Tuberculosis in the Swiss HIV Cohort Study

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SWISS HIV COHORT STUDY

Outline

- HIV/AIDS
- The Swiss HIV Cohort Study
- Diagnostic tools: TST and IGRA
- Treatment challenges

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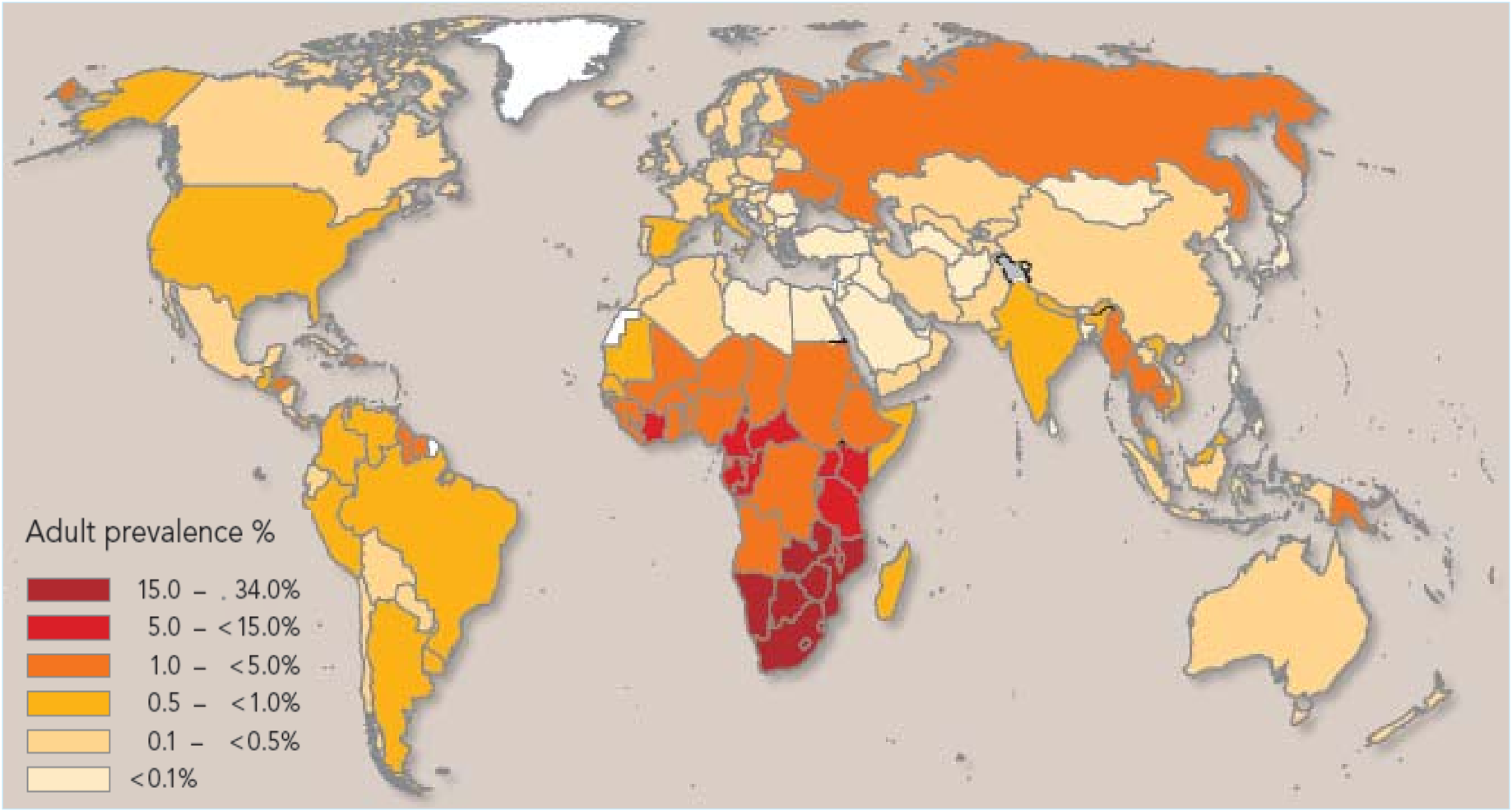
A global view of HIV infection:
33 million people living with HIV/AIDS in 2007



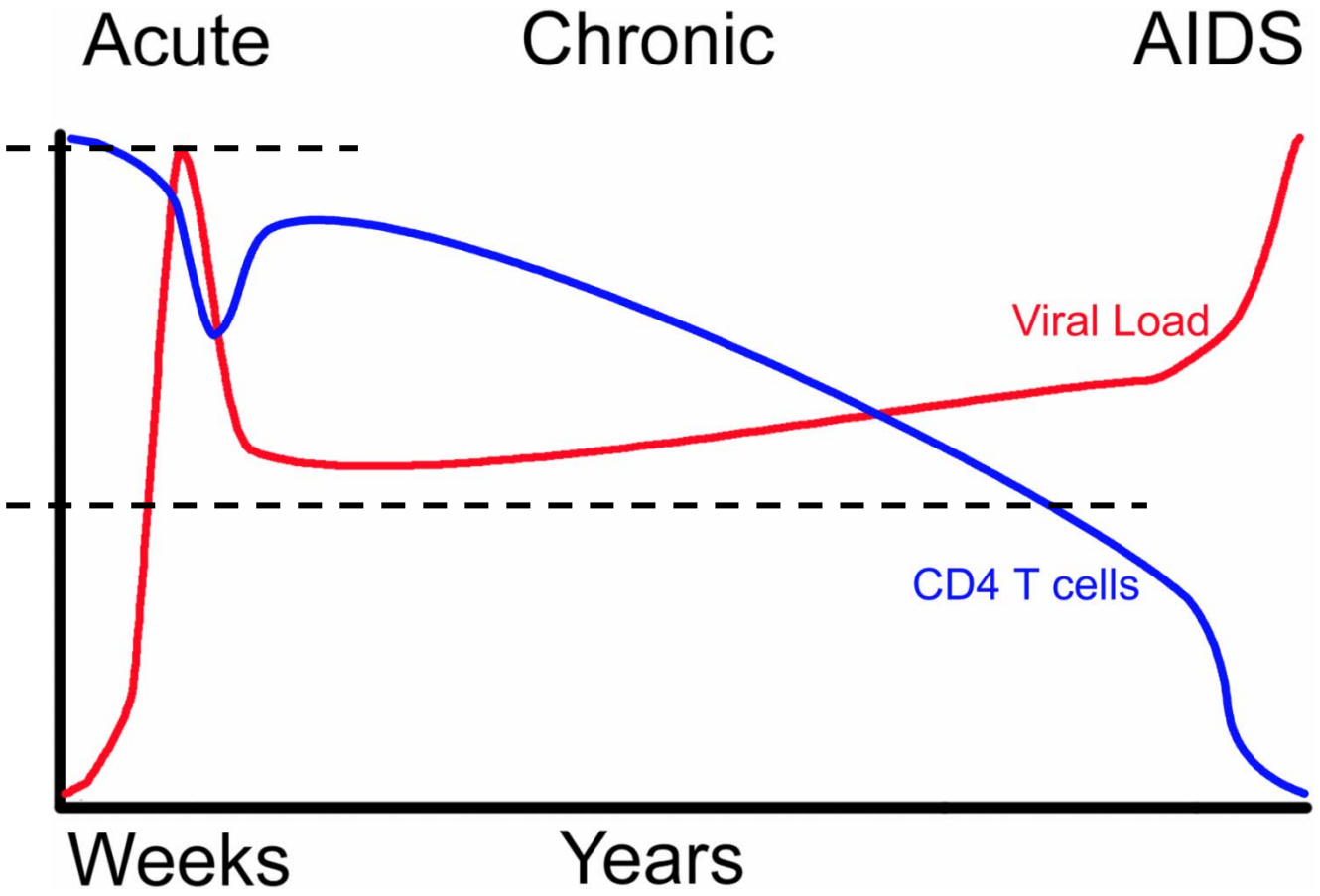
www.unaids.org

Tuberculosis & HIV/AIDS

- TB is the third most common AIDS-defining disease in Switzerland[1]
- Increased risk of primary progressive disease and reactivation of latent TB
- Low sensitivity of tuberculin skin testing
- Treatment challenging (immune reconstitution syndrome, drug-drug interactions)

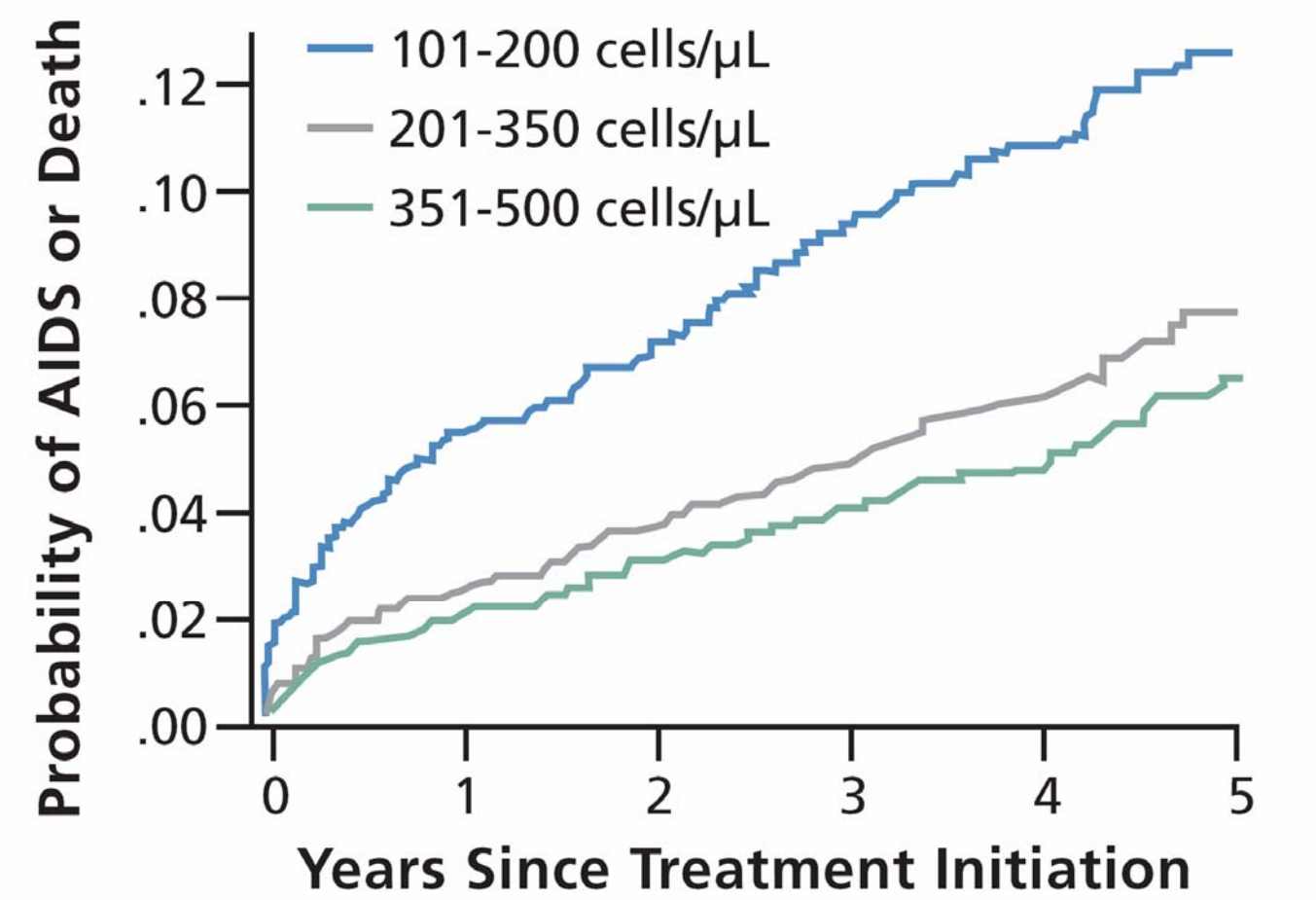
[1] www.bag.admin.ch

Natural history of HIV



The bulk of CD4 T cell depletion that leads to AIDS occurs over the 10 year period of chronic infection

Cumulative probability of AIDS or death by initial CD4+ cell count



ART-CC, May et al, AIDS 2007

cART dramatically improves life expectancy

Study			≈ Decrease Mortality %
1996 Delta	RCT	AZT vs dual ART	30
1996 ACTG 175	RCT	AZT vs dual ART	50
1997 ACTG 320	RCT	Dual vs HAART	70 – 80
1997 SHCS	OS	No HAART vs HAART	
1998 HOPS	OS	No HAART vs HAART	
2003 EUROSIDA	OS	96/97 HAART vs 98-02 HAART	86
2005 SHCS	OS	No HAART vs HAART	
2007 Danish Coh.	OS	HIV versus non HIV	

2008 **20 year old: another 43 years life prolongation with cART ≈ normal life expectancy (?), The ART-CC, 2008, The Lancet**

Hammer et al NEJM 1996; NEJM 1997; Gulick et al, NEJM 1998, Lancet 1996; Lancet 1997, Egger et al, The SHCS, BMJ 1997; Palella et al, NEJM 1998; Jaggy et al, Lancet 2003; Mocroft et al, EuroSIDA, Lancet 2003; Sterne et al, The SHCS, Lancet, 2005, Lohse N et al, Ann Med, 2007

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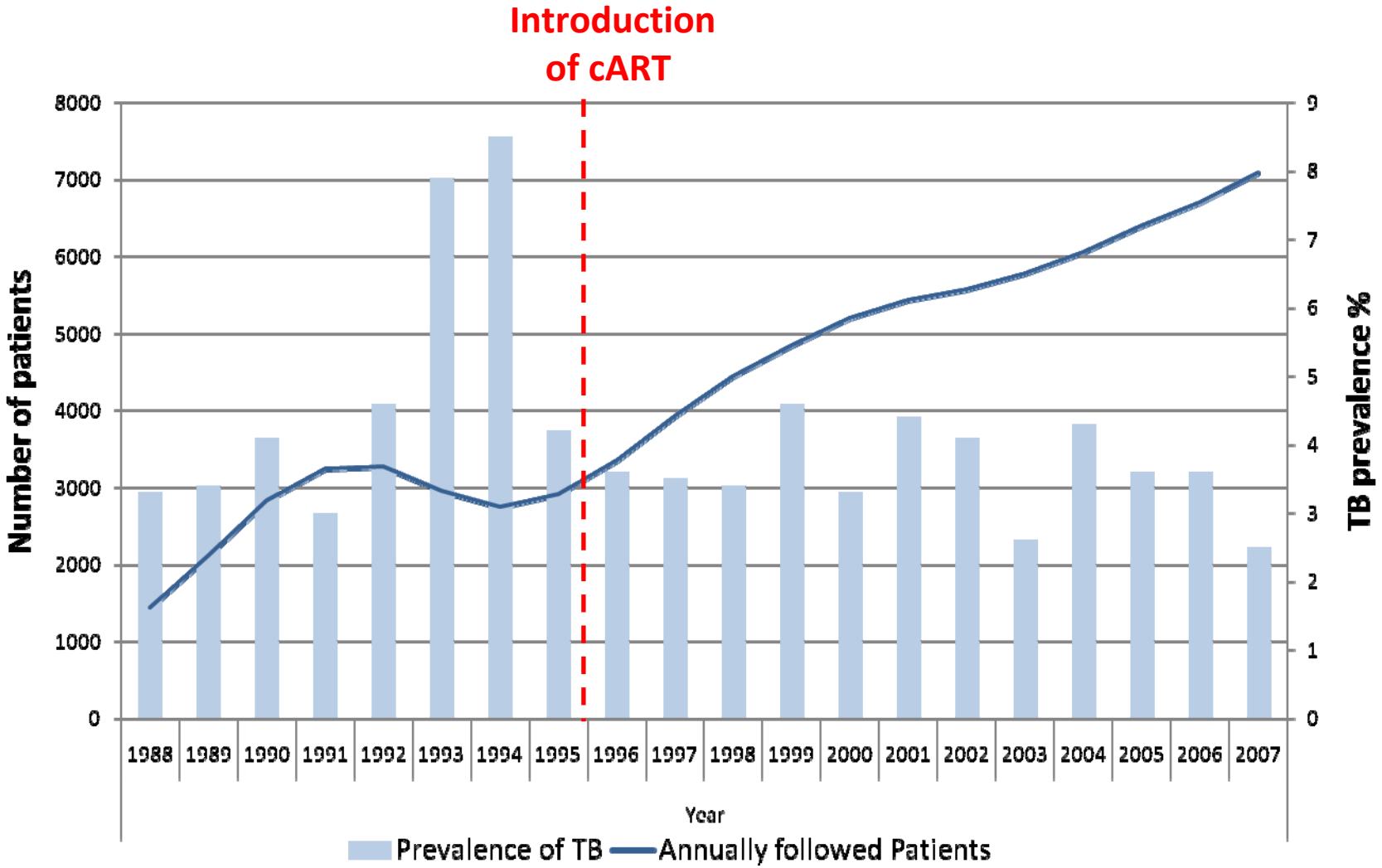
The Swiss HIV Cohort Study

- Prospective enrollment of HIV-infected individuals aged >16 years
- >15,000 individuals included
- 70% of all AIDS cases in Switzerland
- Every 6 months data collection (clinical and laboratory parameters)
- TST performed in the first 2 years after enrollment

www.shcs.ch

Tuberculosis in the SHCS



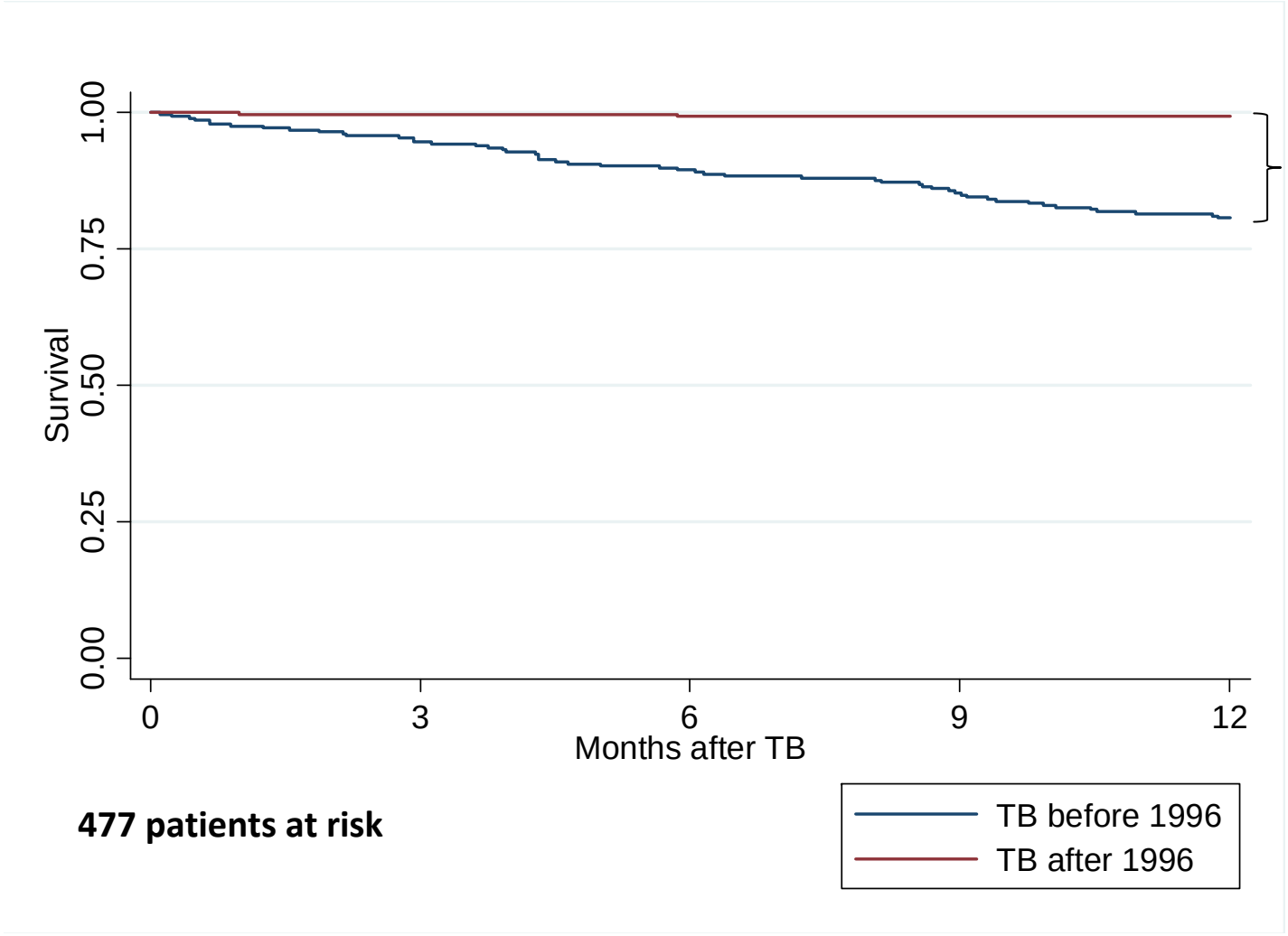
SHCS, Data on file

Tuberculosis in the SHCS

Characteristics of 477 HIV-infected individuals with active tuberculosis between 1988-2007		
Median age (IQR)		34 (29-40)
Males		66%
Ethnicity	White	57%
	Black	36%
	Asian	6%
Transmission risk	MSM	20%
	Heterosexual	46%
	Intravenous drug use	30%
Prior AIDS-defining condition		18%
Median CD4 T-cell count (IQR)		291 (136-440)

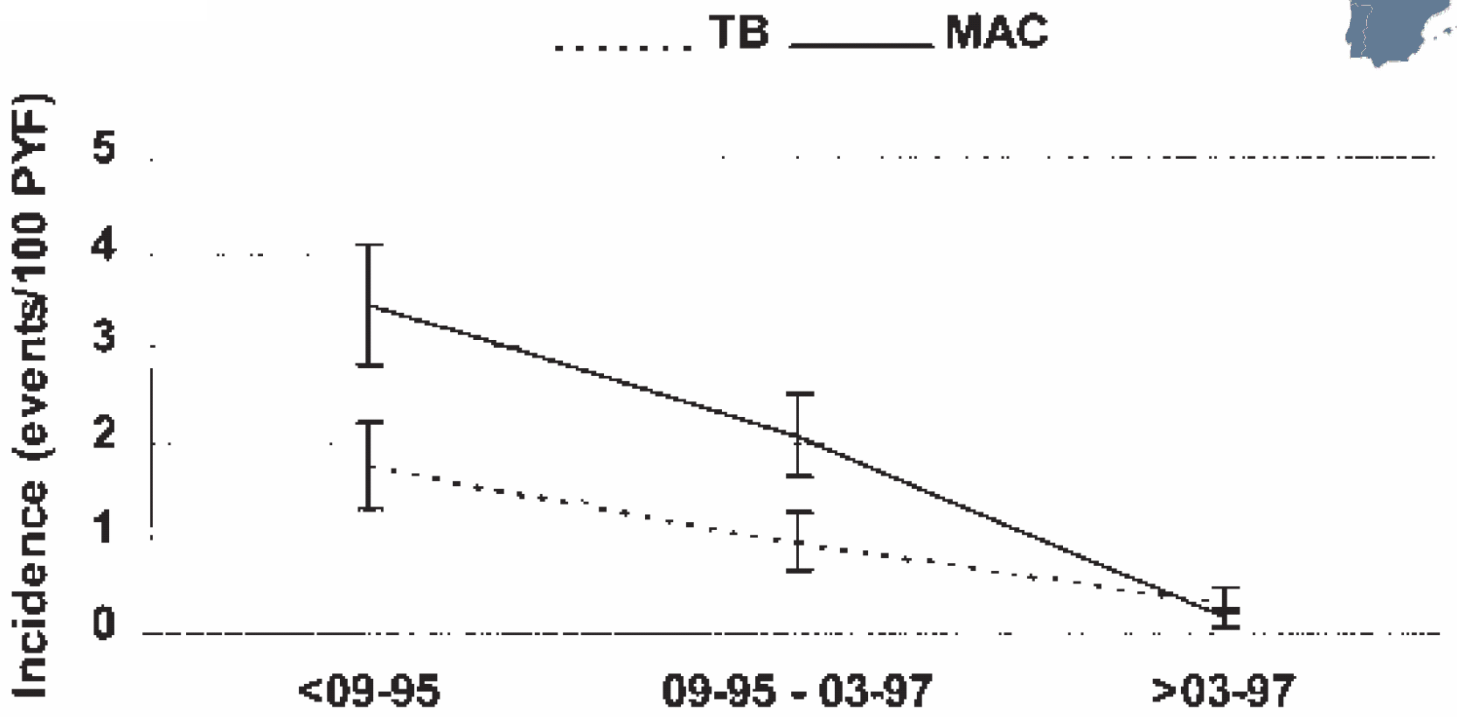
SHCS, Data on file

Survival after Tuberculosis



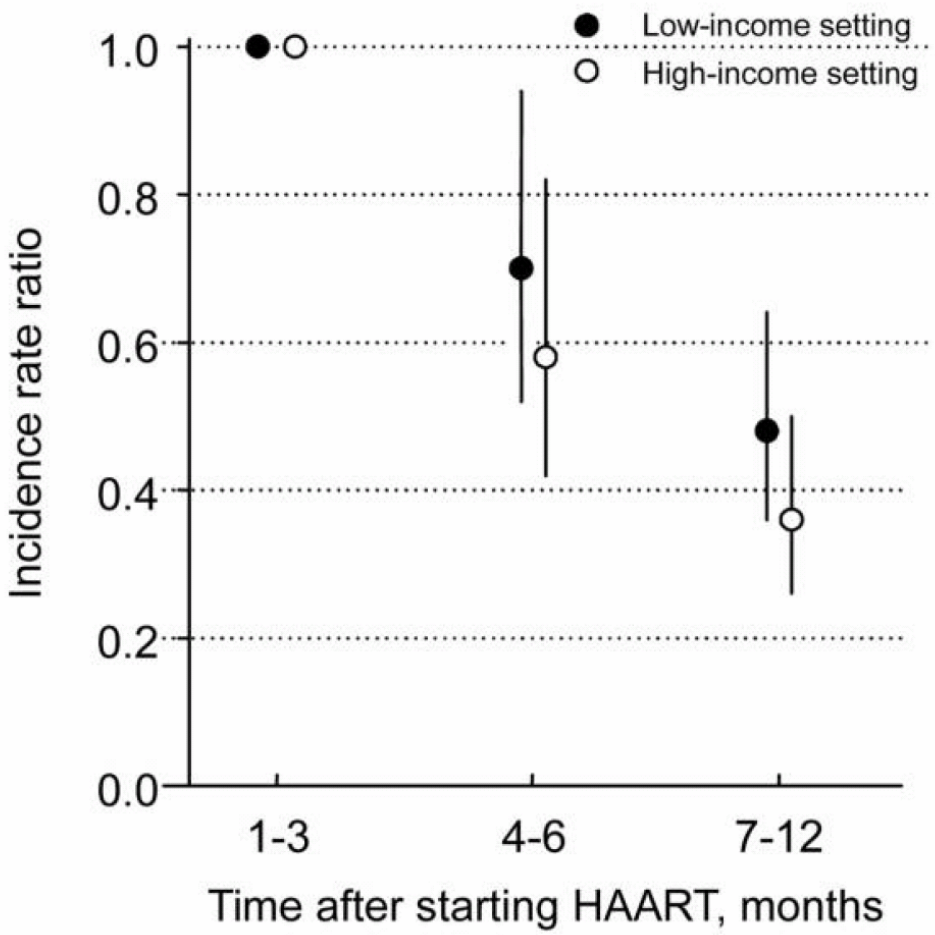
SHCS, Data on file

Tuberculosis in Europe: The EuroSIDA Study



Kirk O, Am J Resp Crit Care Med, 2000

Incidence of TB after starting cART



N=22,117
N=4,540

IeDEA, ART-CC

Brinkhof MW, Clin Infect Dis, 2007

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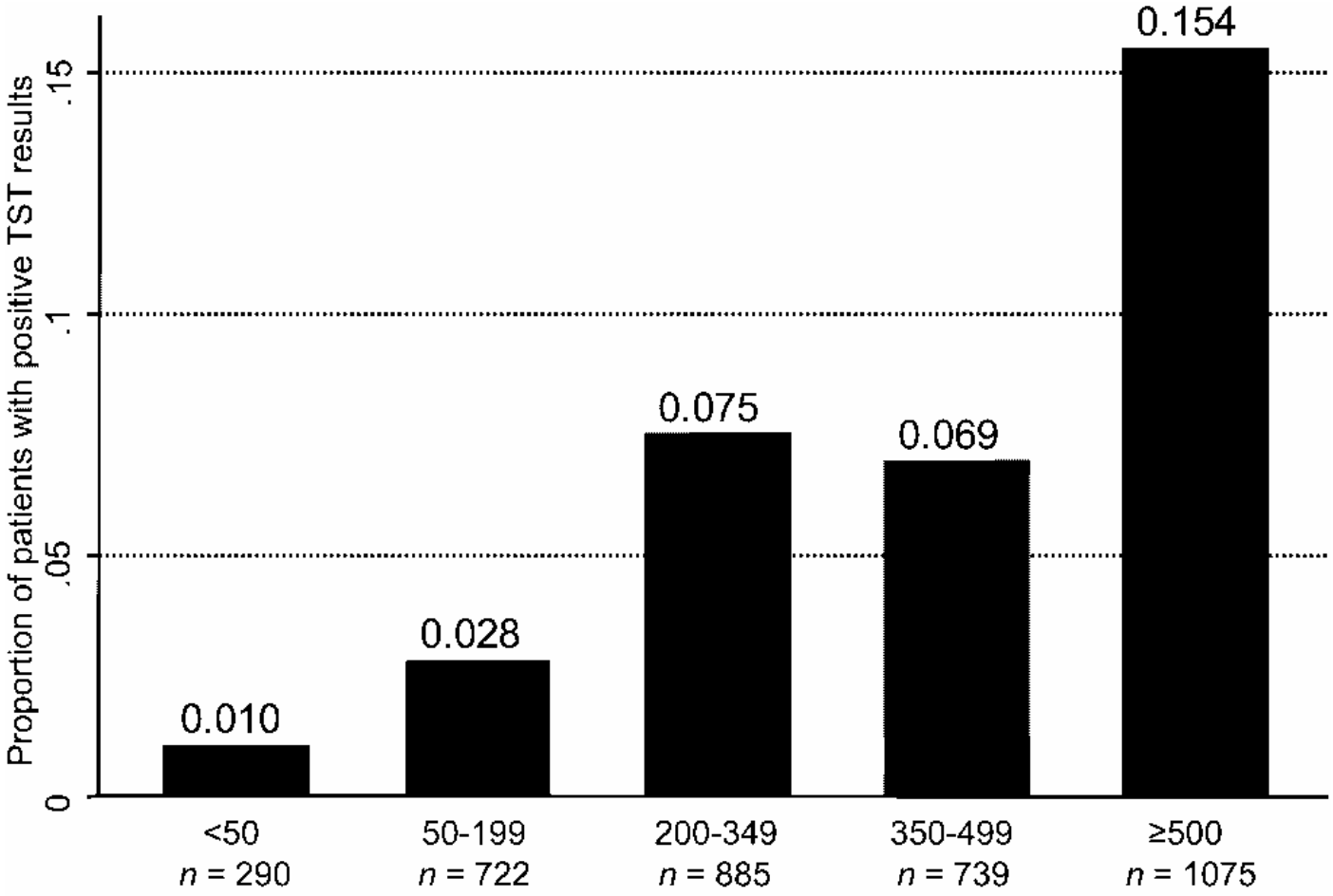
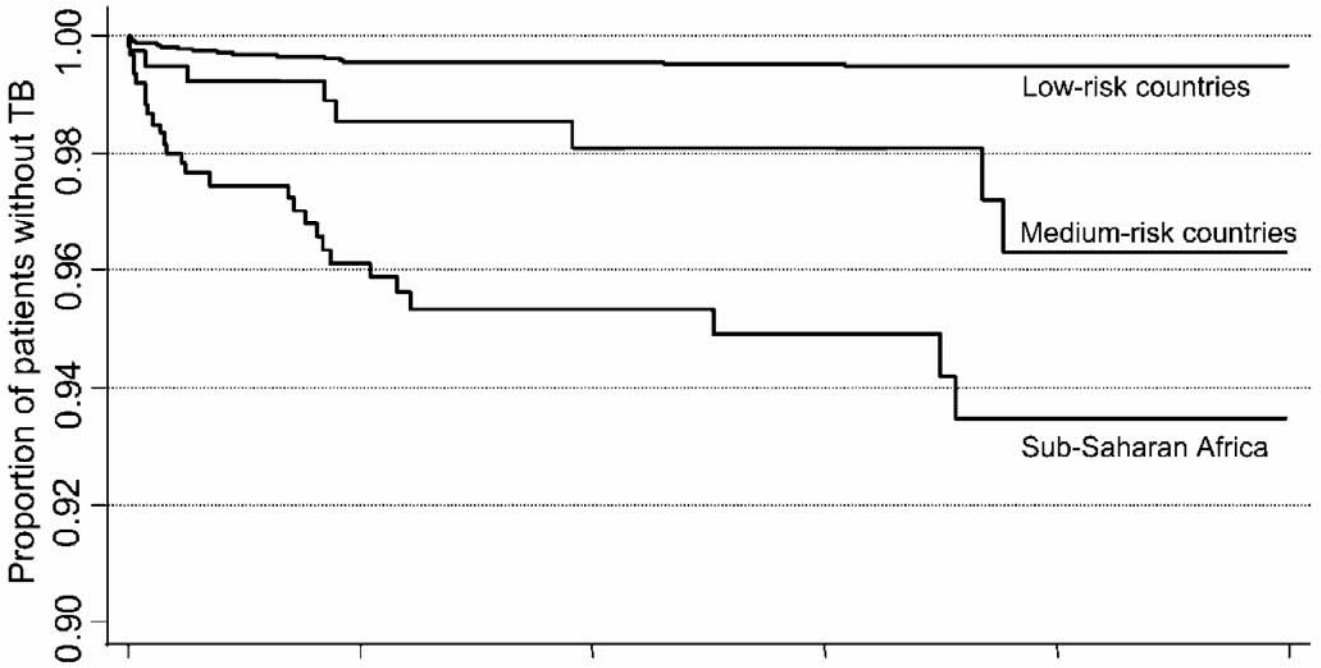
Tuberculin Skin Testing



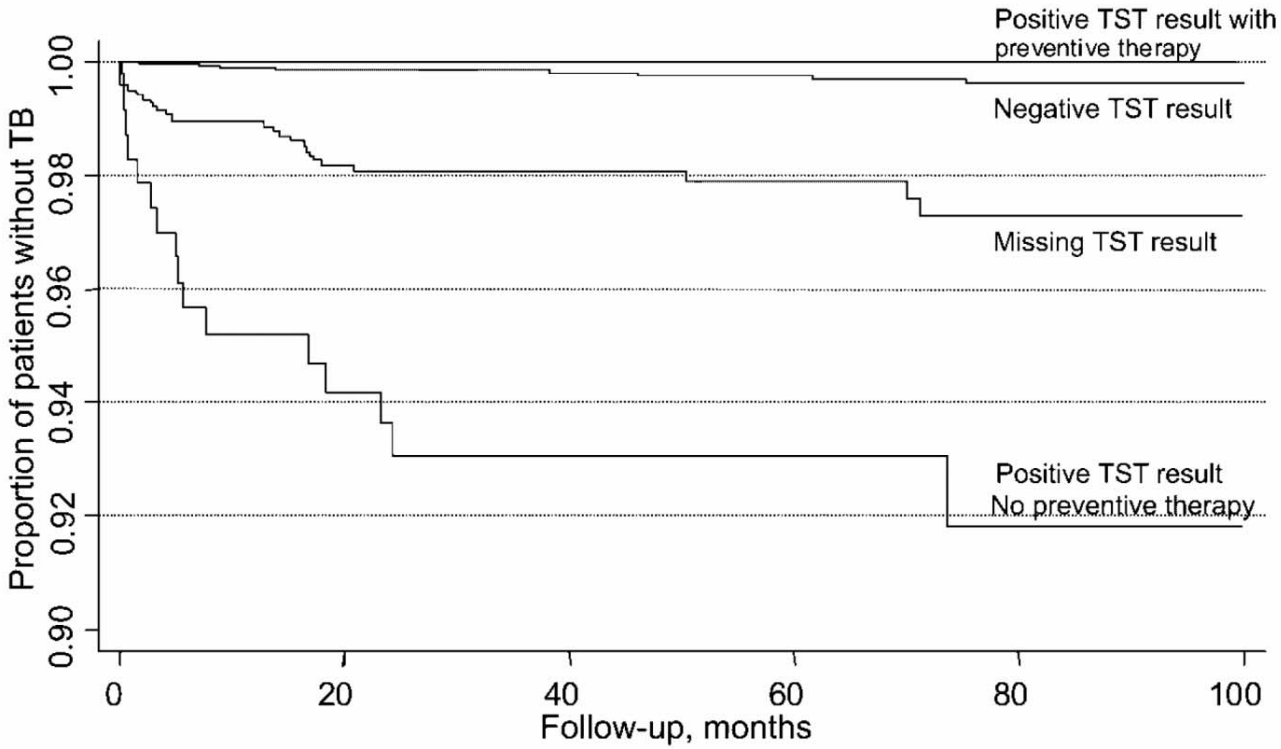
Elzi et al., Clin Infect Dis, 2007

Reactivation of latent TB



No. of patients at risk:						
Sub-Saharan Africa	608	391	271	170	103	37
Low-risk countries	4506	3548	2786	2101	1417	662
Medium-risk countries	388	284	212	158	92	27

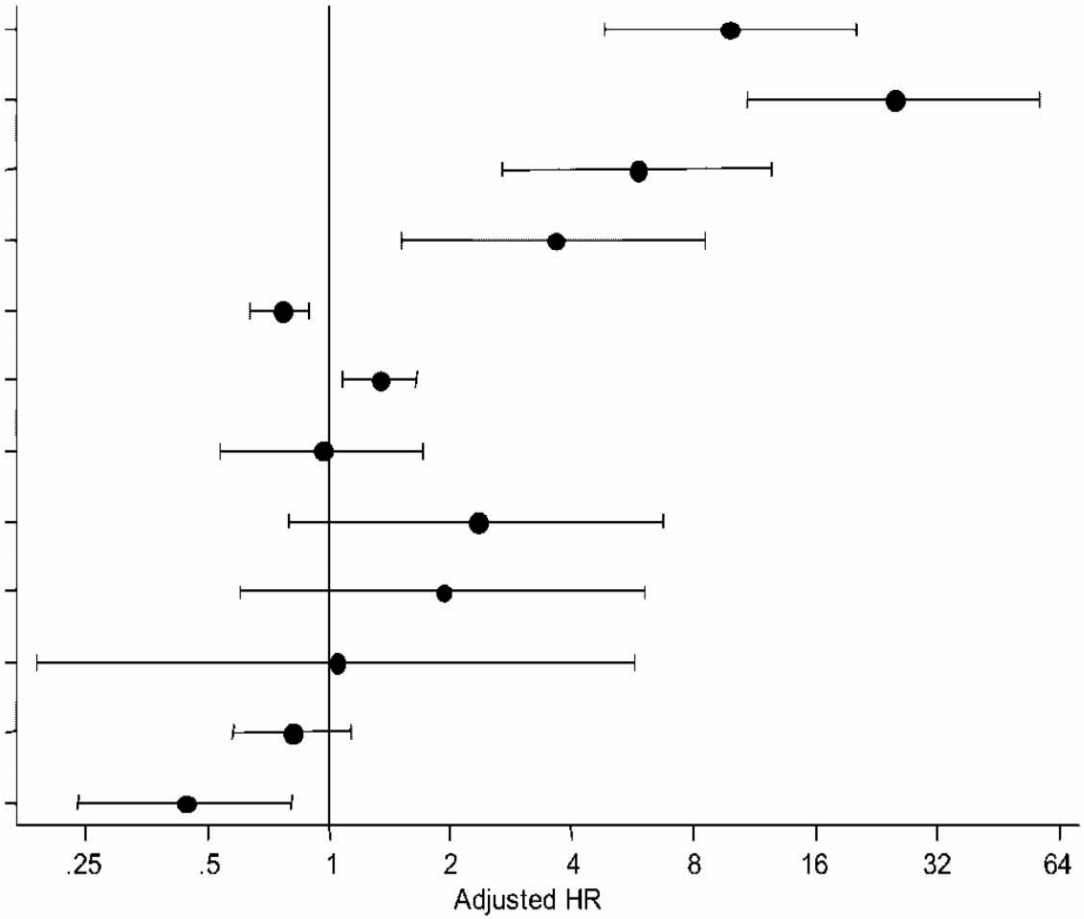
Reactivation of latent TB



No. of patients at risk:						
Missing TST result	1636	1009	689	461	226	87
Negative TST result	3680	3078	2473	1898	1343	628
Positive TST result with no preventive therapy	233	176	137	97	65	22
Positive TST result with preventive therapy	140	123	84	55	32	17

Reactivation of latent TB

Parameter	Adjusted HR (95% CI)	*P*
TST result missing (as compared with negative TST result)	9.9 (4.8-20.3)	<.001
TST result positive (as compared with negative TST result)	25 (10.8-57.4)	<.001
Sub-Saharan Africa (as compared with low-risk region)	5.8 (2.7-12.5)	<.001
Medium-risk region (as compared with low-risk region)	3.6 (1.5-8.6)	.003
Baseline $CD4^+$ cell count (per 100 cells/μL increase)	0.76 (0.65-0.89)	.001
Baseline plasma HIV RNA level (per $\log_{10}$ increase)	1.33 (1.08-1.7)	.007
Female sex	0.96 (0.54-1.7)	.9
Heterosexual HIV transmission (as compared with MSM)	2.32 (0.80-6.7)	.1
IDU HIV transmission (as compared with MSM)	1.91 (0.61-6.0)	.3
Other/unknown HIV transmission (as compared with MSM)	1.05 (0.19-5.7)	1.0
Age per 10-year increase	0.81 (0.58-1.13)	.2
Start of triple ART	0.44 (0.24-0.81)	.008



Elzi et al., Clin Infect Dis, 2007

Interferon-gamma releasing assay

Patients and methods:

- Retrospective analysis of 64 HIV-infected individuals who developed TB after enrollment in the SHCS
- IGRA (T Spot-TB®) performed using frozen lymphocytes stored at a median of 3 months before active TB was diagnosed
- Comparison with TST

Elzi et al, SHCS, manuscript in preparation

Interferon-gamma releasing assay

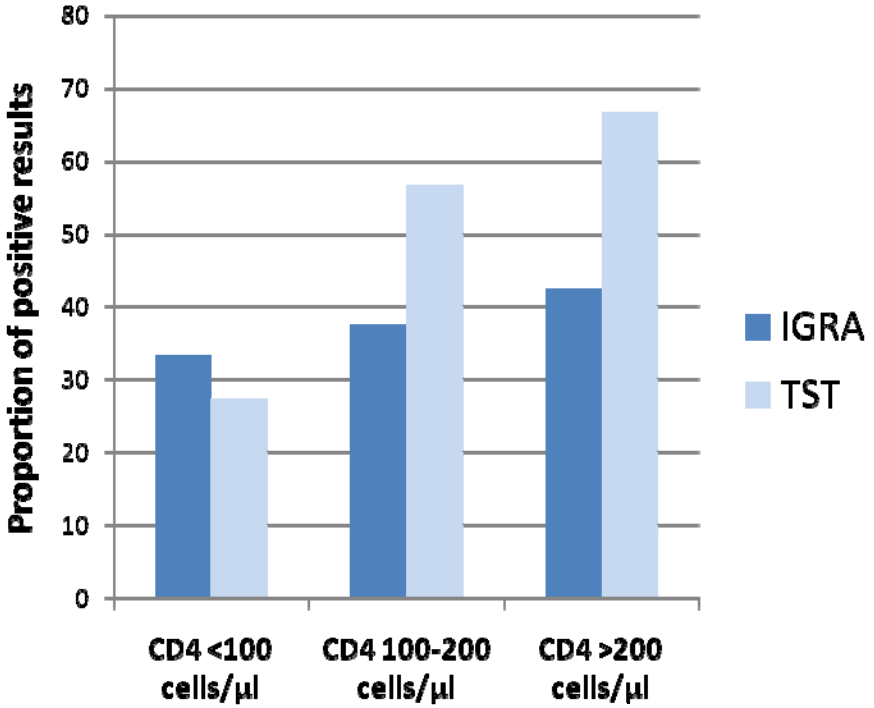
Results:

Characteristics of 64 HIV-infected individuals	
Median age (IQR)	35 (31-42)
Males	64%
Non-white ethnicity	54%
Prior AIDS-defining condition	18%
Median CD4 cell count (IQR)	223 (103-339)

IGRA (T Spot-TB®)	
• Positive:	39%
• Indeterminate:	33%

Sensitivity of T Spot-TB®:	**58%* (43-74)**
Sensitivity of TST:	**50% (35-65)**

**if indeterminate results excluded*



Interferon-gamma releasing assay

In 32 HIV-infected individuals with results of both tests:

Concordance between IGRA and TST in only 56% of individuals
Kappa 0.122 (p=0.246)

If IGRA and TST combined: sensitivity 66% (95% CI 51-80%)

Both tests negative in 25%
Multivariate analysis (adj. for CD4, age, ethnicity, prior AIDS, cART): older age associated with higher risk of having both tests negative (OR 3.2, 95% CI 1.2-8.3, p=0.02, per 10 years older)

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Treatment of HIV/Tuberculosis

- WHEN TO START ?

  Immune Reconstitution Syndrome

- WHAT TO START ?

  Drug-drug interactions

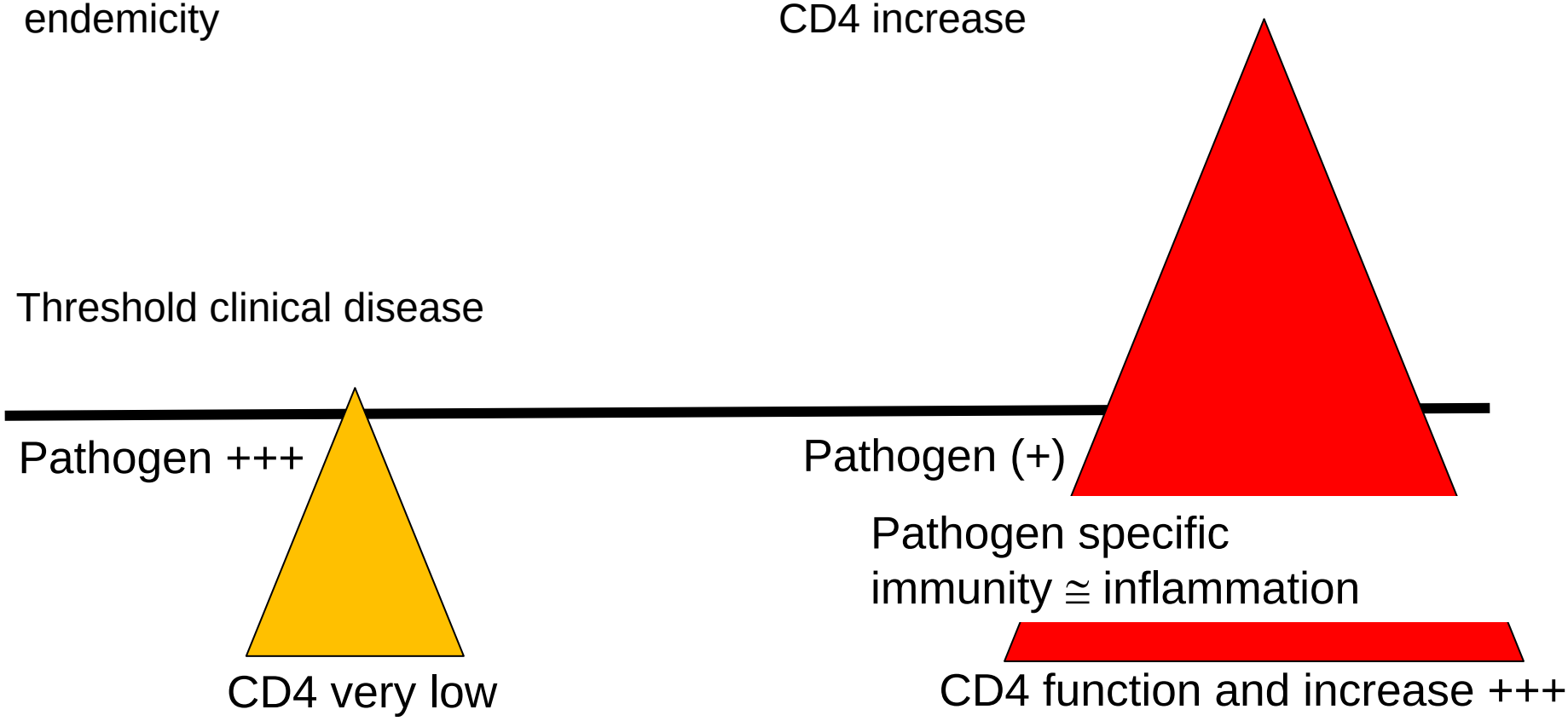
Immune Reconstitution Inflammatory Syndrome
Incidence 3-25%

Before ART

Advanced disease
High pathogen
endemicity

After ART initiation

ART early initiation
VL decrease
CD4 increase



Battegay et al, JAC, 2008, Hirsch et al, CID 2004, French et al, AIDS 2004; Shelbourne et al, Med 2002

Tuberculosis-associated IRIS
Start ART rather earlier than too late

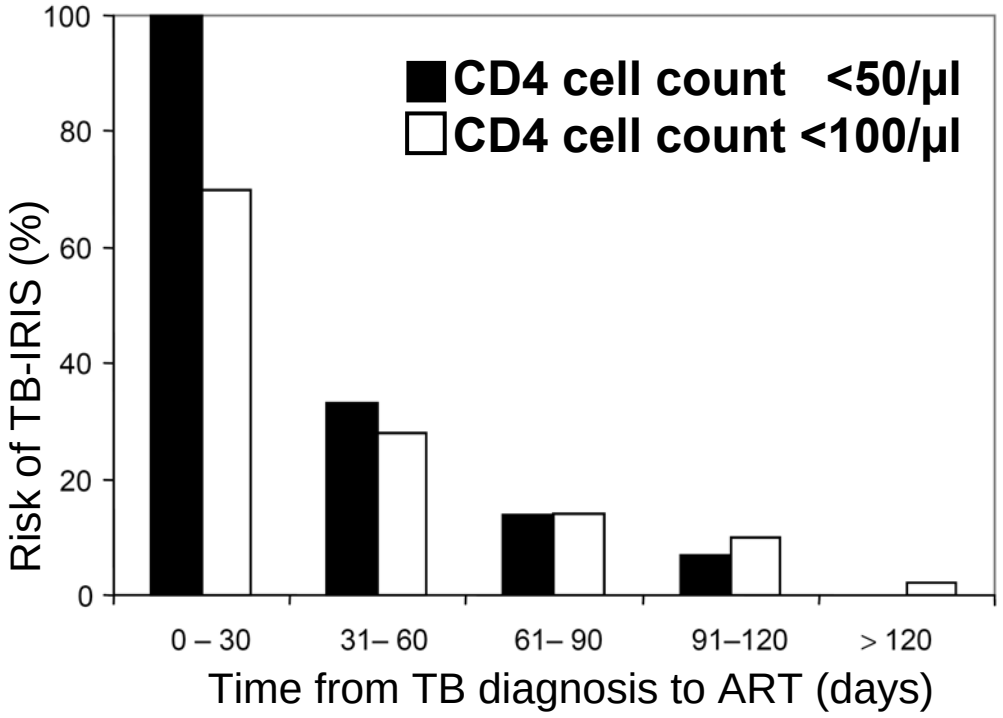
Retrospective study, 160 pts

Baseline CD4 68 cells/µl

ART start after 105 d (median)

IRIS in 12%

- Immediate TB treatment
- postpone ART if HIV allows
- NSAID (BIII) and/or prednison (CIII) 1 mg/kg/d; reduce after 1-2 wks

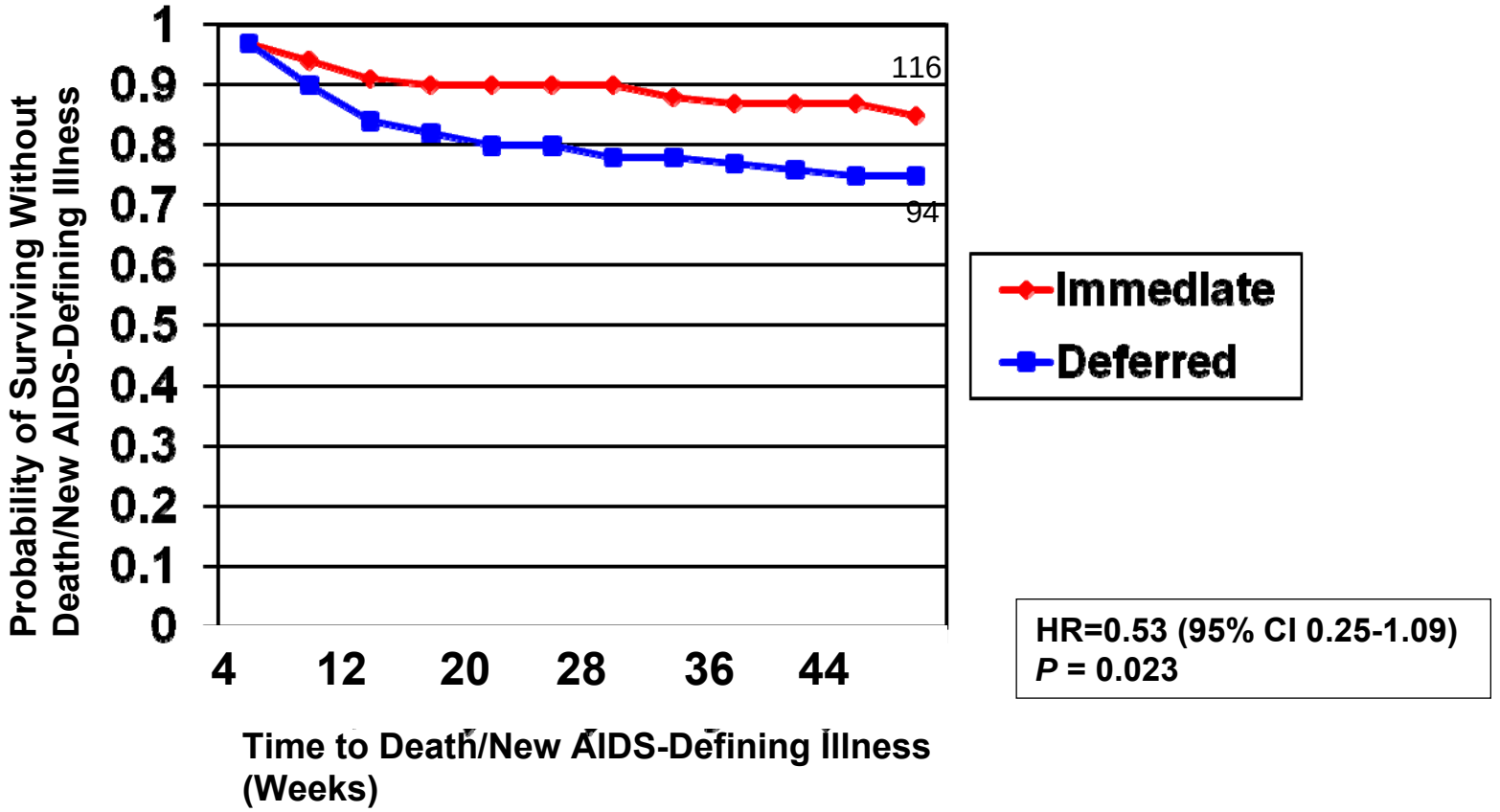


Risk of Tb-associated IRIS +++ with early ART and low CD4-T-cells, but most cases self-limiting! (2 deaths due to IRIS)

[1] Very similar results

Pozniak et al., AIDS 1992; Lawn et al., AIDS 2007,
[1]Murdoch DM, AIDS 2008

A5164: Immediate versus deferred ART
Time to AIDS progression or death



Better CD4 increase, non significantly different VL results
Less clinical progression

Adapted from Andrew Zolopa. CROI 2008; abstract 142

NIH DHHS Guidelines

Recommended timing of initiation of cART in treatment-naive patients with active TB disease according to CD4 cell counts

- CD4 <100 — ART after 2 weeks
- CD4 =100–200 — ART after 8 weeks
- CD4 = 200–350 — ART after 8 weeks*
- CD4 >350 — ART after 8-24 weeks or after end of TB treatment*

* Individual evaluation

Rifabutin is the preferred rifamycin in HIV-infected patients with active TB due to its lower risk of drug interactions with cART (AII)

Compiled from Benson et al at http://aidsinfo.nih.gov/guidelines/ 2008

Acknowledgements

- All HIV-infected individuals participating in the Swiss HIV Cohort Study

- Manuel Battegay

- The members of the Swiss HIV Cohort Study are:

M. Battegay, E. Bernasconi, J. Böni, HC Bucher, Ph. Bürgisser, A. Calmy, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the SHCS), H. Furrer (Chairman of the Clinical and Laboratory Committee), C. Fux, M. Gorgievski, H. Günthard (Chairman of the Scientific Board), H. Hirsch, B. Hirschel, I. Hösli, Ch. Kahlert, L. Kaiser, U. Karrer, C. Kind, Th. Klimkait, B. Ledergerber, G. Martinetti, B. Martinez, N. Müller, D. Nadal, F. Paccaud, G. Pantaleo, A. Rauch, S. Regenass, M. Rickenbach (Head of Data Center), C. Rudin (Chairman of the Mother & Child Substudy), P. Schmid, D. Schultze, J. Schüpbach, R. Speck, P.Taffé, A. Telenti, A. Trkola, P. Vernazza, R. Weber, S. Yerly.

www.shcs.ch