moro et al AIDS 1998

Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa

Neel R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Lalloo, Kimberly Zeller, Jason Andrews, Gerald Friedland

Summary

Background The epidemics of HIV-1 and tuberculosis in South Africa are closely related. High mortality rates in

Lancet 2006; 368: 1575-80

HIV and Tuberculosis in Western Europe

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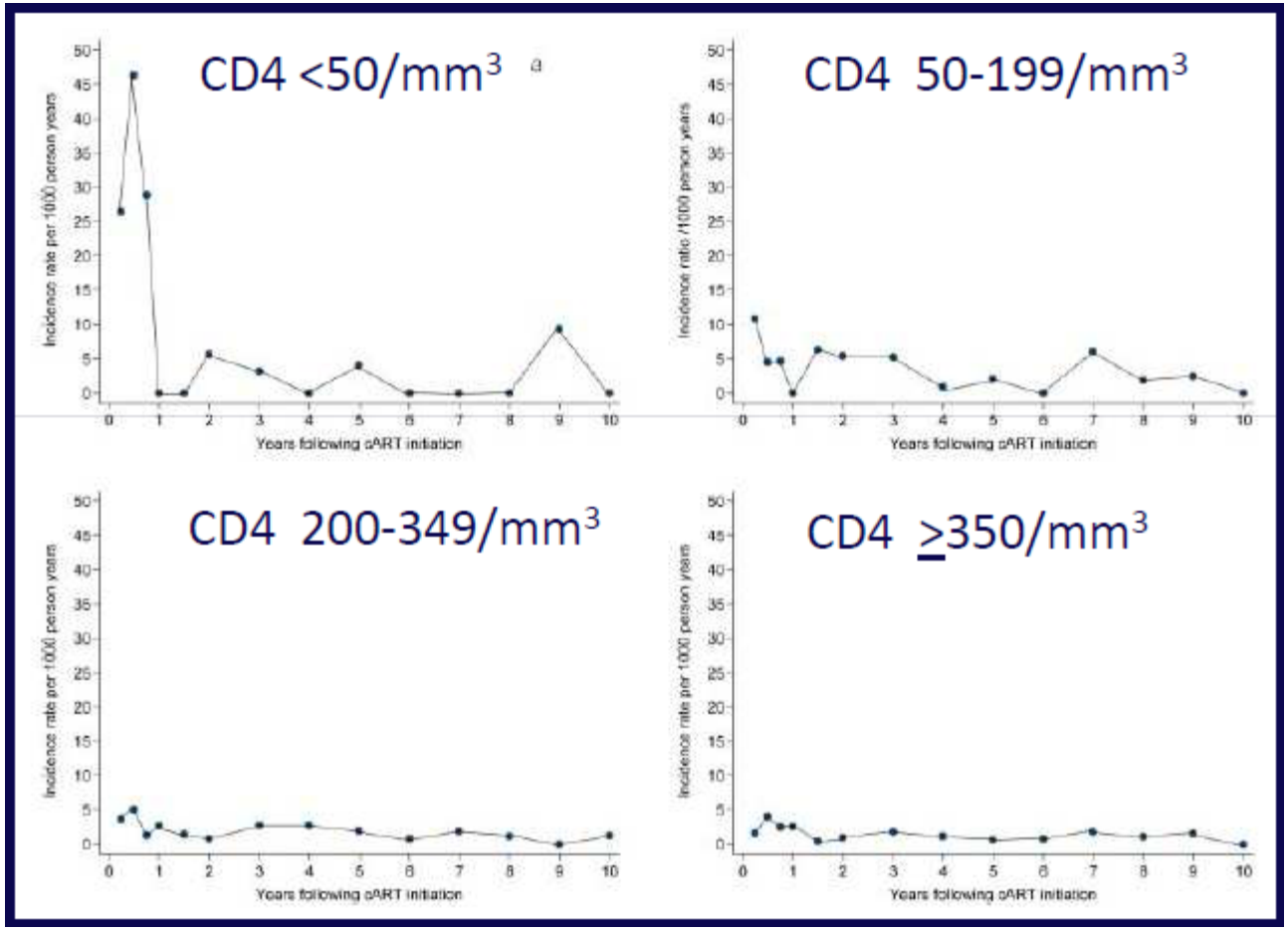
cART has changed the presentation of HIV-associated TB (1995-96 vs 1997-98)

	1995-96 (n=67)	1997-98 (n=51)	p
Median CD4 count (range)	43 (2-450)	105 (6-513)	<0.05
Typical chest X-rays pattern (%)	17 (25)	23 (45)	<0.05
HIV diagnosis at TB	5 (7)	17 (33)	<0.05

Girardi et al JAIDS 2001

TB-HIV incidence shortly after starting cART
CASCADE collaboration



Lodi et al Thorax 2013

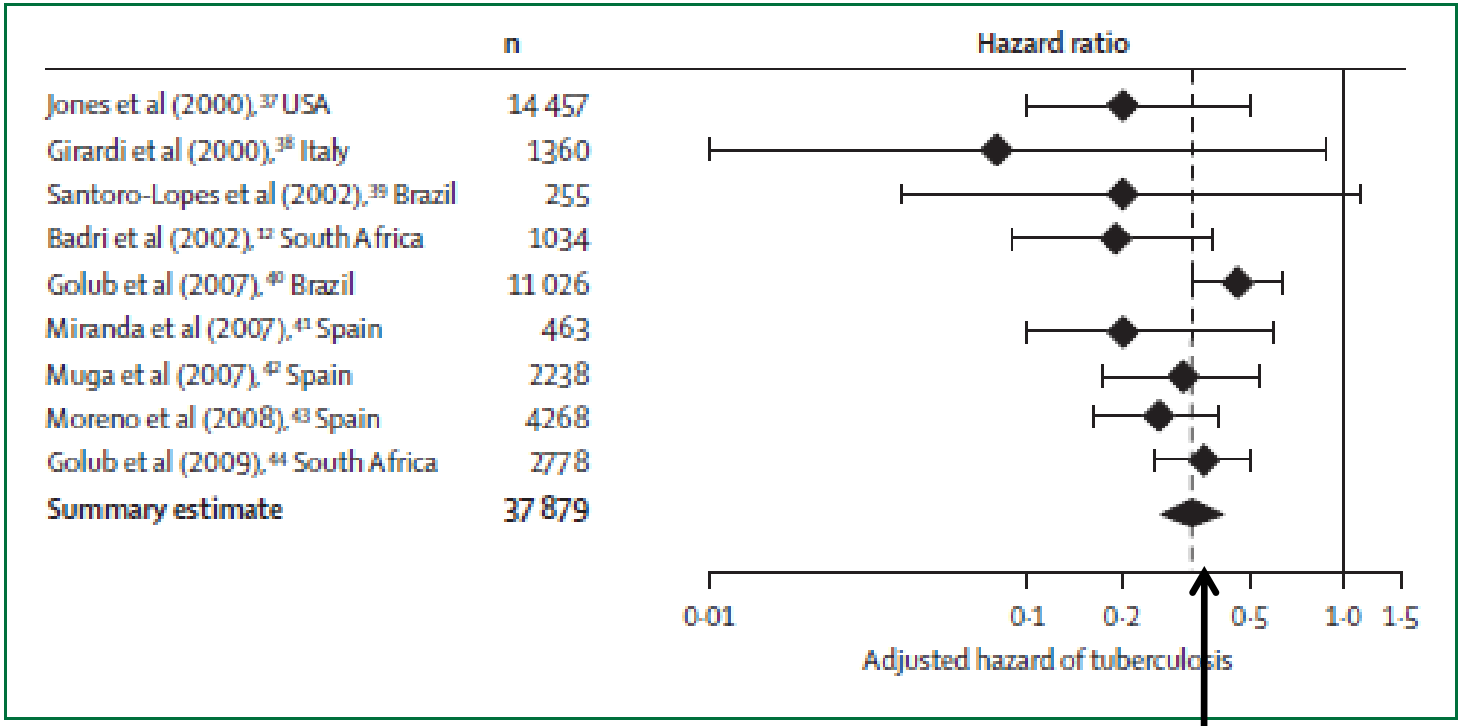
cART dramatically reduces TB risk for PLWHIV

Table 2. Adjusted hazard ratio of tuberculosis by antiretroviral therapy.

Antiretroviral therapy	No. individuals[a]	No. with tuberculosis	Adusted hazard ratio (95% CI)[b]	
			Model 1[c]	Model 2[d]
No therapy	483	9	1.00	1.00
One drug	320	7	1.18 (0.38–3.63)	
Two drugs	637	1	0.14 (0.03–0.65)	0.16 (0.03–0.74)
Three drugs	387	1		0.08 (0.01–0.88)

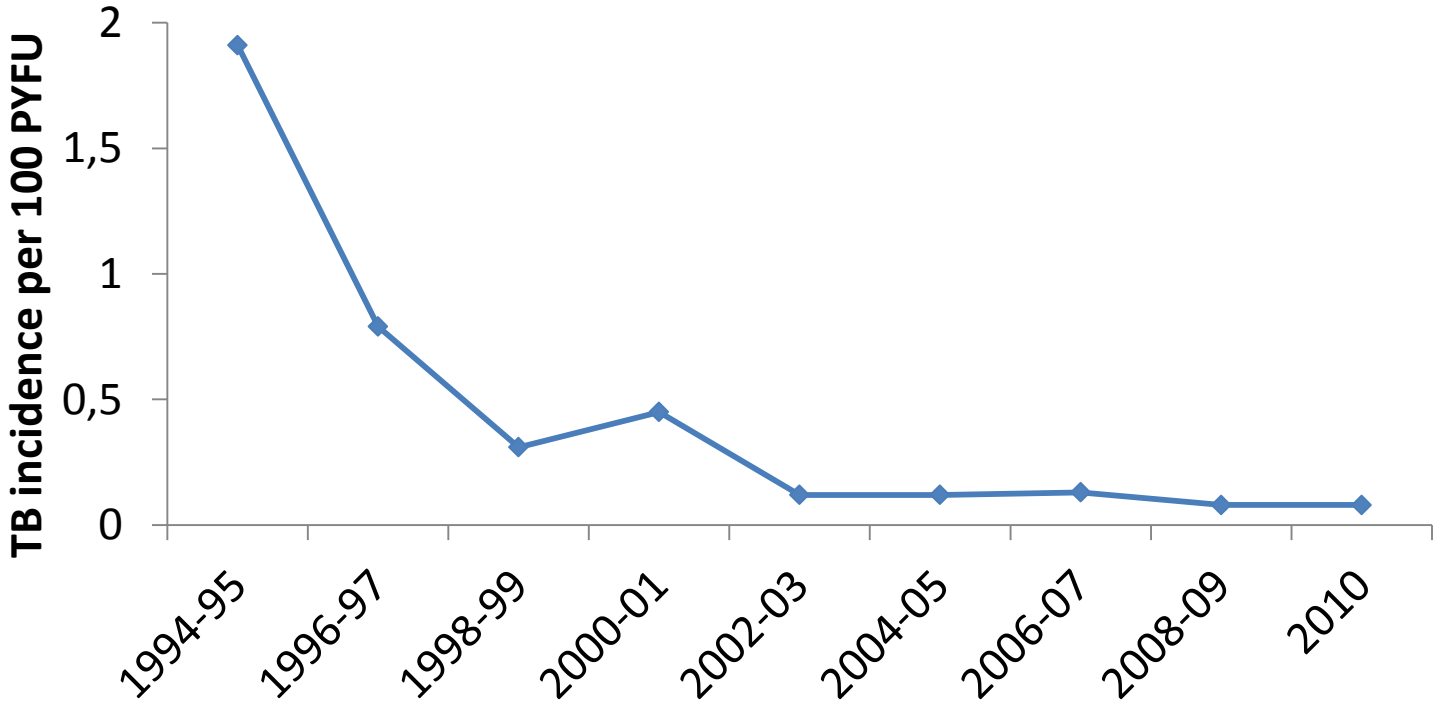
Girardi et al. AIDS 2000

cART dramatically reduces TB risk for PLWHIV



Summary estimate :
reduction of incidence 60%

Decreasing incidence of TB in PLWHIV in Western Europe in the cART era



Source: Kruk et al – EuroSIDA _ AIDS 2011

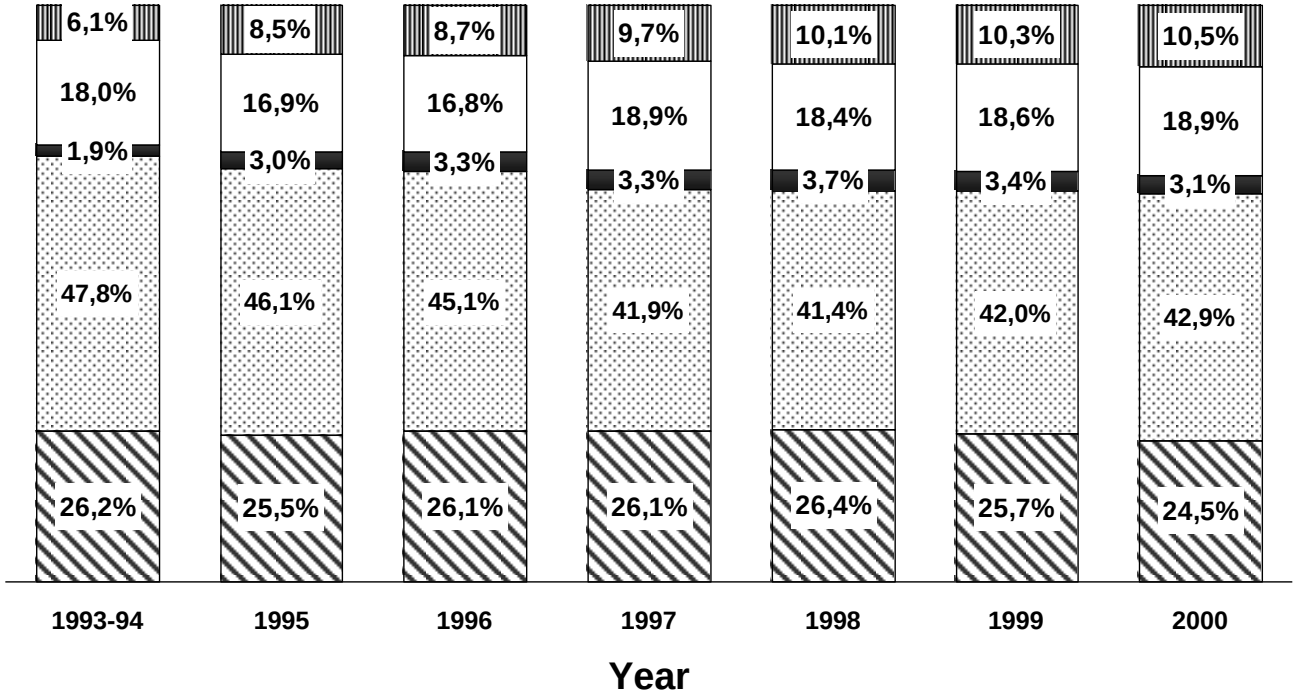
TB in PLWHIV in Western Europe in the cART era

Univariable and multivariable incidence rate ratios of tuberculosis in Europe, 2001–2010.

	Univariable		Multivariable	
	IRR (95% CI)	*P* value	IRR (95% CI)	*P* value
Origin				
Same as clinical center	1.00		1.00	
Other European country	0.65 (0.29–1.48)	0.308	0.72 (0.29–1.80)	0.487
Africa	0.98 (0.50–1.93)	0.952	2.79 (1.30–5.99)	0.009
America/Asia	0.73 (0.27–1.98)	0.541	2.19 (0.79–6.12)	0.134
Unknown	0.72 (0.41–1.28)	0.263	1.49 (0.79–2.81)	0.219
HIV transmission risk group				
MSM	1.00		1.00	
IDU	4.15 (2.80–6.16)	<0.001	1.85 (1.04–3.28)	0.036
Heterosexual	1.48 (0.93–2.36)	0.094	1.08 (0.64–1.84)	0.763

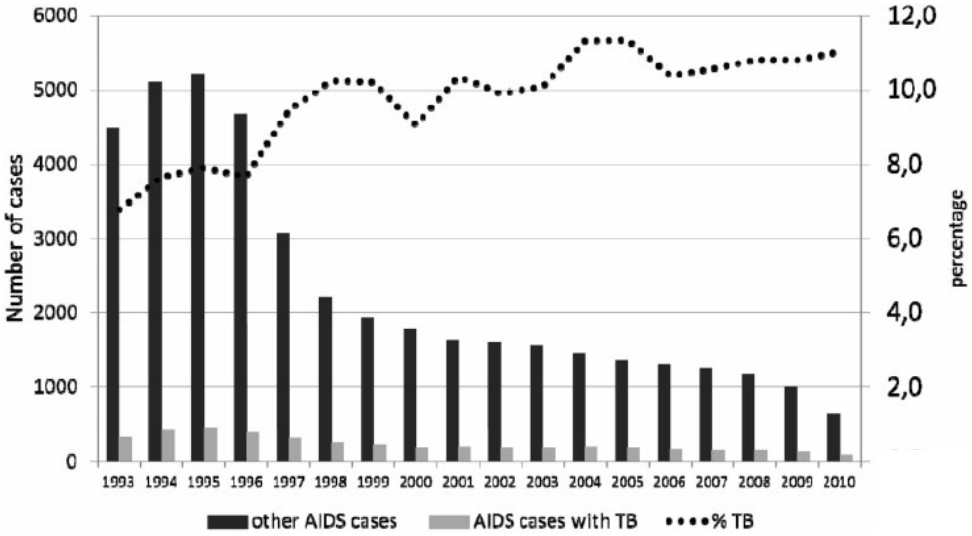
Source: Kruk et al – EuroSIDA _ AIDS 2011

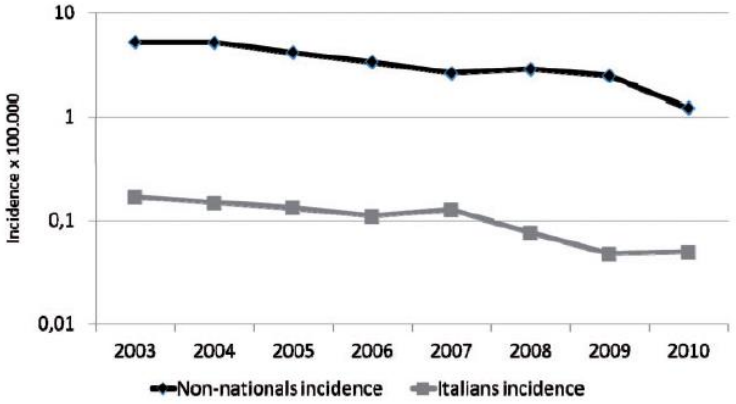
Proportion of AIDS cases with Pulmonary TB increased in Western Europe in cART Era



Serraino et al. AIDS 2003

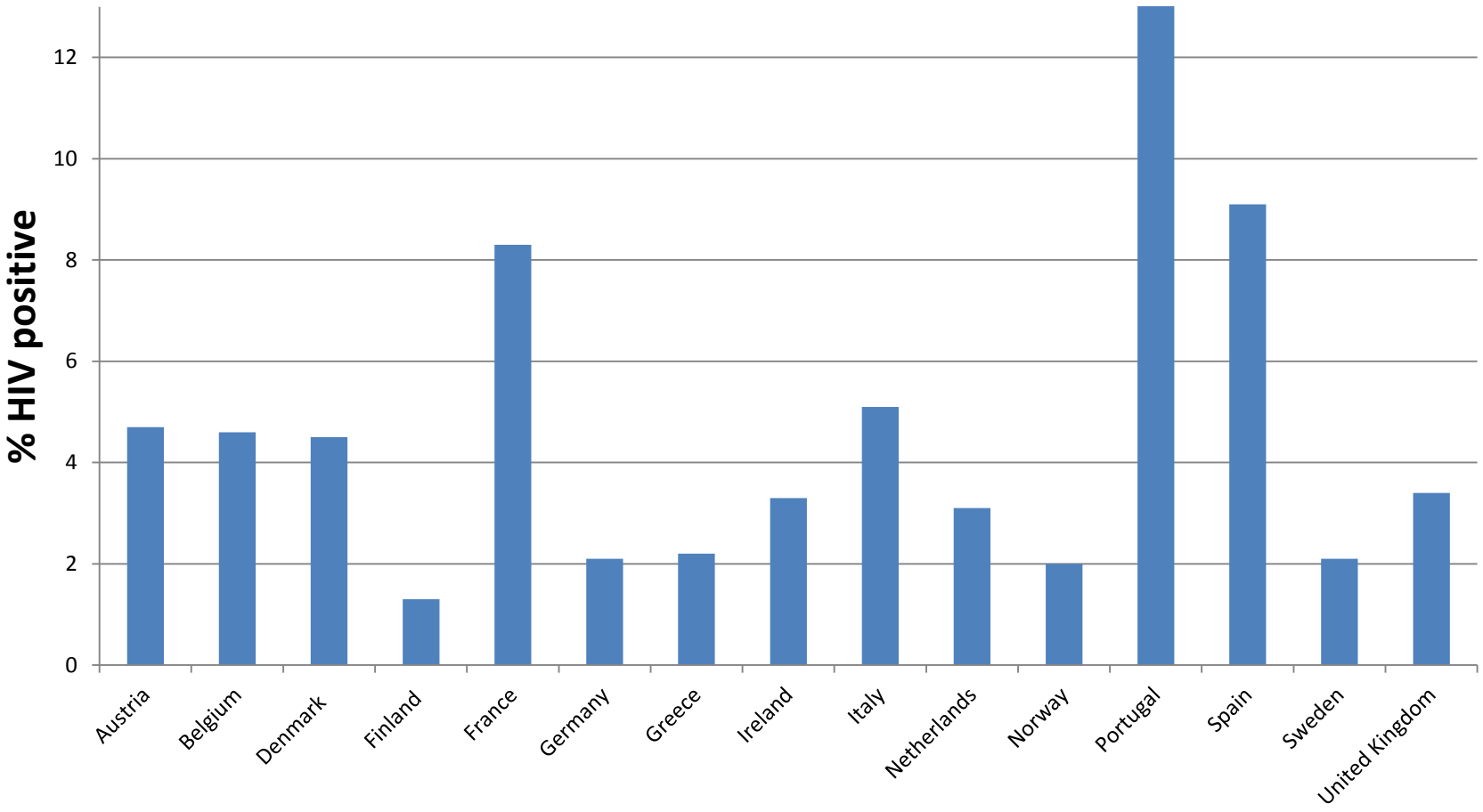
TB as AIDS presenting illness Italy 1993-2010





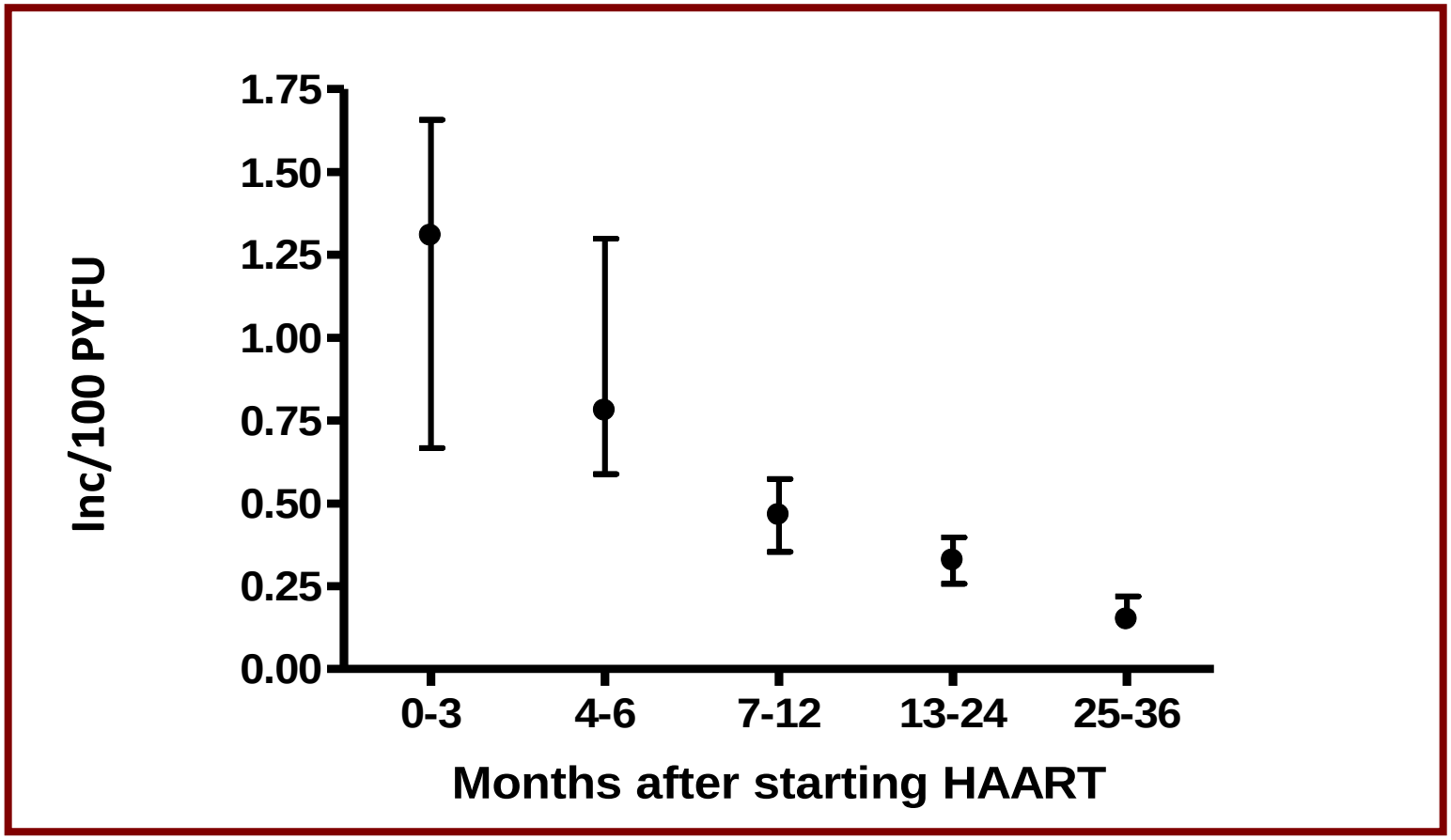
Camoni et al. Eur J Pub Health 2012

Estimated prevalence of HIV-infection among TB patients in Western European Countries , 2011



Source: ECDC Tuberculosis surveillance and monitoring in Europe 2013

Decreasing TB incidence with increasing time on cART



Girardi et al – ART-CC, CID2005

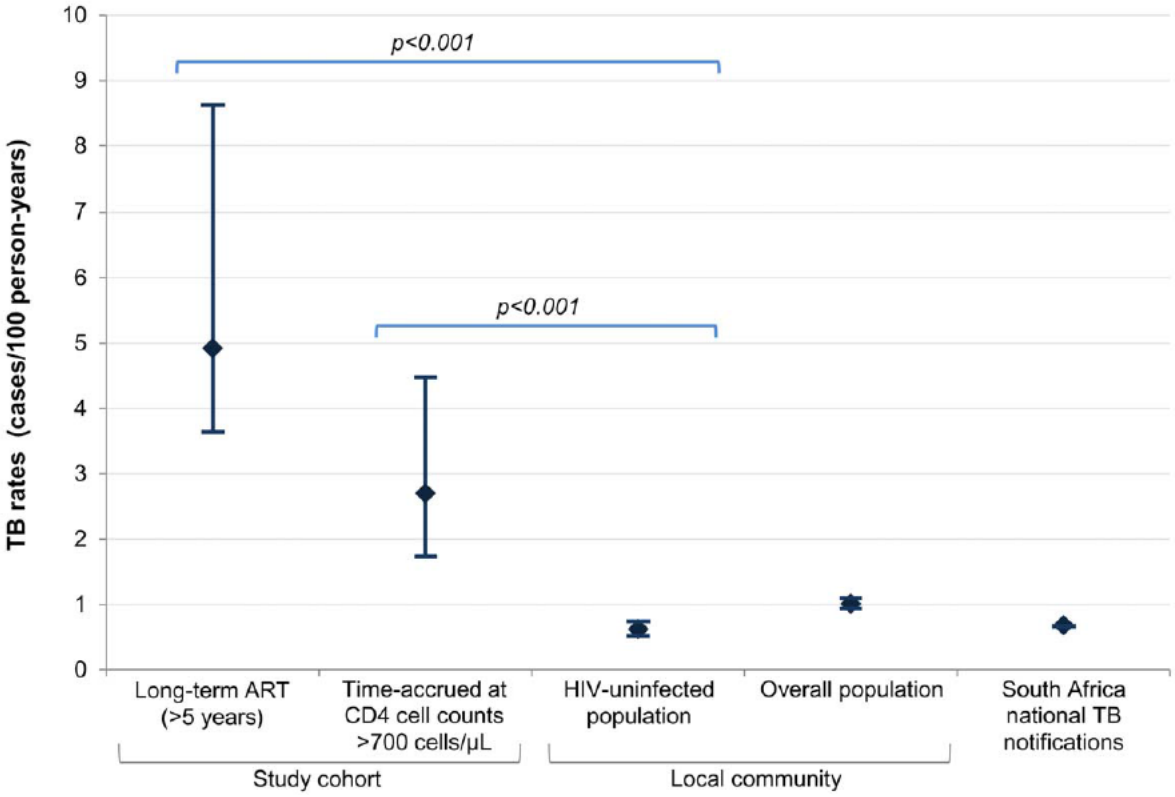
TB incidence in patients on cART by CD4

CD4 count at 6 months	TB cases	PYFU	Incidence per 100 PYFU
<50	6	303	1.98
50-199	25	3668	0.68
200-349	19	6108	0.31
350-499	16	6613	0.24
≥500	12	9551	0.12

Girardi et al – ART-CC, CID2005

In cART treated patients with strong immunological recovery TB risk remain higher than that of background population

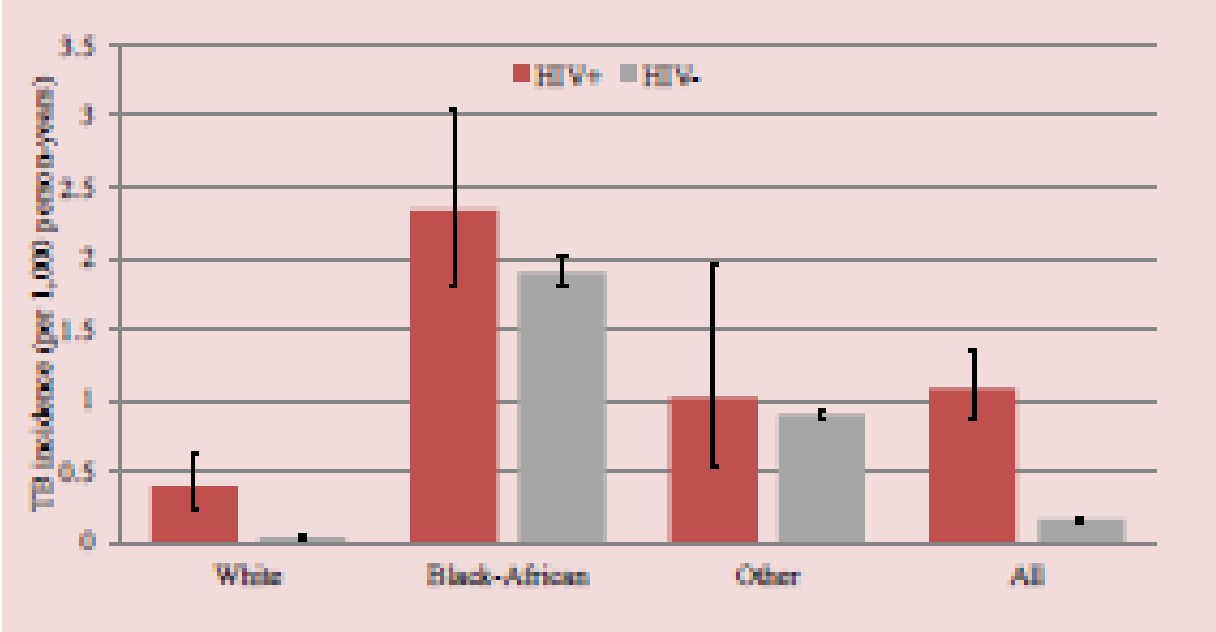
South Africa



Gupta A et al PlosONE 2012

In cART treated patients with strong immunogical recovery TB risk remain higher than that of background population

United Kingdom



Gupta et al CROI 2014

In cART treated patients TB risk remains higher than the background population risk

Study	Setting	N	Median / Mean Follow-up (Months)	Median Baseline CD4 Cell Count (Cells/μL)	TB Incidence, Cases/100 PY (Months of ART)	Estimated National TB Incidence Rate (Per 100 Population)[a]
High-income countries						
Girardi et al, 2005[18]	Germany, Switzerland, France, Netherland, UK, Canada, United States	17,142	25.8	280	1.31 (0–3) 0.78 (4–6) 0.46 (7–12) 0.33 (13–24) 0.15 (25–36)	0.005–0.016
Brinkhof et al, 2007[15]	Europe, North America	22,217	11.0	234	1.7 (0–3) 1.0 (4–6) 0.6 (7–12)	<0.015
Moreno et al, 2008[63]	Spain	4268	46.0	324	0.5	0.035
Resource-limited settings						
Badri et al, 2002[12]	South Africa	1034	16.8	254	2.4	0.406
Santoro-Lopes et al, 2002[60]	Brazil	284	22.0	–	8.4	0.071
Lawn et al. 2005[14]	South Africa	346	40.0	242	3.35 (0–12) 1.56 (13–24) 1.36 (25–36) 0.90 (37–48) 1.01 (49–60)	0.576
Seyler et al, 2005[20]	Côte d'Ivoire	129	26.0	125	4.8	0.368
Lawn et al, 2006[13]	South Africa	1002	0.9	96	23.0 (0–3) 10.7 (4–6) 7.0 (7–12) 3.7 (13–24)	0.898

Lawn SD et al Clin Chest med 2010

A simulation of TB incidence among persons diagnosed with HIV in Italy

Baseline characteristics		CD4	
Born in Italy (%)	72,2	Mean	341
IDU (%)	3,6	Median	300
Aids(%)	14,2	%<200	33,8
Age (years)		% <350	53,2
Mean	39,07		
median	38,00		
TST Positive (%)	**10.4**	**Rate active TB (x100)**	**1,68**
		TST positive	7,94
		TST negative	0,8

Angeletti, Sanè Schepisi, Girardi - 2014

A simulation of TB incidence among persons diagnosed with HIV in Italy

	No cART/No IPT	cART/No IPT
Sample (n)	10000	10000
Life expectancy (years)	5,1	30,9
Rate of active TB (x100 PYFU)	1,68	0,2
TB episodes	**760**	**620**

Angeletti, Sanè Schepisi, Girardi - 2014

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- The early HIV-TB epidemic in Western Europe
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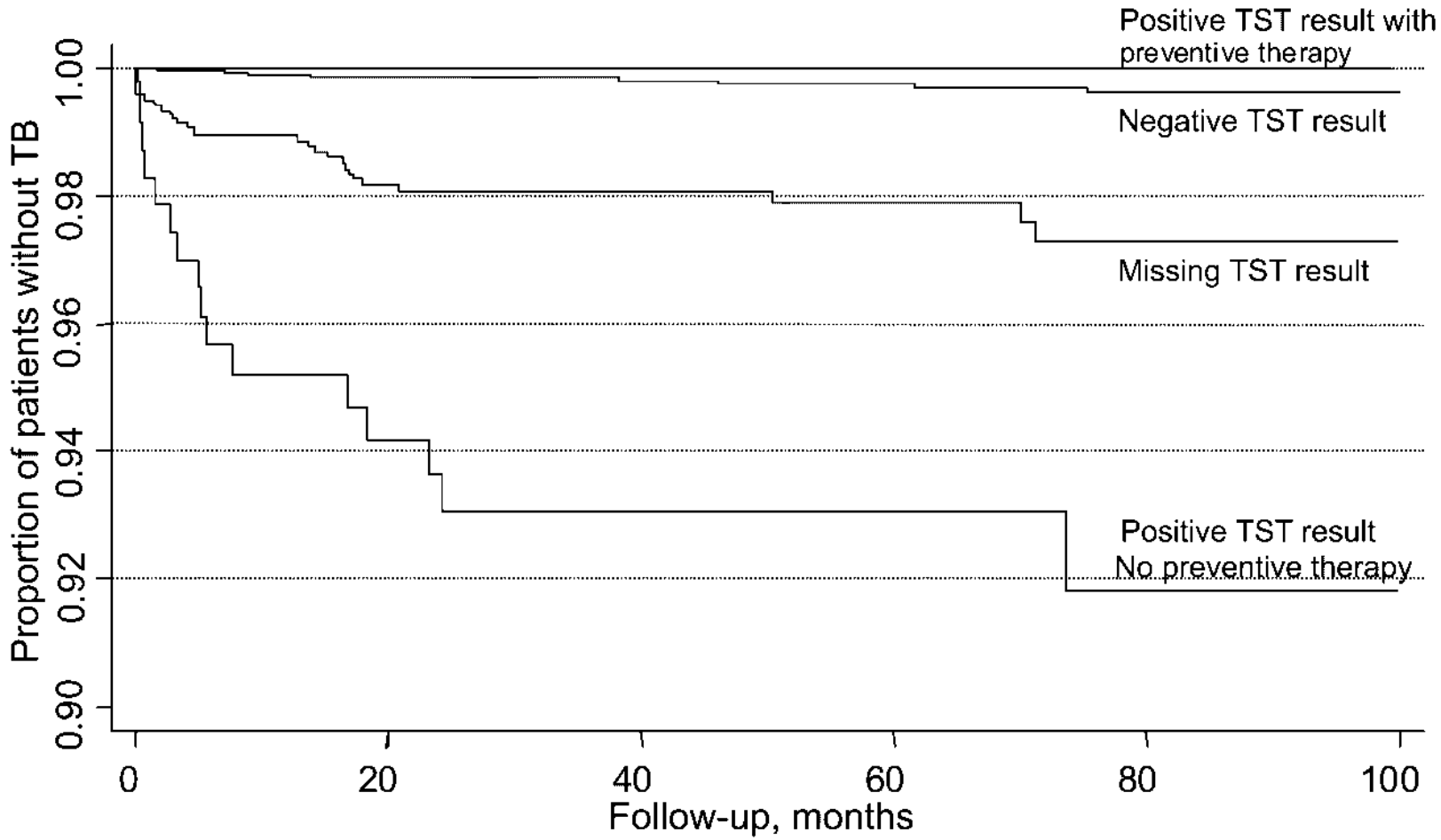
- **Can we eliminate the HIV-TB epidemic in Western Europe ?**
  - **Preventive therapy**

Preventive treatment reduces the risk of TB in the context of wide cART use – Switzerland



Elzi L et al, CID 2007

A simulation of TB incidence among persons diagnosed with HIV in Italy

	No cART/ No IPT	cART/ No IPT	cART+ IPT
Sample (n)	10000	10000	10000
Life expectancy (years)	5,1	30,9	31,2
Rate active TB (x100 PYFU)	1,68	0,2	1,34
TB episodes	**760**	**620**	**480**
TST positive	440	360	220
TST negative	320	260	260

Angeletti, Sanè Schepisi, Girardi - 2014

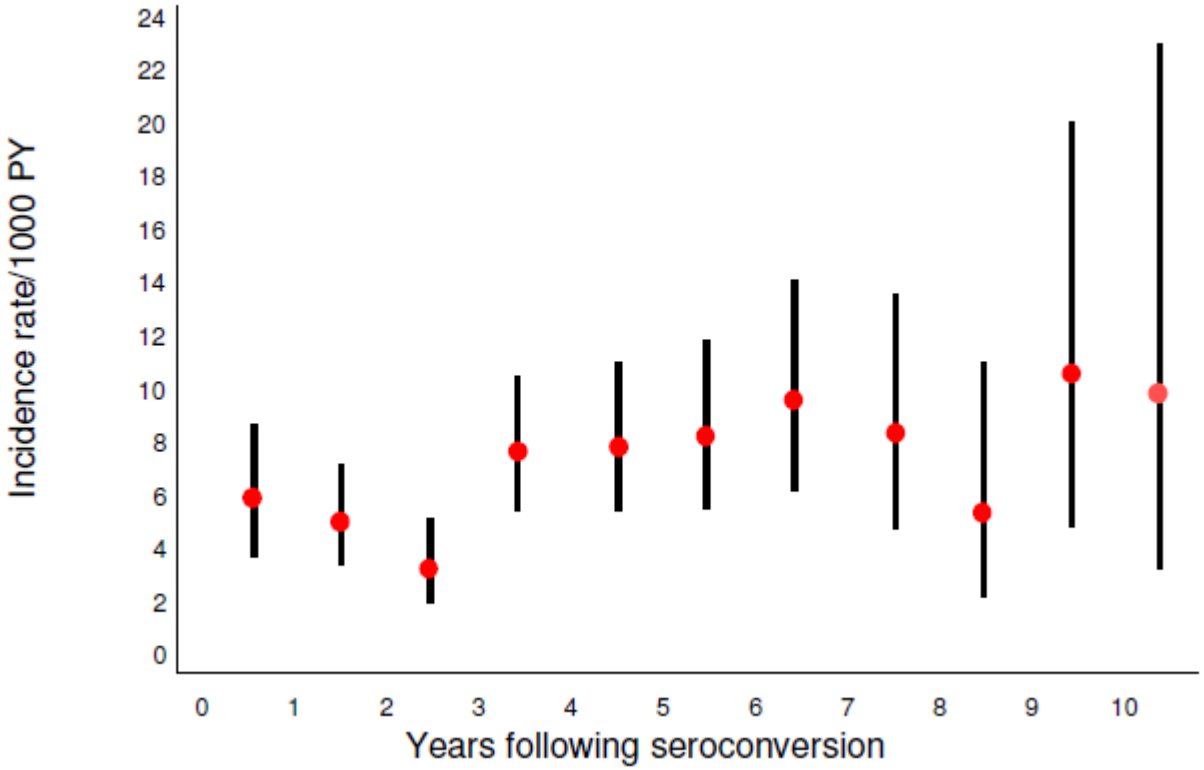
Why IPT has only a moderate effect on incidence of TB-HIV ?

- Many TB cases occur in patients that are TST negative (or IGRA negative) when screened
- Uptake of screening for LTBI and IPT is suboptimal
- Adherence to IPT is suboptimal
- IPT protection is not 100%

HIV and Tuberculosis in Western Europe

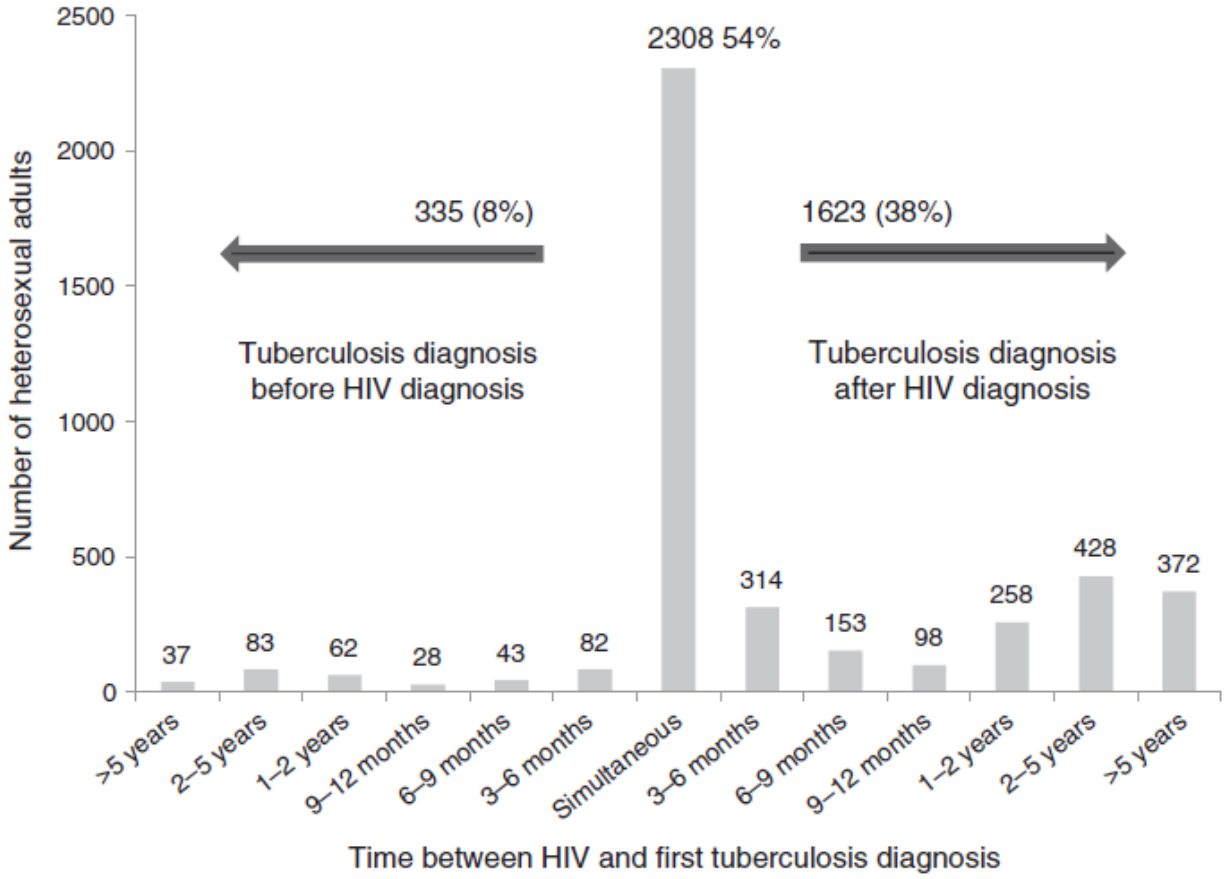
- The early HIV-TB epidemic in Western Europe
- The impact of cART on the epidemic
- **Can we eliminate the HIV-TB epidemic in Western Europe ?**
  - Preventive therapy
  - **Timely HIV diagnosis**

The risk of TB increases soon after HIV infection



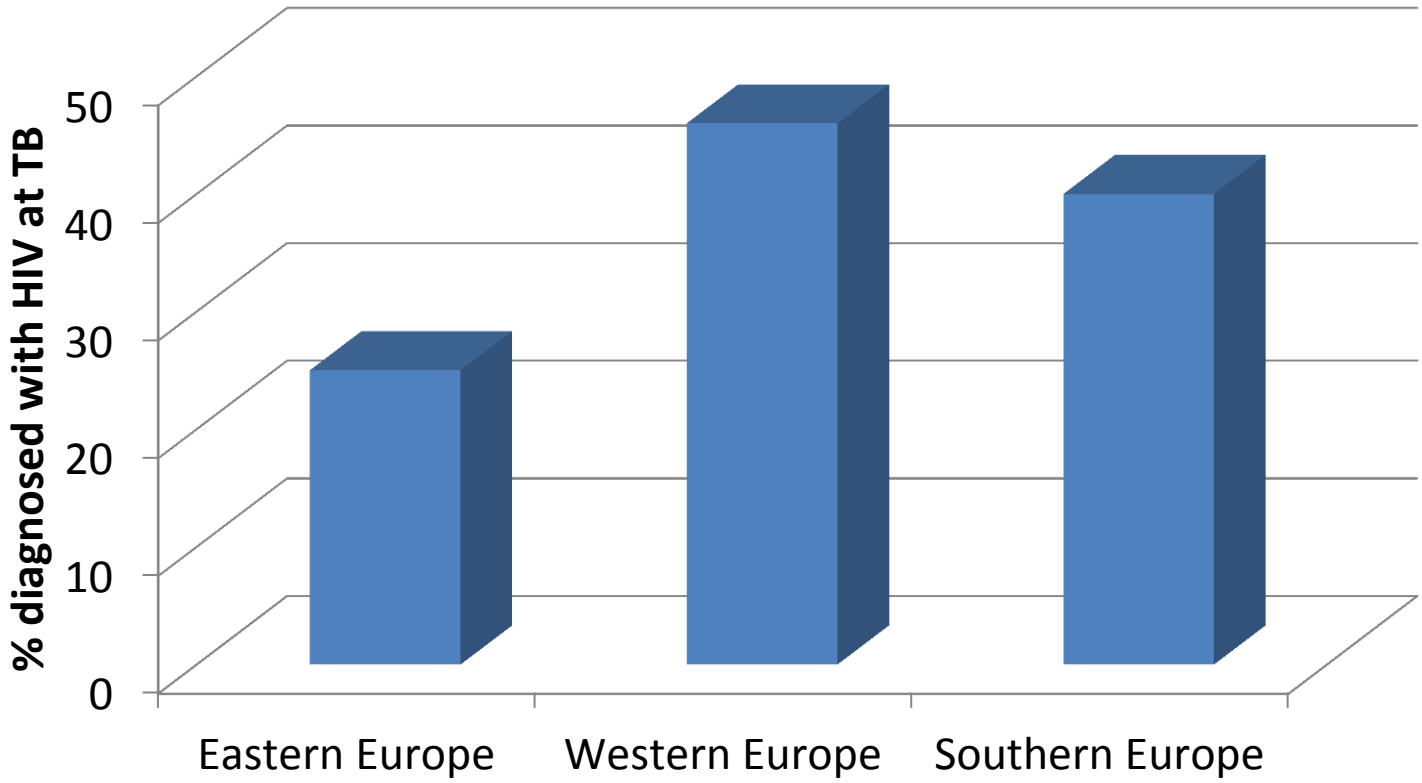
Lodi et al, Thorax 2013

Most of TB cases occur at or before HIV diagnosis England and Wales



Rice B et al. AIDS 2013

HIV diagnosis at the time of TB in Europe



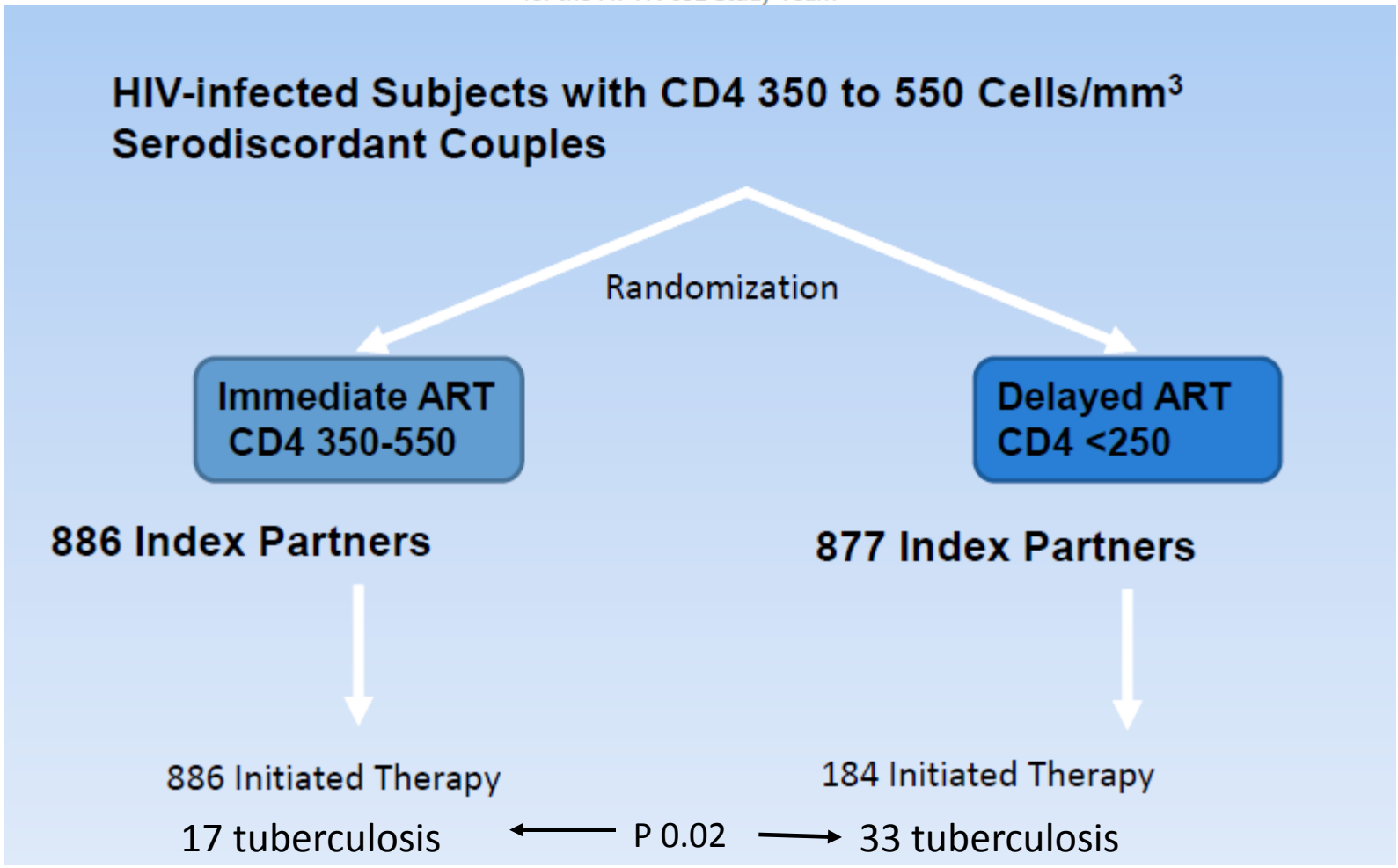
Source:TB:HIV study group in EuroCoord, 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., for the HPTN 052 Study Team



What do we need to end the TB HIV epidemici in Europe?

- Better tools to identify those at risk to develop TB
- More effective LTBI treatment regimens
- New strategies to increase uptake of screening and adherence to preventive treatment
- Earlier identification and linkage to care of PLWHIV

END

HIV