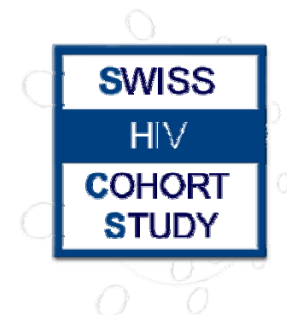


# Tuberculosis in the Swiss HIV Cohort Study

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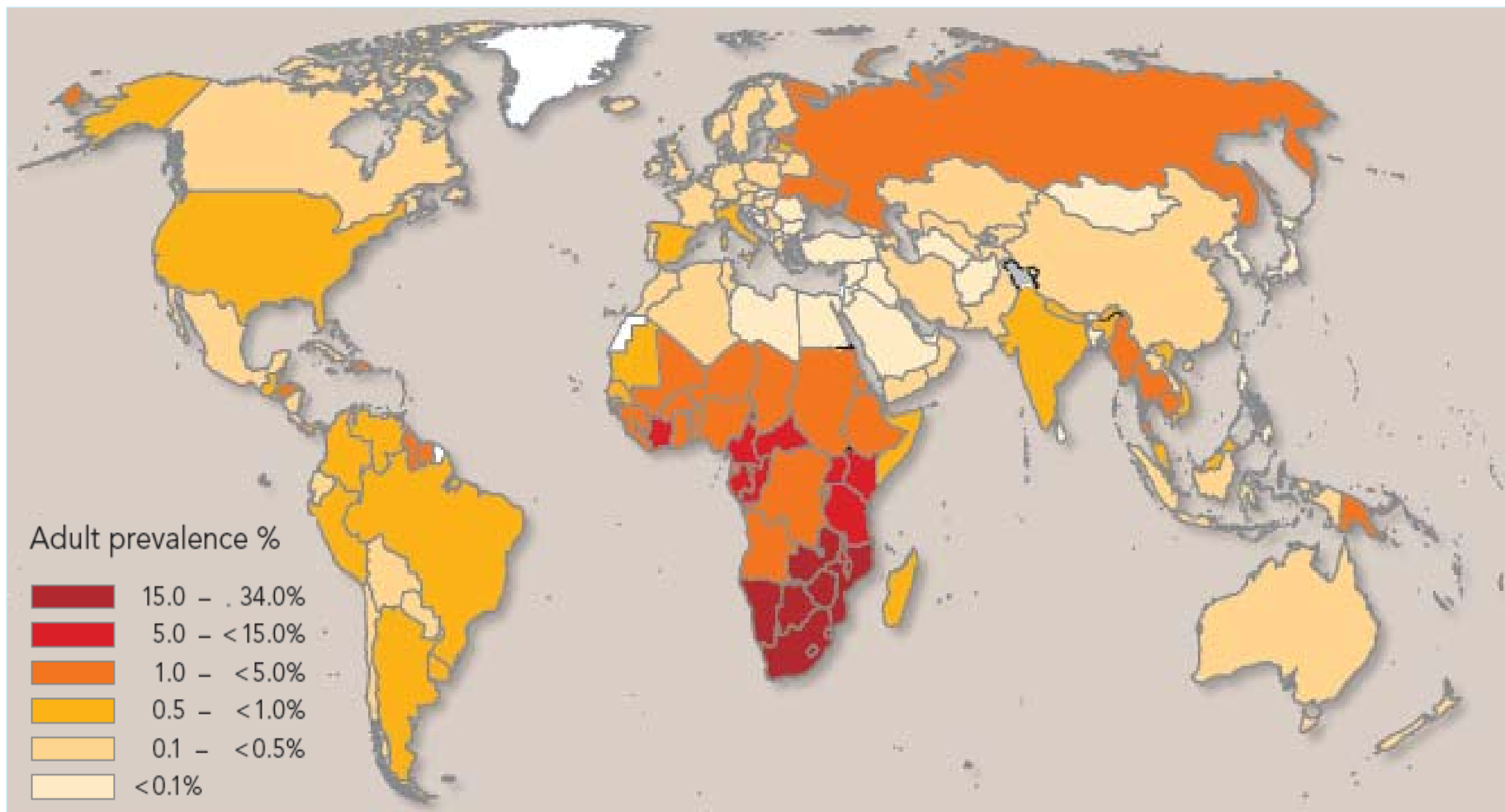
# Outline

- 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

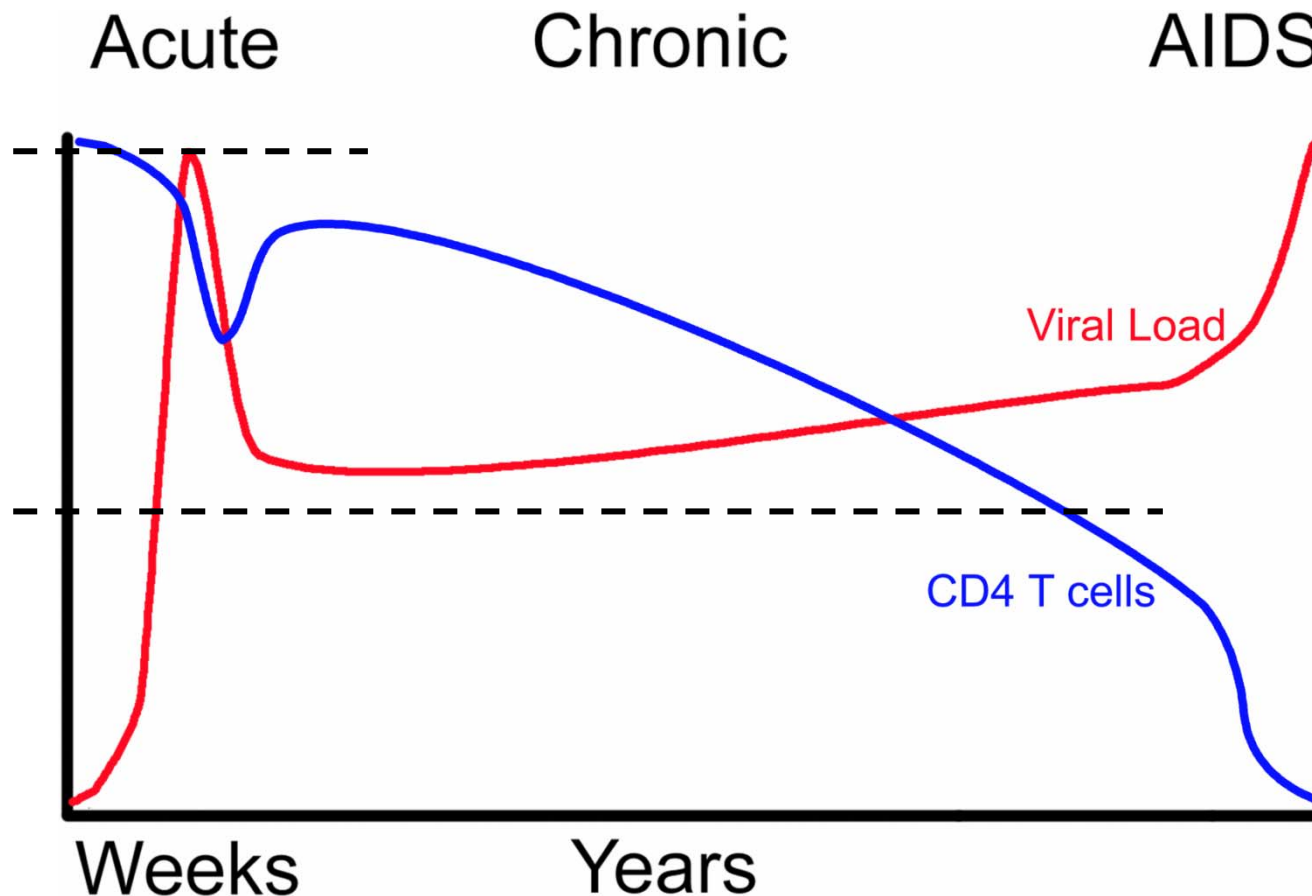


# Tuberculosis & HIV/AIDS

- TB is the third most common AIDS-defining disease in Switzerland<sup>1</sup>
- 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)

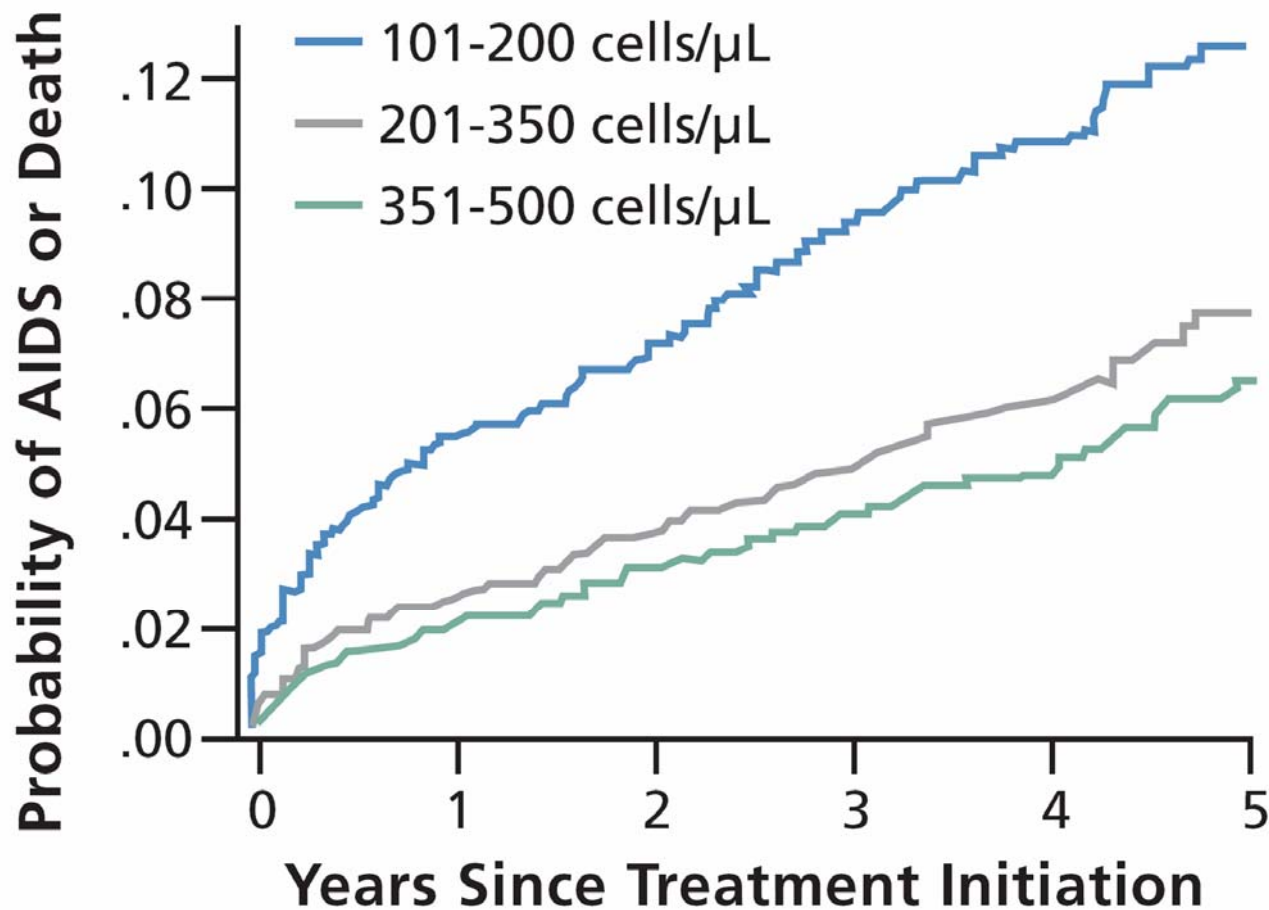
<sup>1</sup> [www.bag.admin.ch](http://www.bag.admin.ch)

# 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



# 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	86
2003 EUROSIDA	OS 96/97 HAART vs 98-02 HAART	
2005 SHCS	OS No HAART vs HAART	
2007 Danish Coh.	OS HIV versus non HIV	

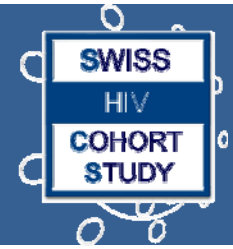
**2008** 20 year old: another 43 years life prolongation with cART  
 ≈ normal life expectancy (?), The ART-CC, 2008, The Lancet



# Outline

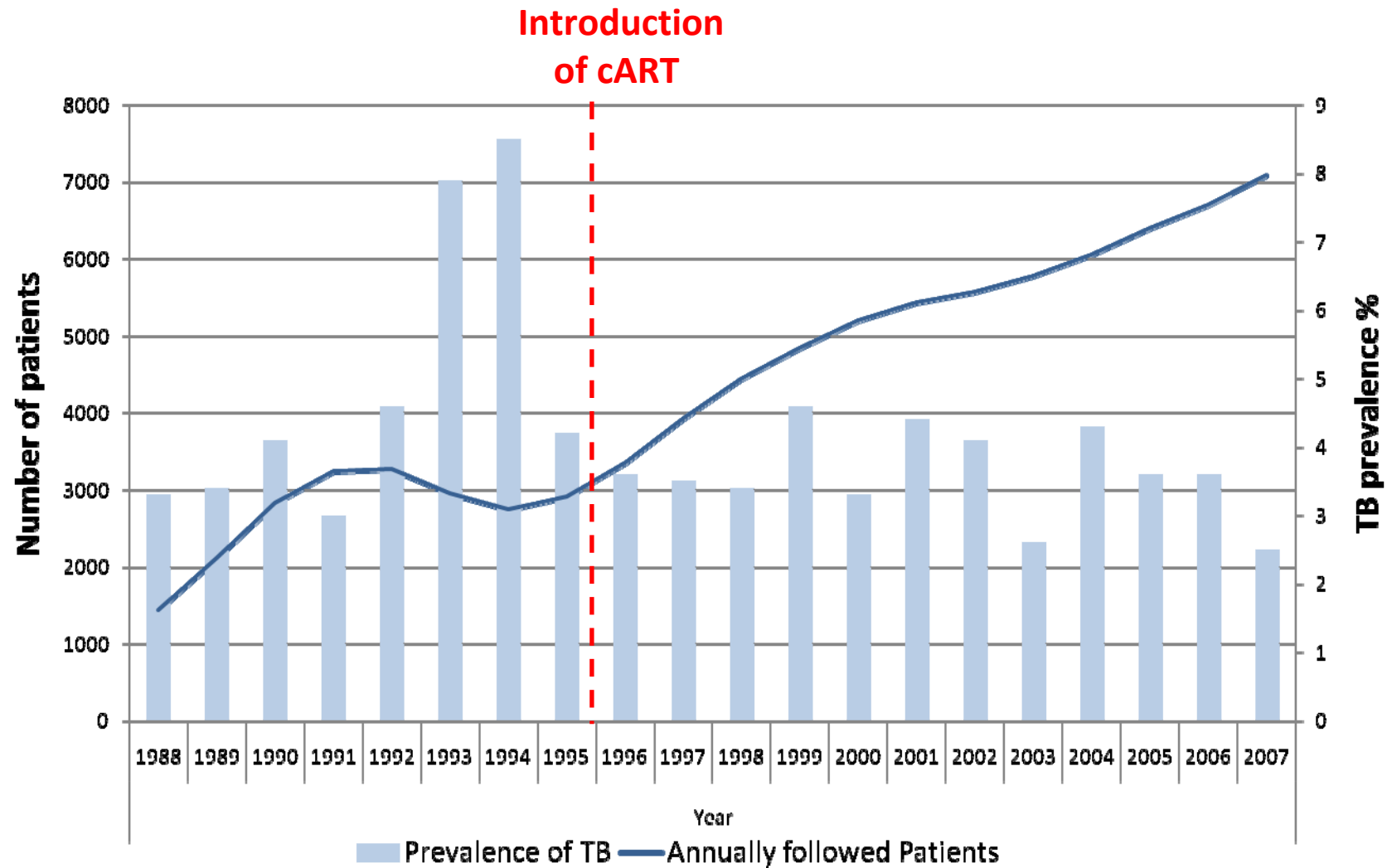
- HIV/AIDS
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# The Swiss HIV Cohort Study



- 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

# Tuberculosis in the SHCS



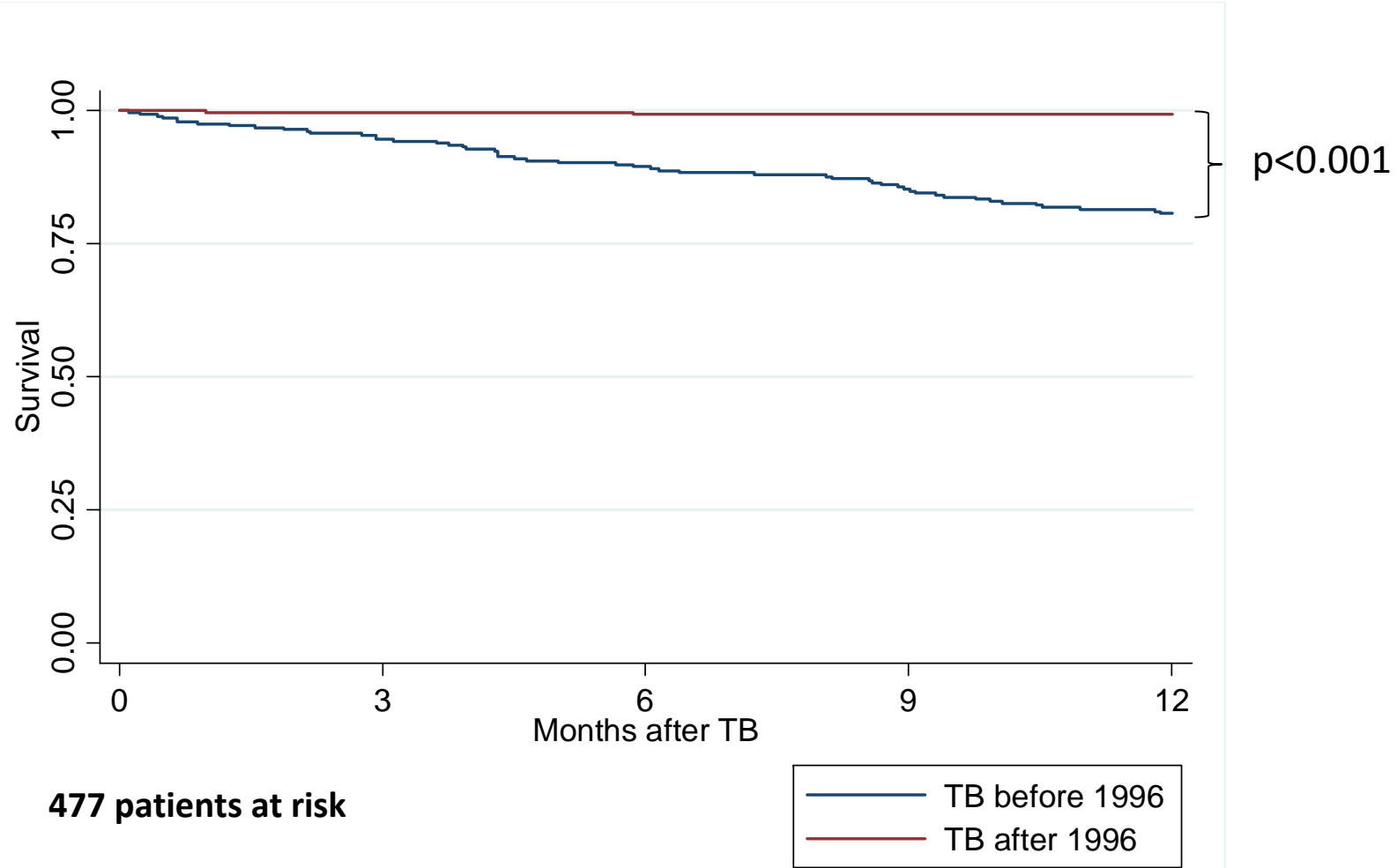
# Tuberculosis in the SHCS



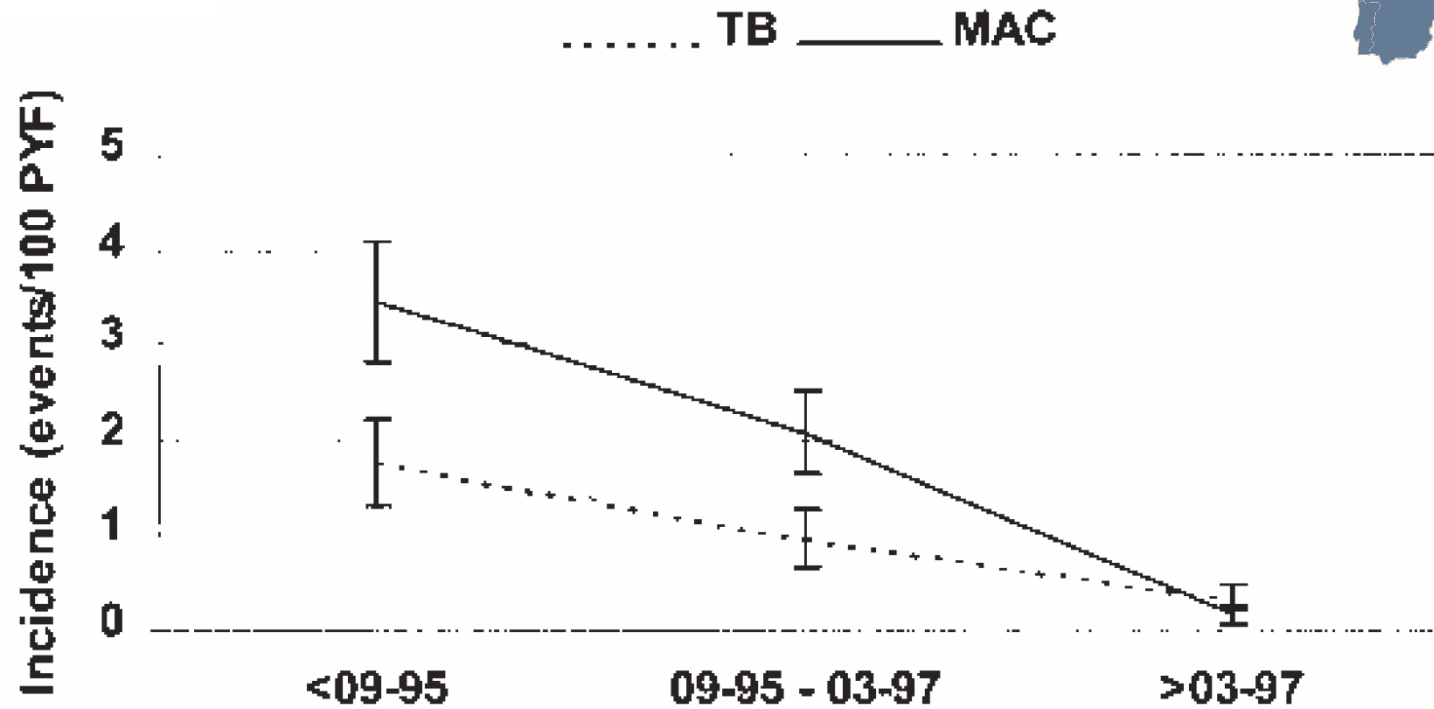
## Characteristics of 477 HIV-infected individuals with active tuberculosis between 1988-2007

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)

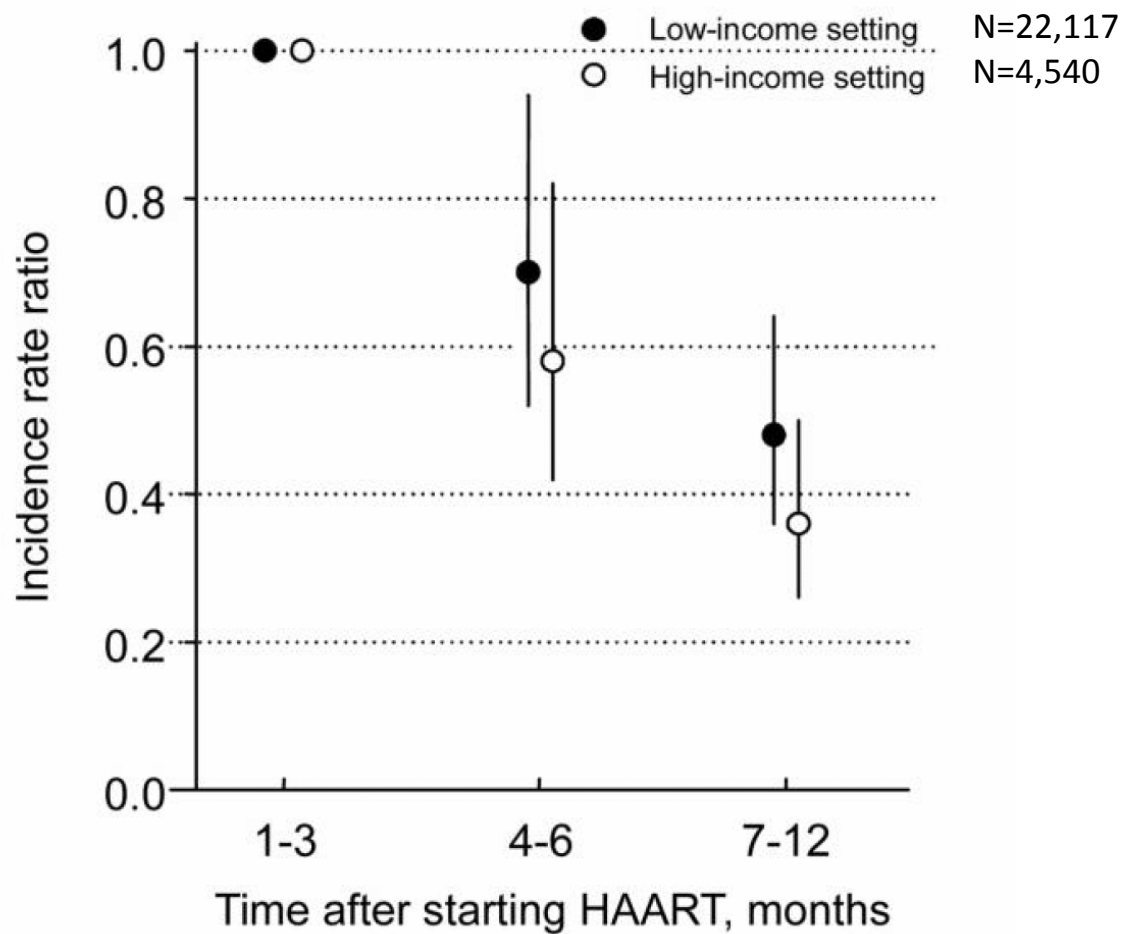
# Survival after Tuberculosis



# Tuberculosis in Europe: The EuroSIDA Study



# Incidence of TB after starting cART



leDEA, ART-CC

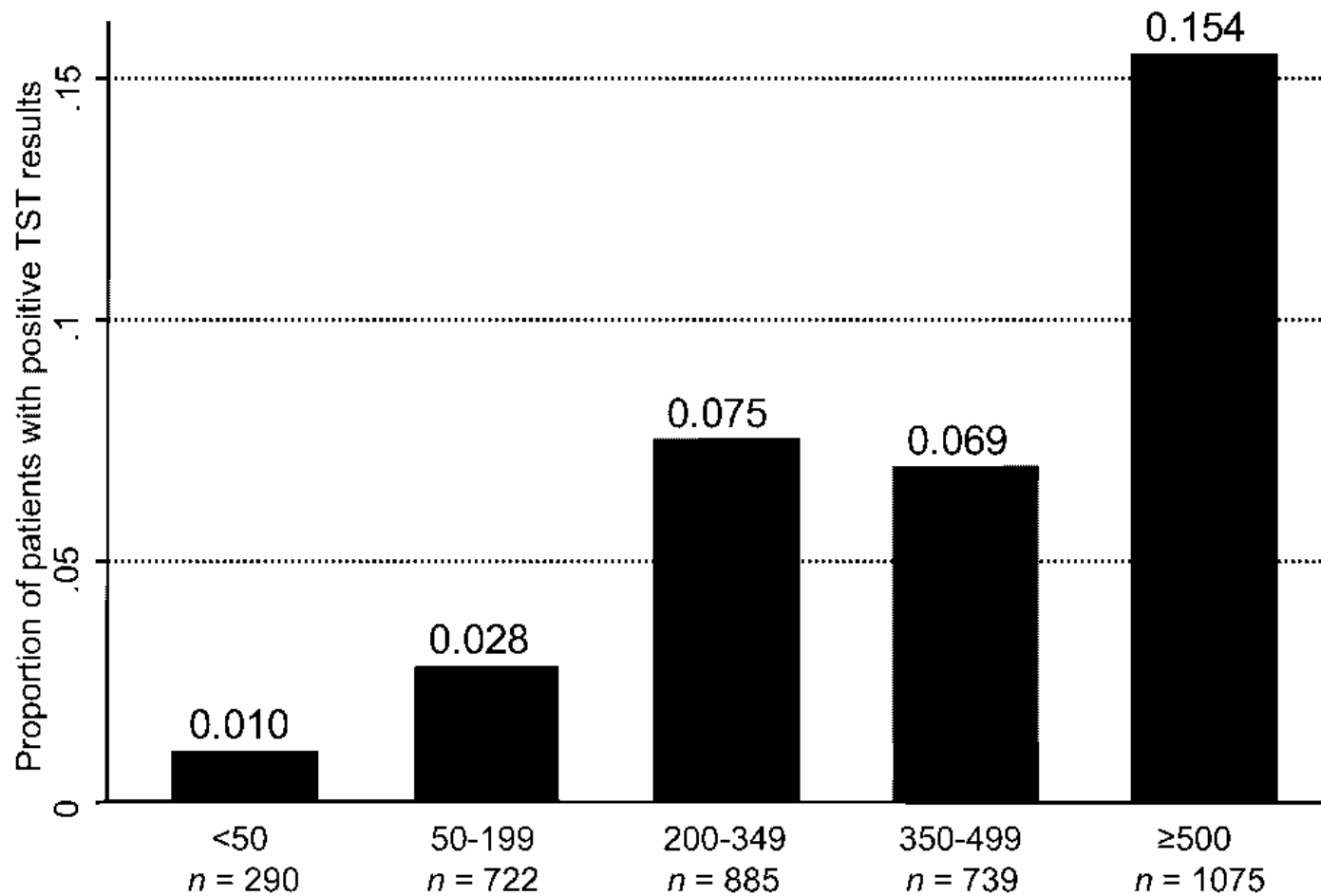
Brinkhof MW, Clin Infect Dis, 2007

# Outline

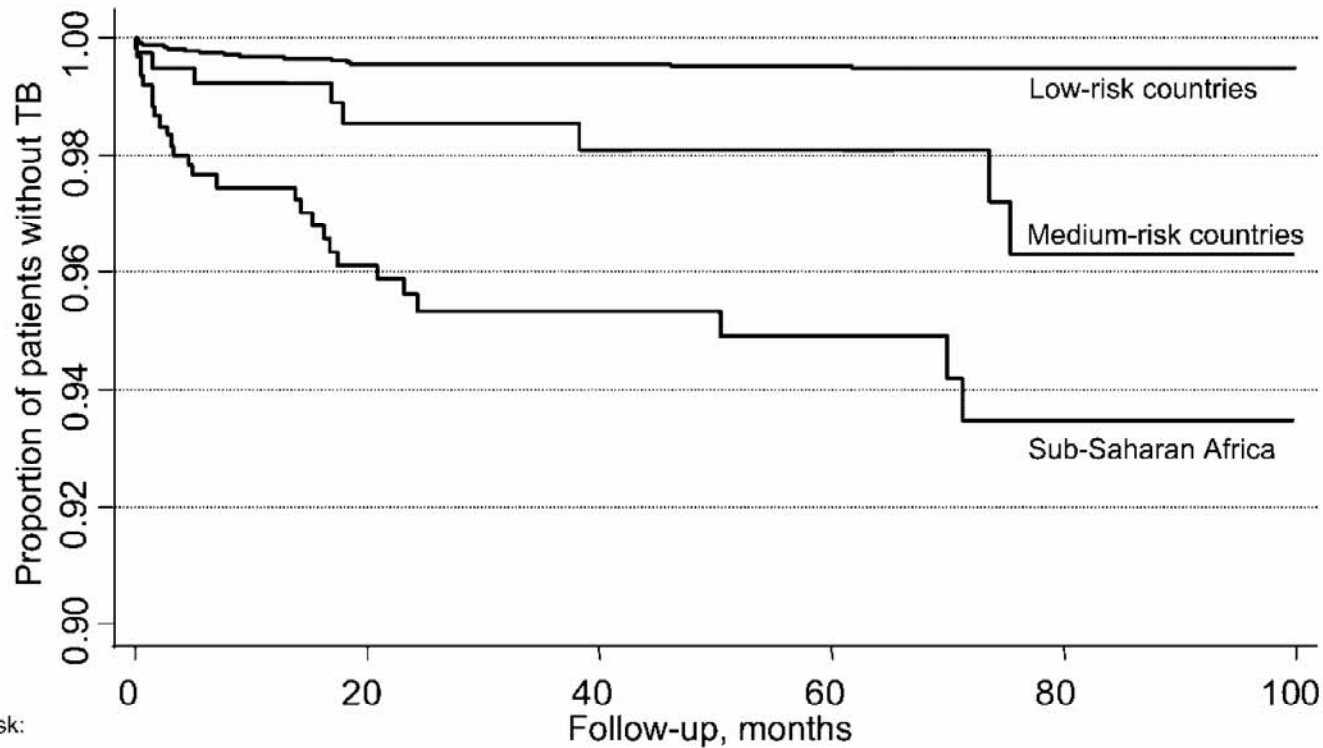
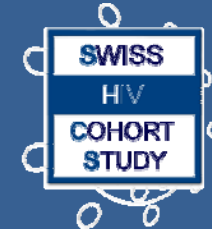
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# Tuberculin Skin Testing



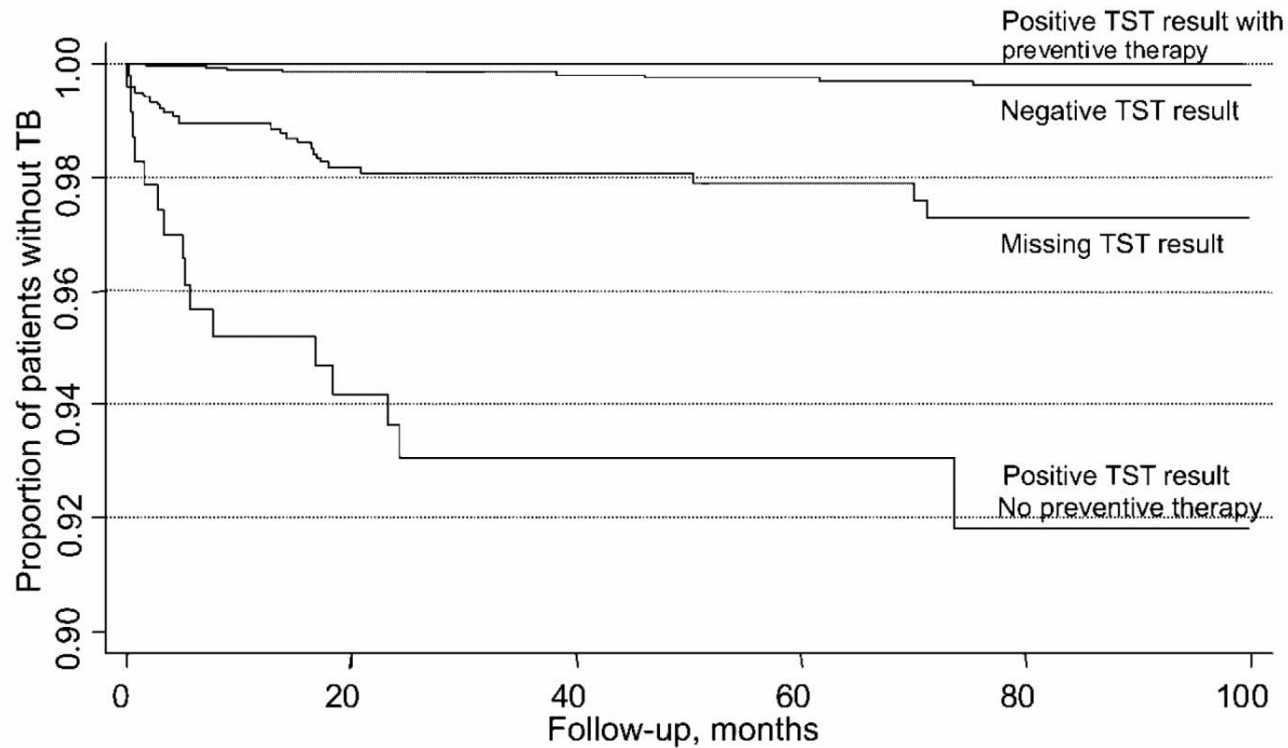
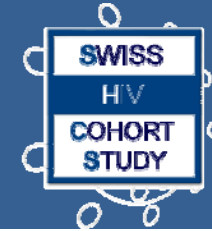
# Reactivation of latent TB



No. of patients at risk:

	0	20	40	60	80	100
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

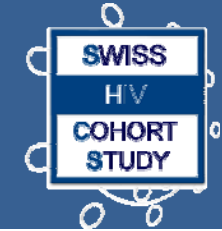
# Reactivation of latent TB



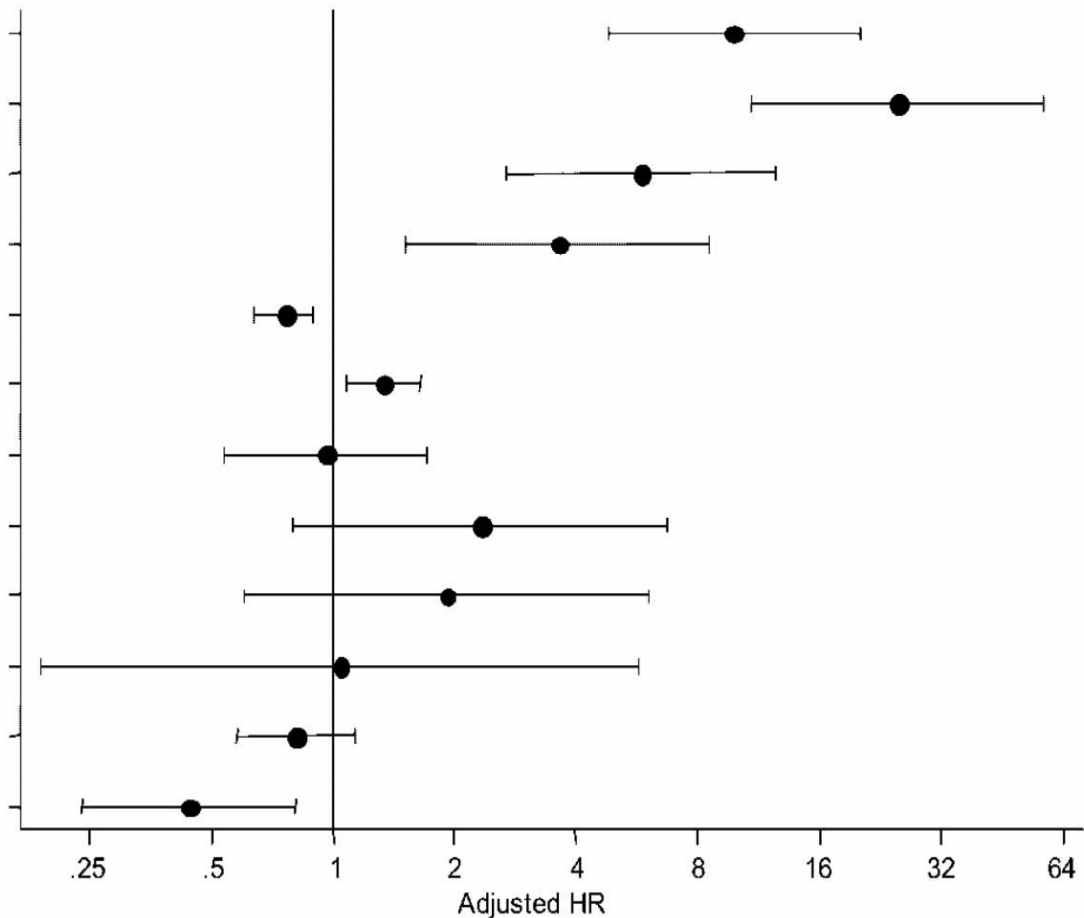
No. of patients at risk:

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



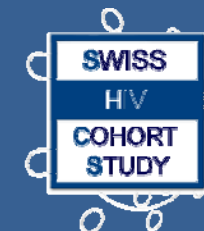
# Interferon-gamma releasing assay



## Patients and methods:

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

# 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)

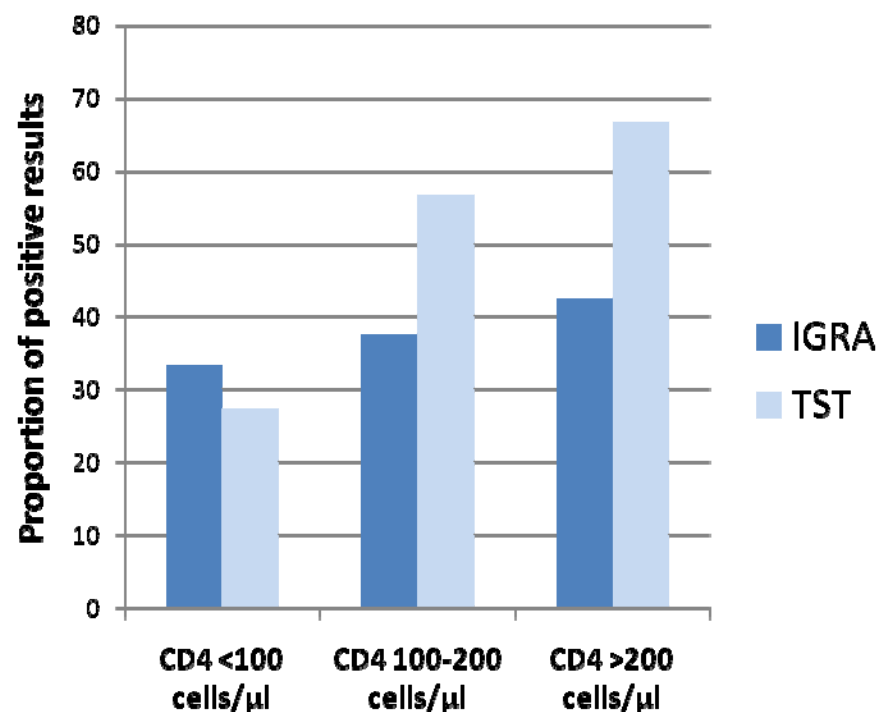
### IGRA (T Spot-TB<sup>®</sup>)

- Positive: 39%
- Indeterminate: 33%

**Sensitivity of T Spot-TB<sup>®</sup>: 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)

# Outline

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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%

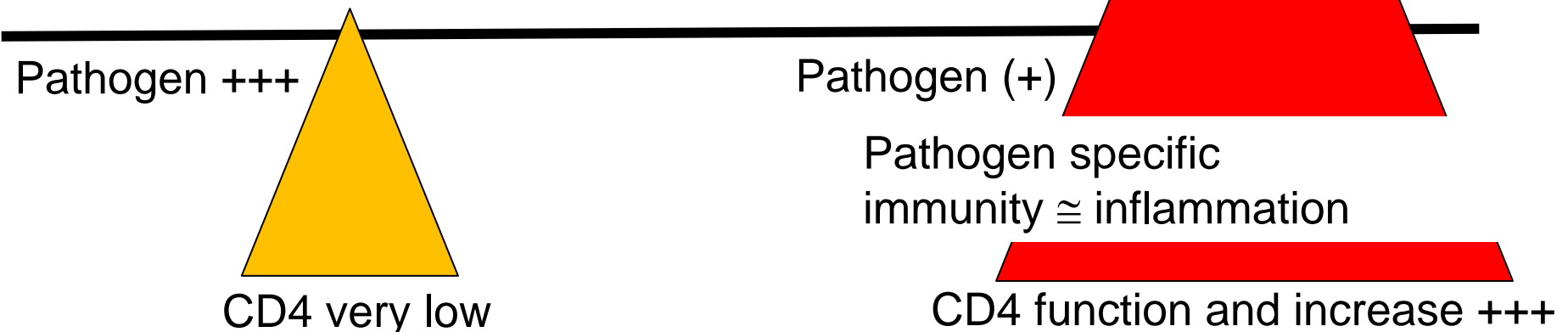
### Before ART

Advanced disease  
High pathogen  
endemicity

### After ART initiation

ART early initiation  
VL decrease  
CD4 increase

Threshold clinical disease

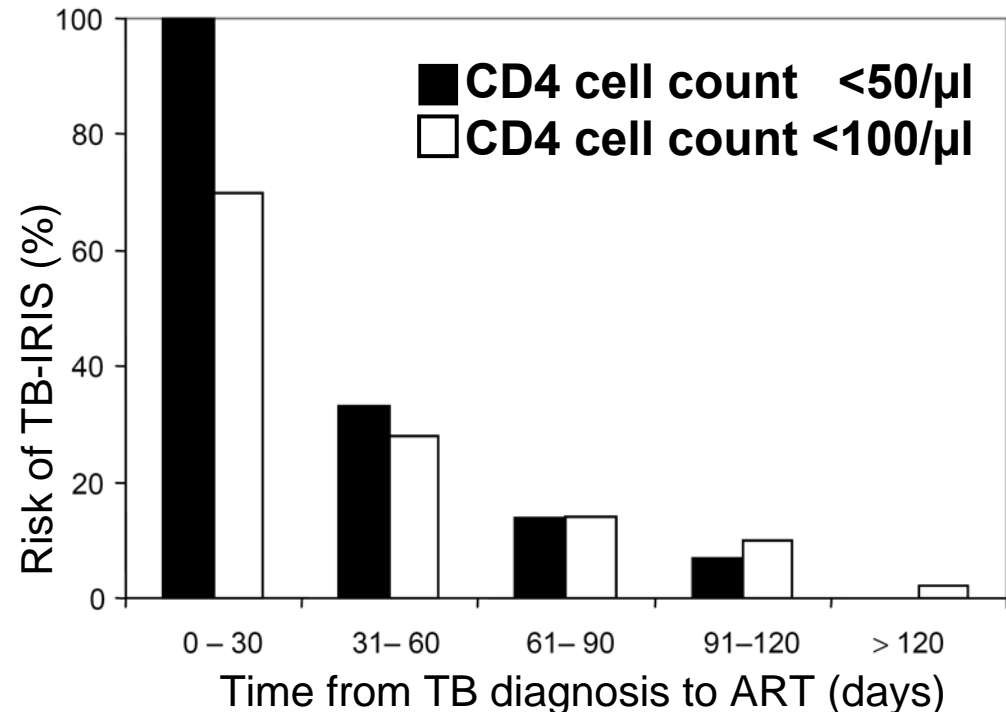


# Tuberculosis-associated IRIS

## Start ART rather earlier than too late

Retrospective study, 160 pts  
Baseline CD4 68 cells/ $\mu$ l  
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

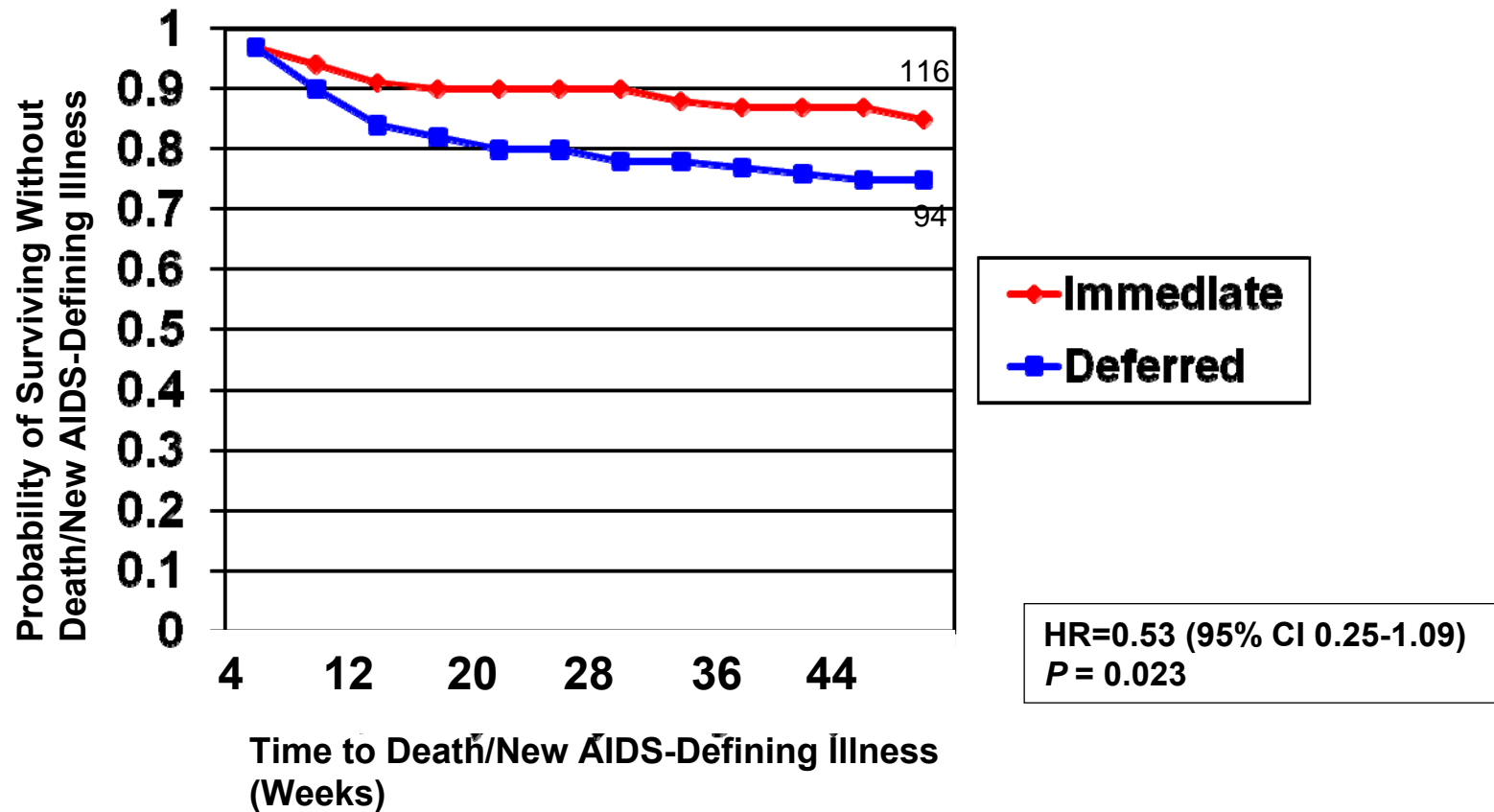


**Risk of Tb-associated IRIS +++ with early ART and low CD4-T-cells, but most cases self-limiting! (2 deaths due to IRIS)**

<sup>1</sup> Very similar results

# A5164: Immediate versus deferred ART

## Time to AIDS progression or death



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

# 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 (All)**

# Acknowledgements

- All HIV-infected individuals participating in the Swiss HIV Cohort Study
- Manuel Battegay
- The members of the Swiss HIV Cohort Study are:

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