

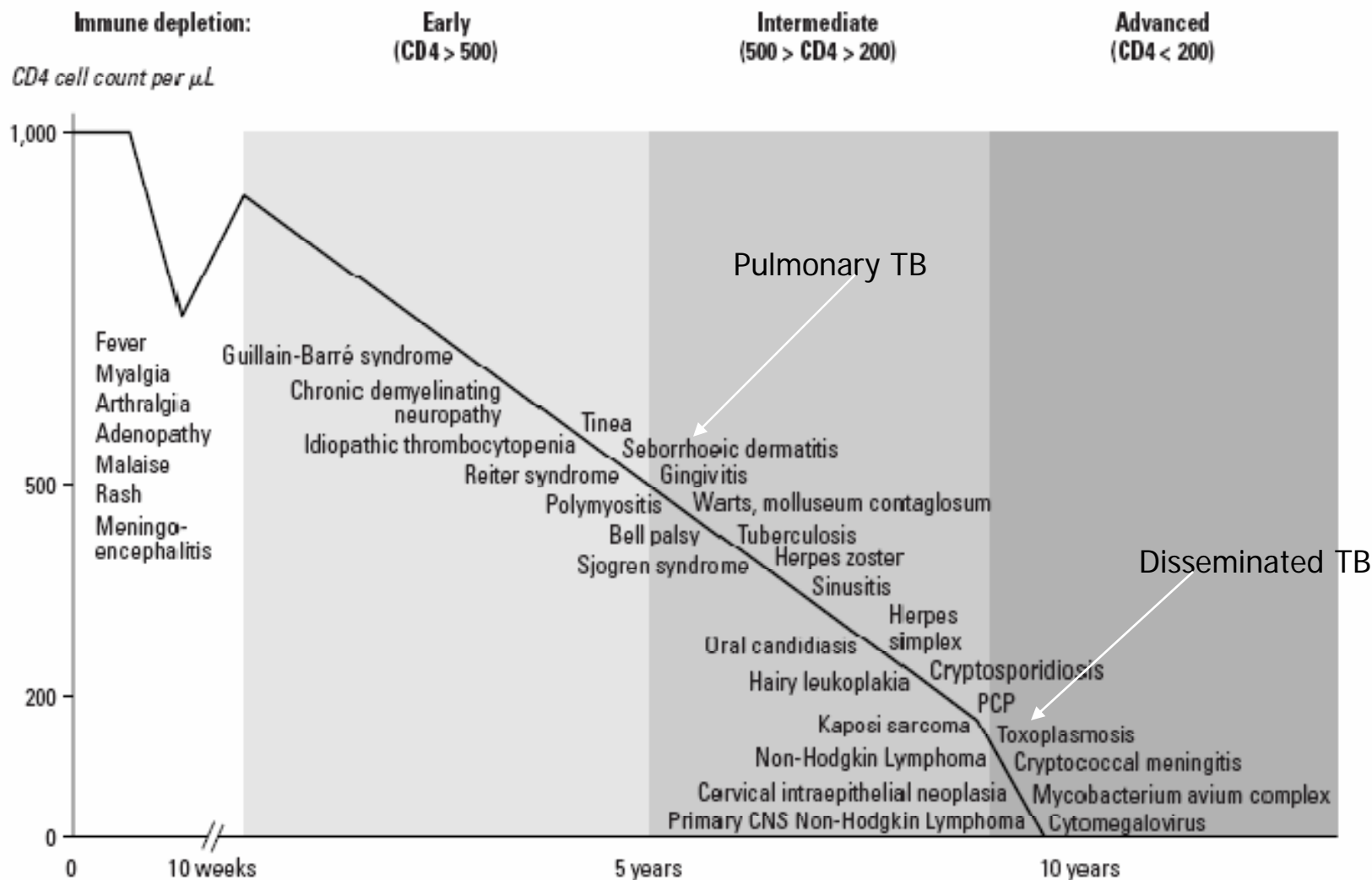
Using IGRA in the diagnosis of Tuberculosis or Latent Infection in HIV positive

Dubrovnik May 2009

Pernille Ravn, University of Copenhagen, Herlev,
Denmark, pravn@dadlnet.

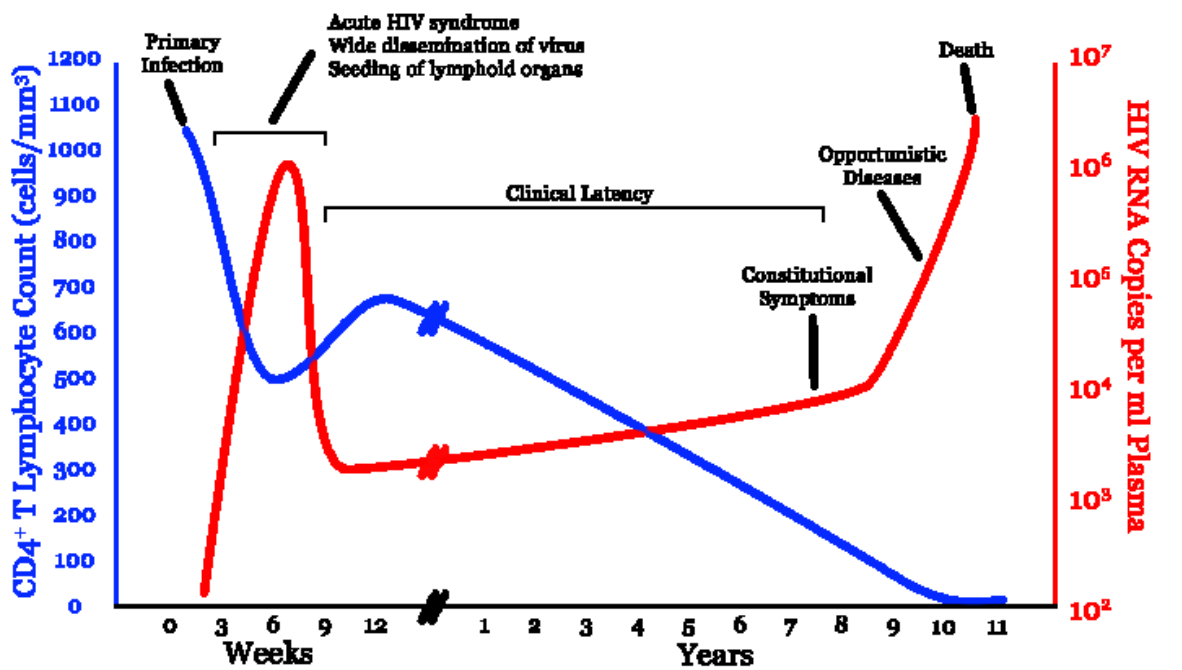
Conflict: I have served as consultant for Cellestis in 2006 (2000Euros)
University of Copenhagen has filed a patent application on IP-10



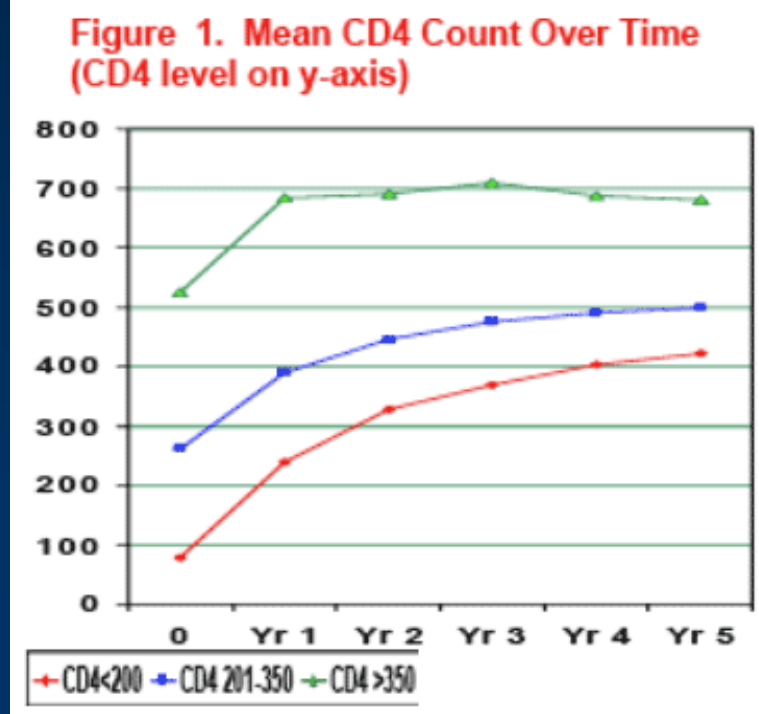


Source: Authors.

Figure 18.1 Cascade of Infections and Cancers That Develop as Immune Function Is Depleted



Natural history of HIV
and effect of HAART



Challenge 1

1: To diagnose patients with active TB

The test should have:

High sensitivity

High specificity

Discriminate between active and latent TB

Assessing IGRA in HIV positive

Aabye 2009	Luetkemeyer 2007
Aichelburg 2009	Lahey 2009
Balcells 2007	Mandelakas 2007
Brock 2006	Markova 2009
Chapman 2002	Pathan 2001
Clarck 2007	Piana 2006
Davies 2009	Raby 2009
Ferrera 2006	Rangaka 2006
Garfein 2009	Richeldi 2006
Geldmacher 2008	Stephan 2008
Hill 2007	Tsiouris 2006
Jones 2007	Talati 2009
Karam 2008	Vinceneti 2007
	+++++

New knowledge and circumstantial evidence

Effect of HIV infection on IFN- γ response in active TB

IU/ml	HIV + N=21	HIV- N=15
ESAT-6/ CFP10	1.05	7.47*
Mitogen	4.23	5.91

Median IFN- γ release after antigen stimulation

Effect of HIV infection on sensitivity of QFT-IT response in active TB

HIV + 81% (17/21)

HIV - 73% (11/15)

- Sensitivity was not impaired significantly

Limitations:

- Indeterminate were excluded
- CD4 cell count not available
- Low n

Performance of QFT-IT in HIV+/- TB pt.

Culture + Median CD4	All (n=161)	HIV (n=93) 519 (317-778)	HIV+(n=63) 272 (172-478)
Pos (%)	74	81	65*
Neg (%)	12	11	13
Indet (%)	14	9	22*

Mwanza Tanzania 2006

Aabye et al PloS ONE January 2009

AFB + Median CD4	All (n=96)	HIV – (n=37) 542 (87-1708)	HIV+(n=59) 212 (6-1015)
Pos (%)	74	84	63*
Neg (%)	12	3	20
Indet (%)	14	13	17

ZAMSTAR study Lusaka 2007

Raby et al PloS ONE June 2008

Effect of HIV infection on sensitivity of QFT-IT response in active TB

IFN- γ Assays and HIV Infection

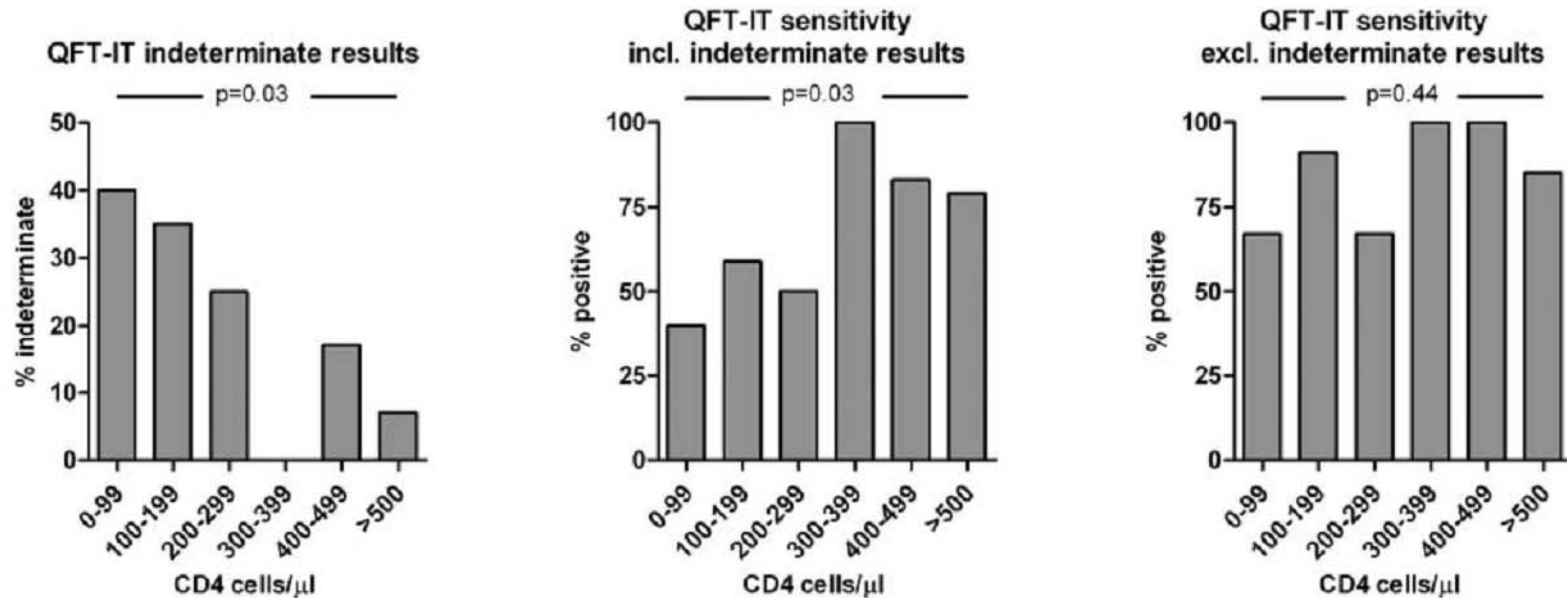
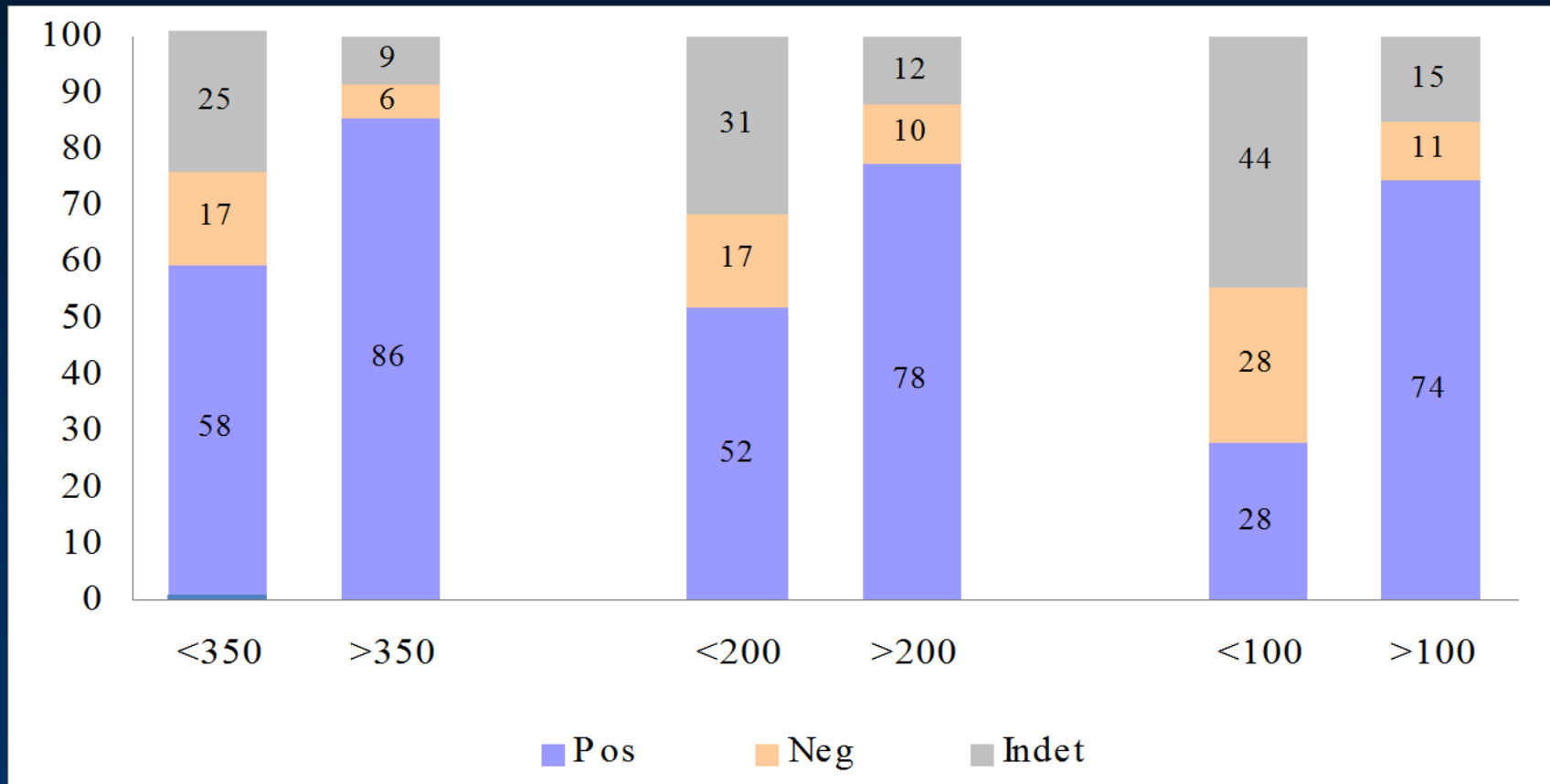


Figure 3. Influence of CD4 cell count on performance of the QuantiFERON-TB[®] Gold In-tube test in HIV-positive patients. For HIV-positive patients the % of indeterminate and positive test responders respectively was grouped by the individual number of CD4 cells/ μ l. P-values are for Cochran-Armitage test for trend. A similar relationship was not found in HIV-negative patients. The number of patients in each CD4 cell group was: 0-99: 5, 100-199: 17, 200-299: 20, 300-399:6, 400-499:6, >500:14. QFT-IT: QuantiFERON-TB[®] Gold In-tube test.

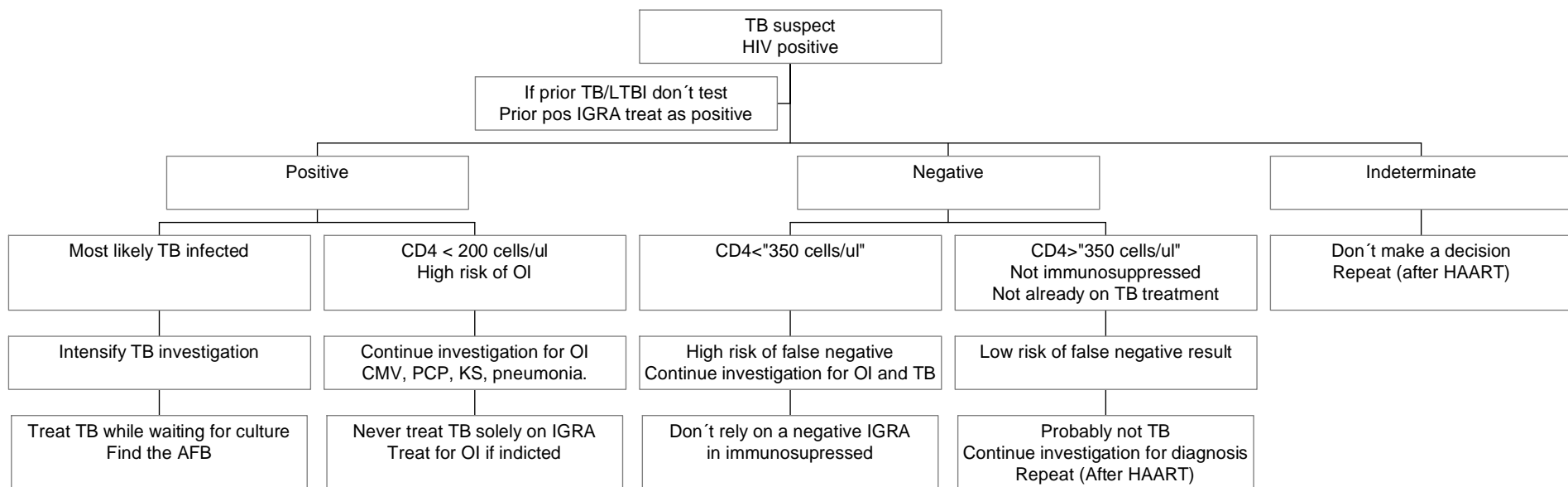
doi:10.1371/journal.pone.0004220.g003

Influence of CD4 cell count on QFT-IT performance



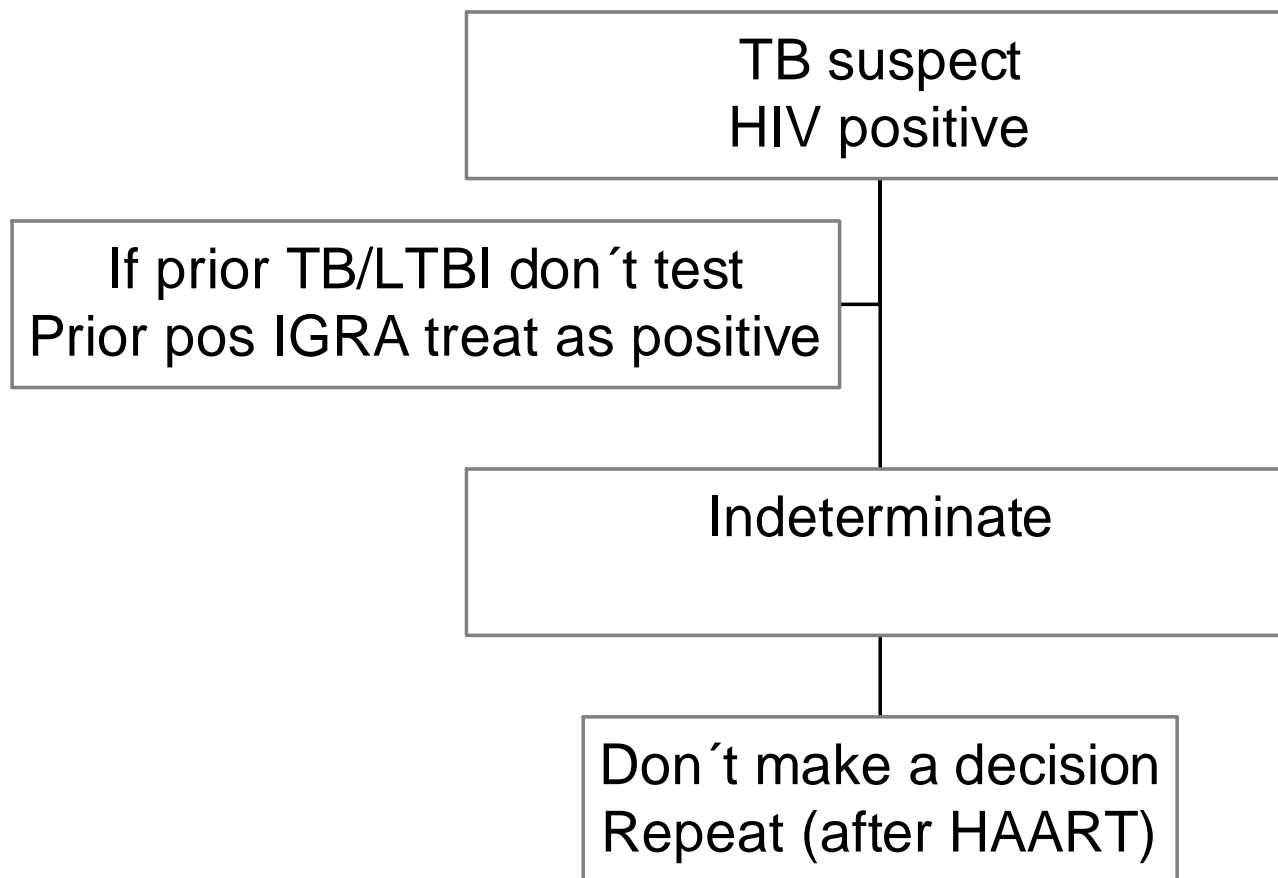
1st draft of a proposal for how to use IGRA in HIV positive

Comments to pravn@dadlnet.dk

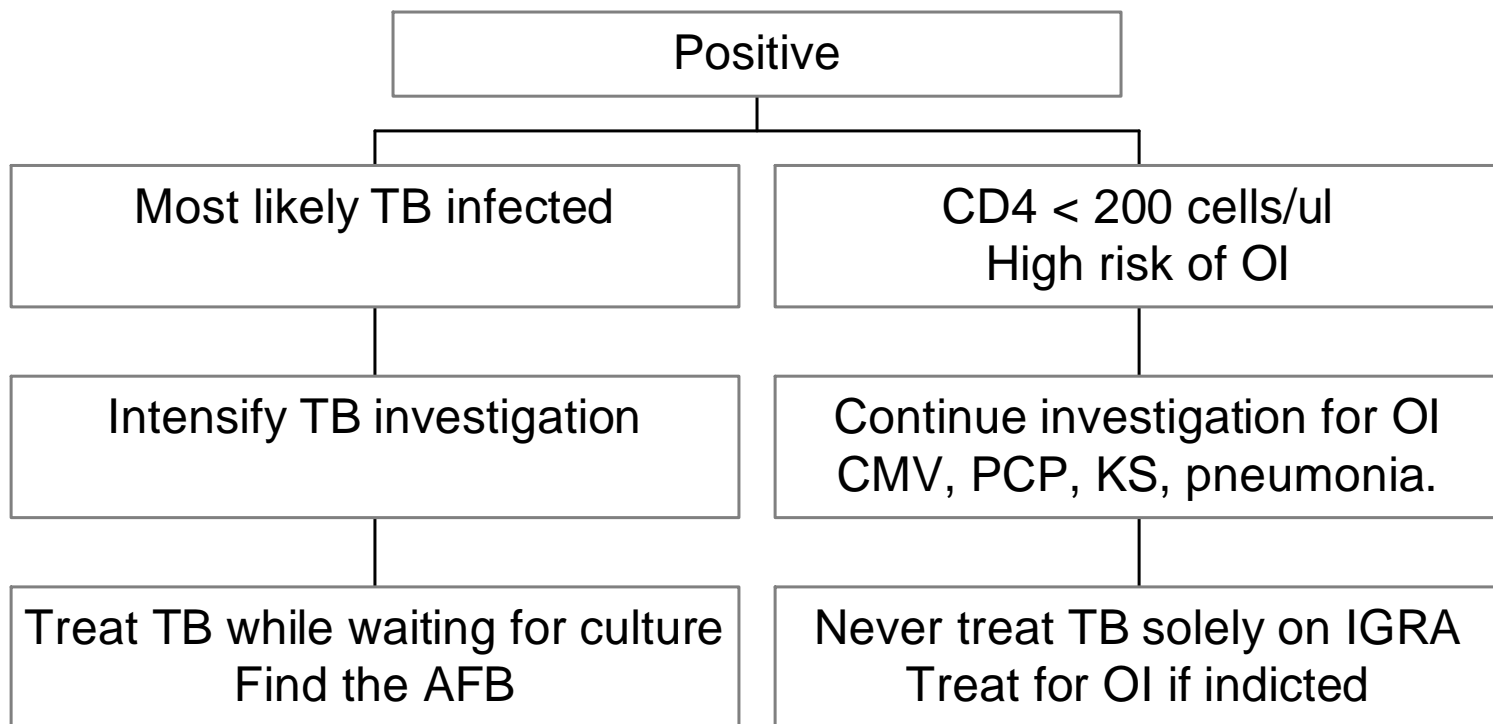


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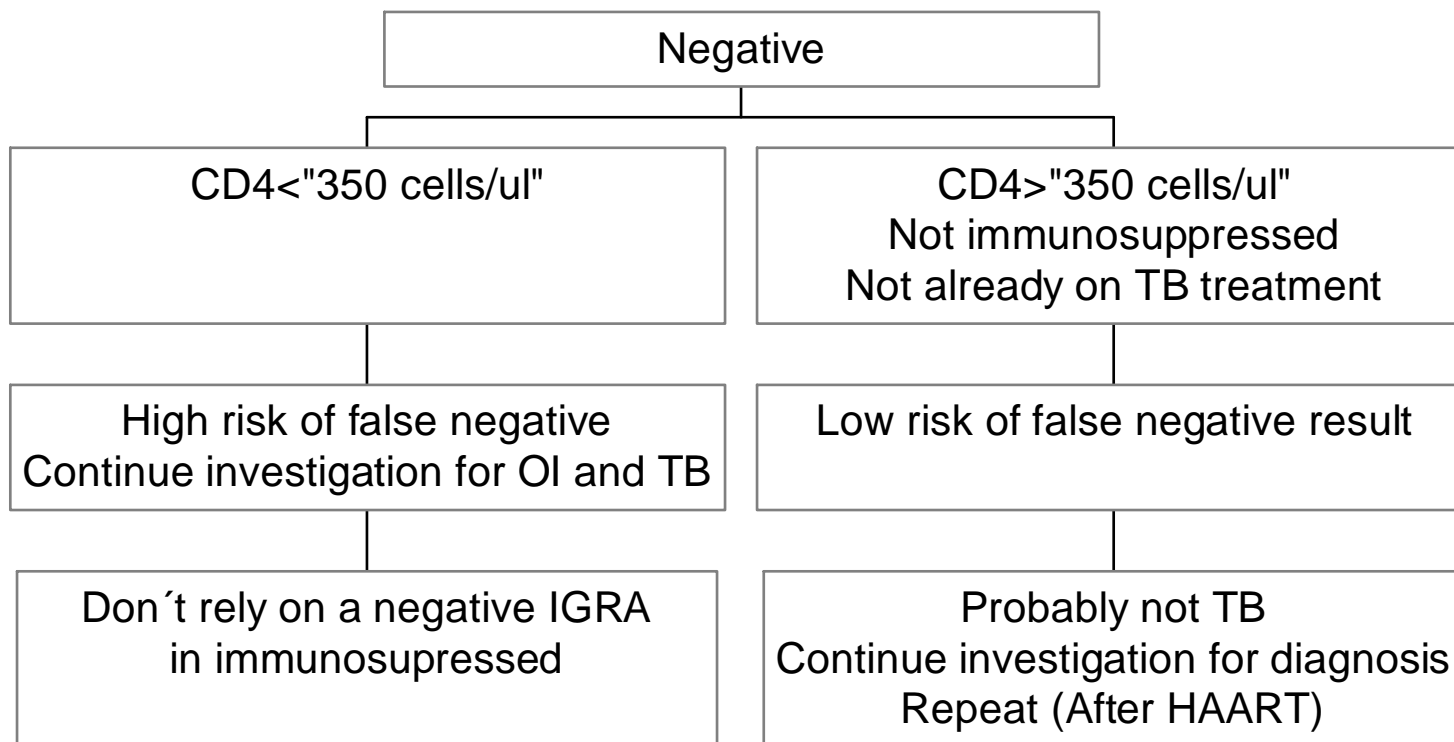
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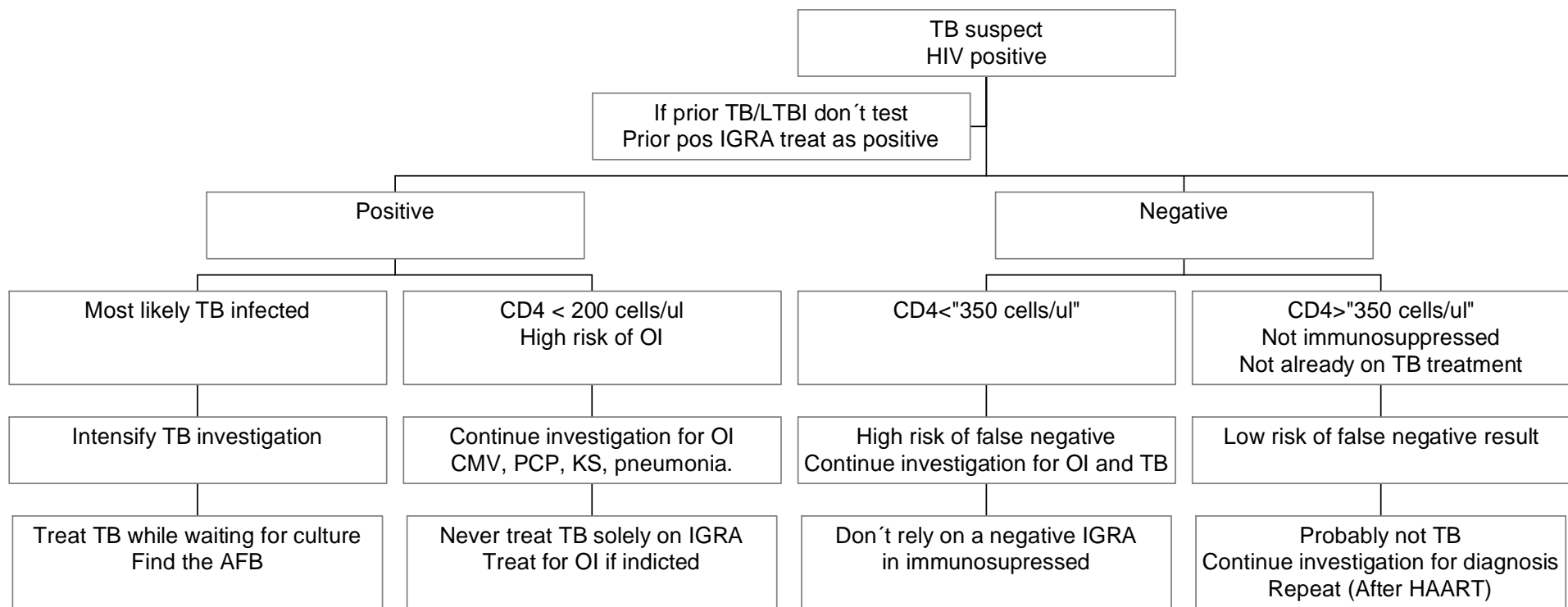


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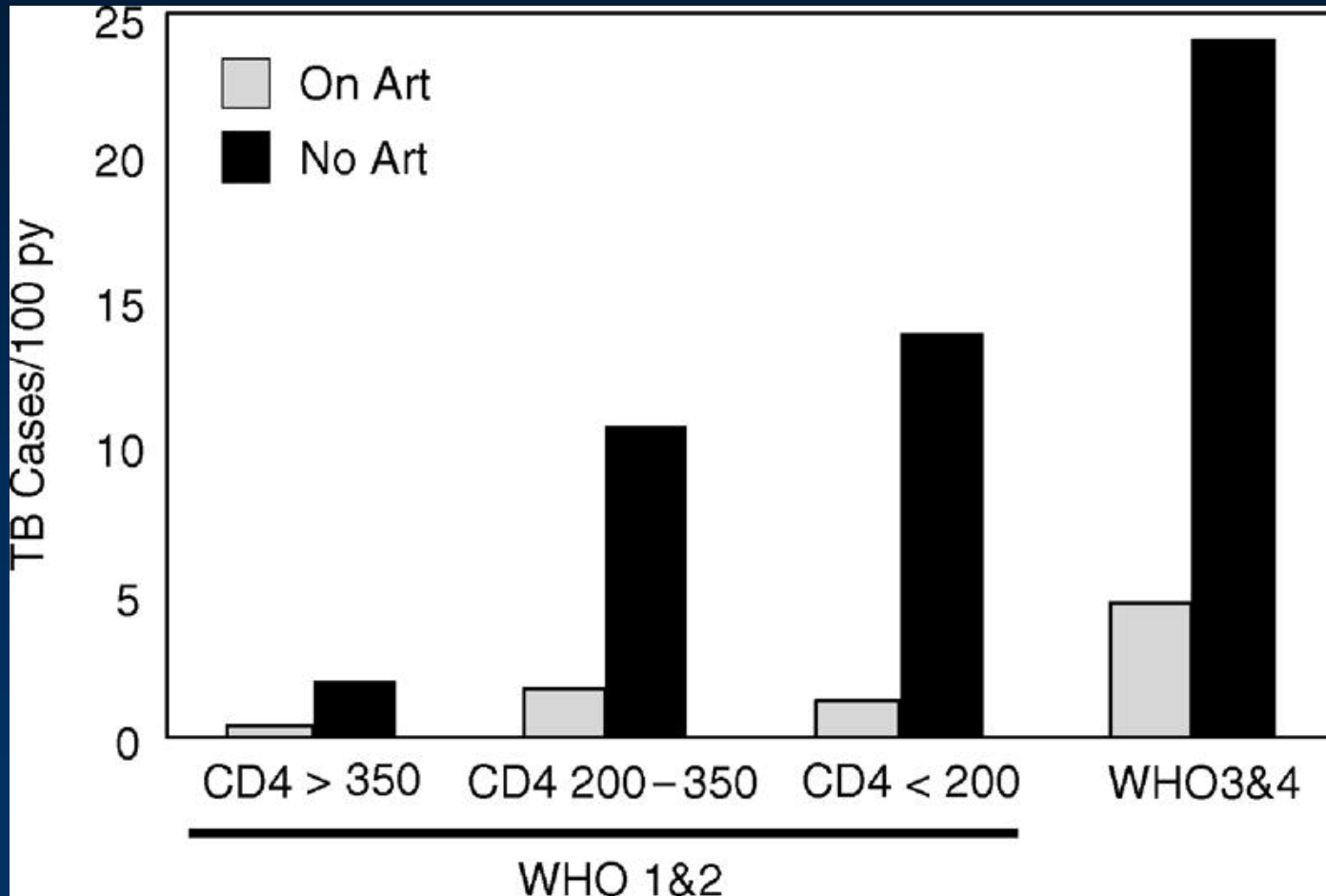


Challenge 2

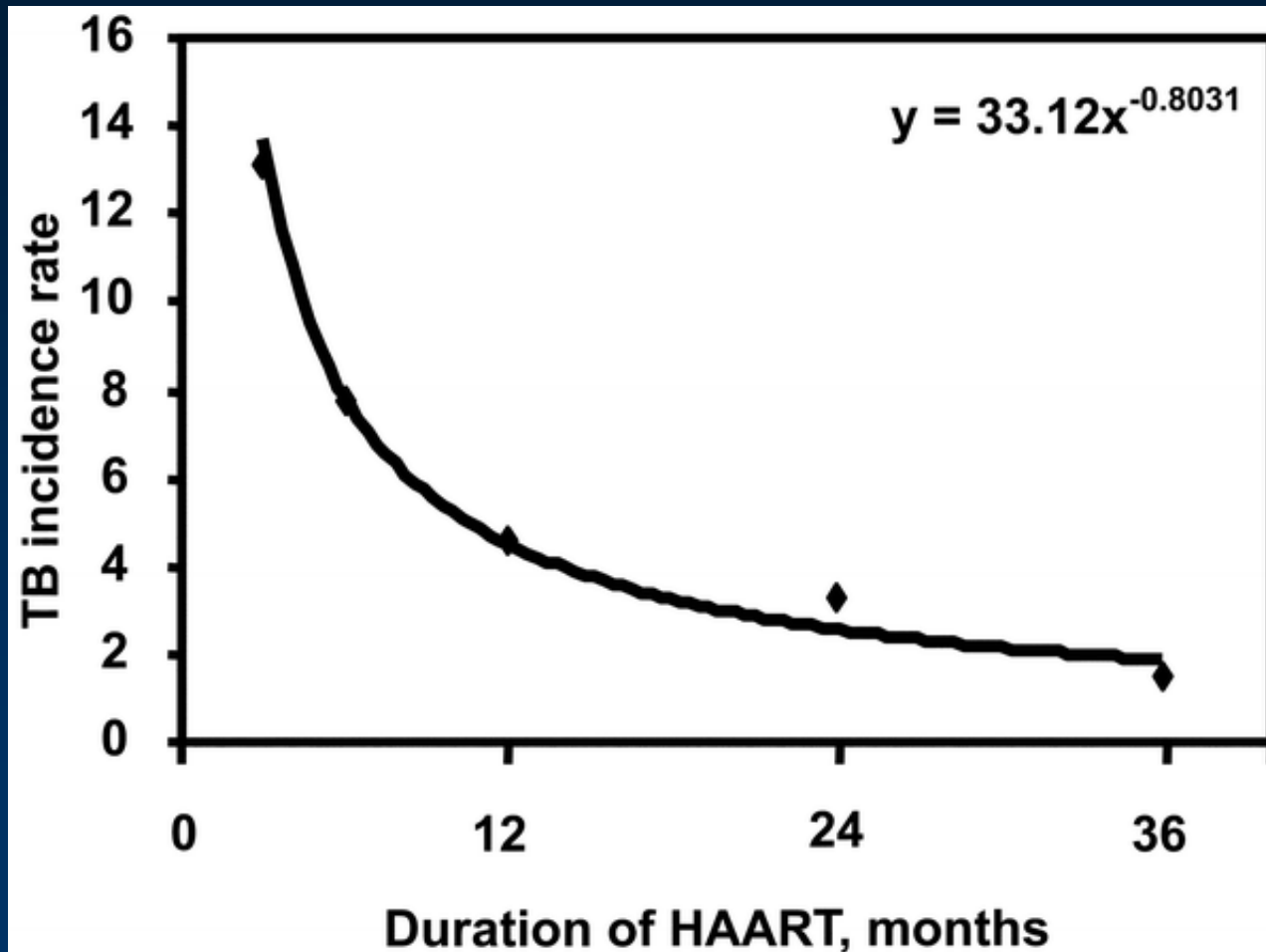
- To prevent new cases of TB in HIV positive individuals



HAART is the best prevention of TB in HIV



Declining TB incidence during the first 3 years of HAART (per 1000 PYFU)



Challenge for the test

Identify those at risk of progression

High sensitivity (NPV)

Safe rule out test in risk group
(HIV, TNF-a treated, children)

High specificity (PPV)

Reduce NNT

Limited number of prognostic studies

Doherty 2002,

(Higuchi 2007)

Diel 2008

Philip Hill 2008

Bakir 2008

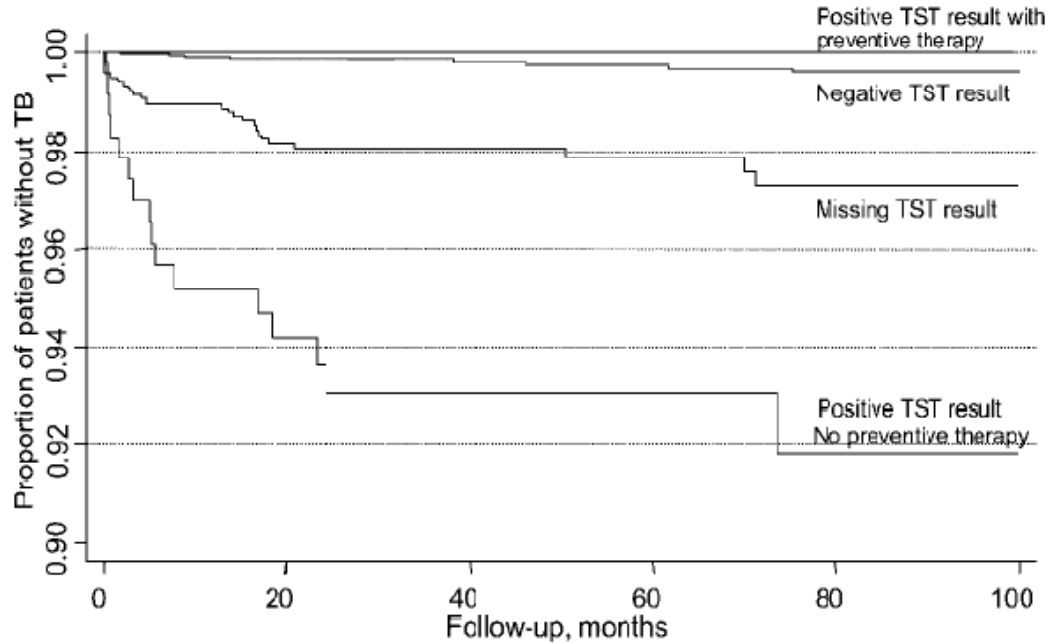
Aichelburg 2009: cohorte 830 HIV positive, Austria

8.6% healthy QFT-IT positive developed TB

Very high NPV 0/736 TB cases in QFT-IT negative

Preventive effect of TST screening and chemoprophylaxis

B



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

NNT = 15

Impact of CD4 cell count on TST results in HIV positive

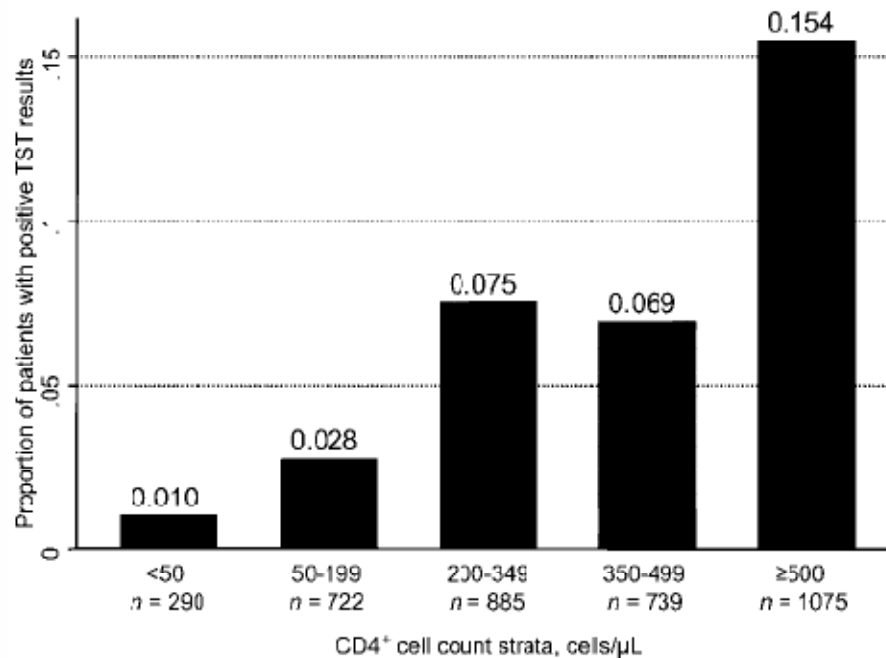


Figure 1. Proportion of patients with positive tuberculin skin test (TST) results according to CD4⁺ cell count stratum at the time of TST ($P < .001$ for trend statistics).

Total: 9,4% TST pos

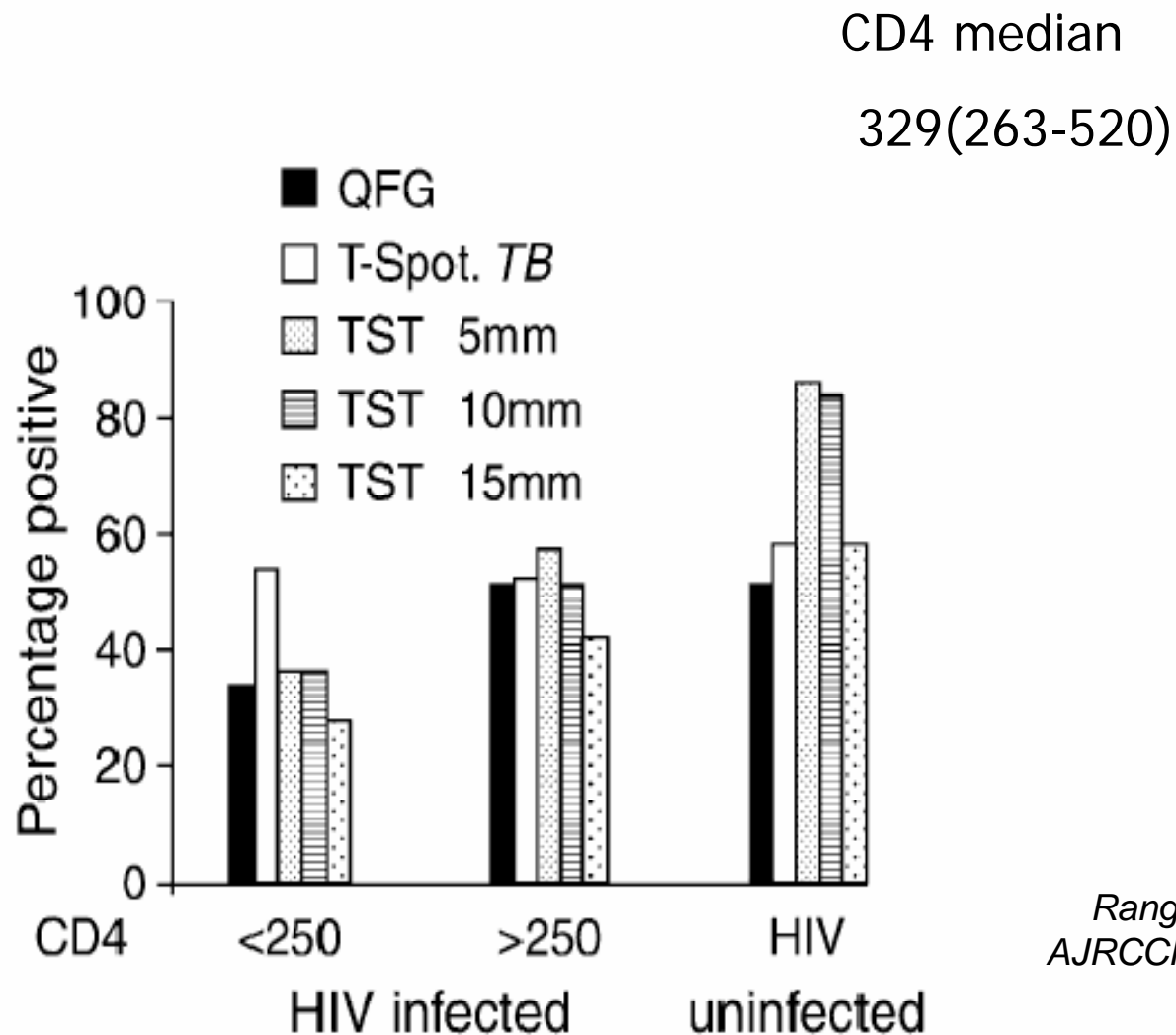
62% (16/26) of those who developed active TB were TST positive

*Elzi et al, CID
2007, 44:94-102*

Sensitivity of IGRA for LTBI is not affected by HIV infection in healthy

	HIV+ N=74	HIV- N=86	
TST	%	%	P=
5 mm	52	86	0.001
10 mm	49	83	0.01
15 mm	37	58	0.01
T-SPOT	52	59	0.41
QFT-IT	43	46	0.89

TST but not IGRA was affected by low CD4 cell count



Rangaka,
AJRCCM, 2007

Impact of CD4 cell count on TST and ELISPOT results in HIV positive

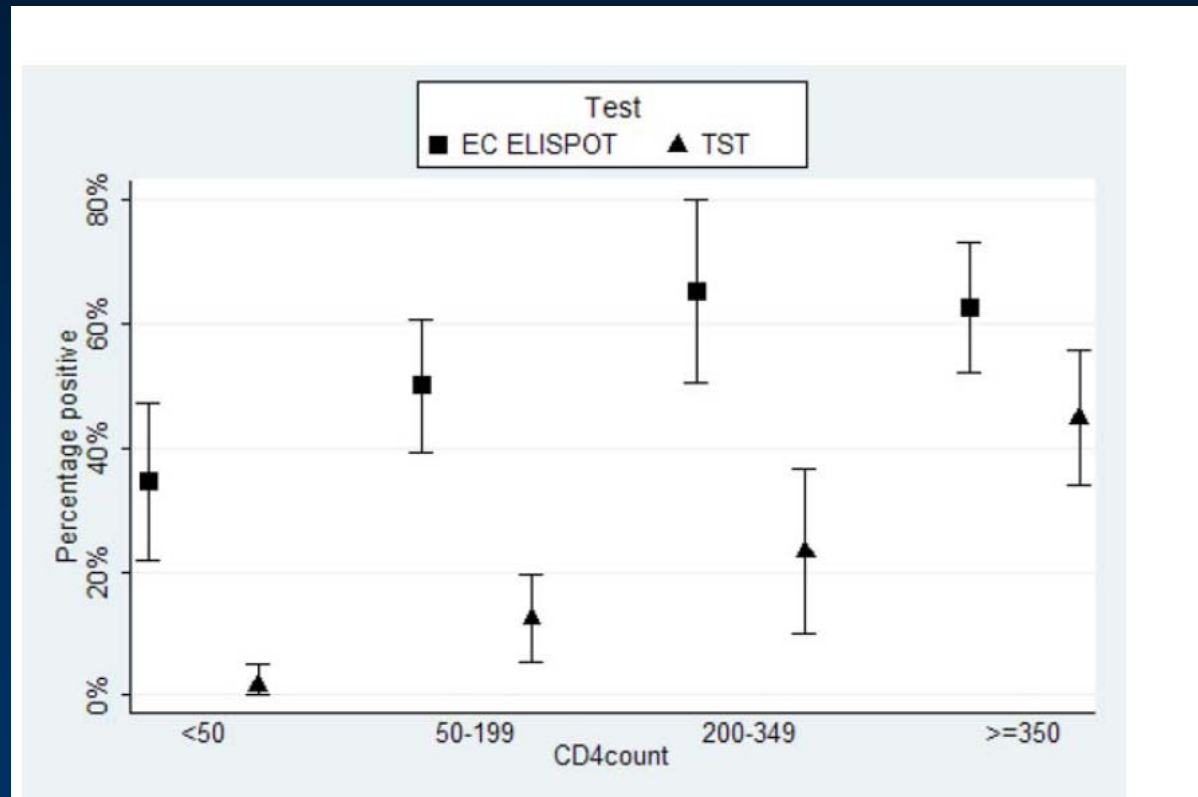
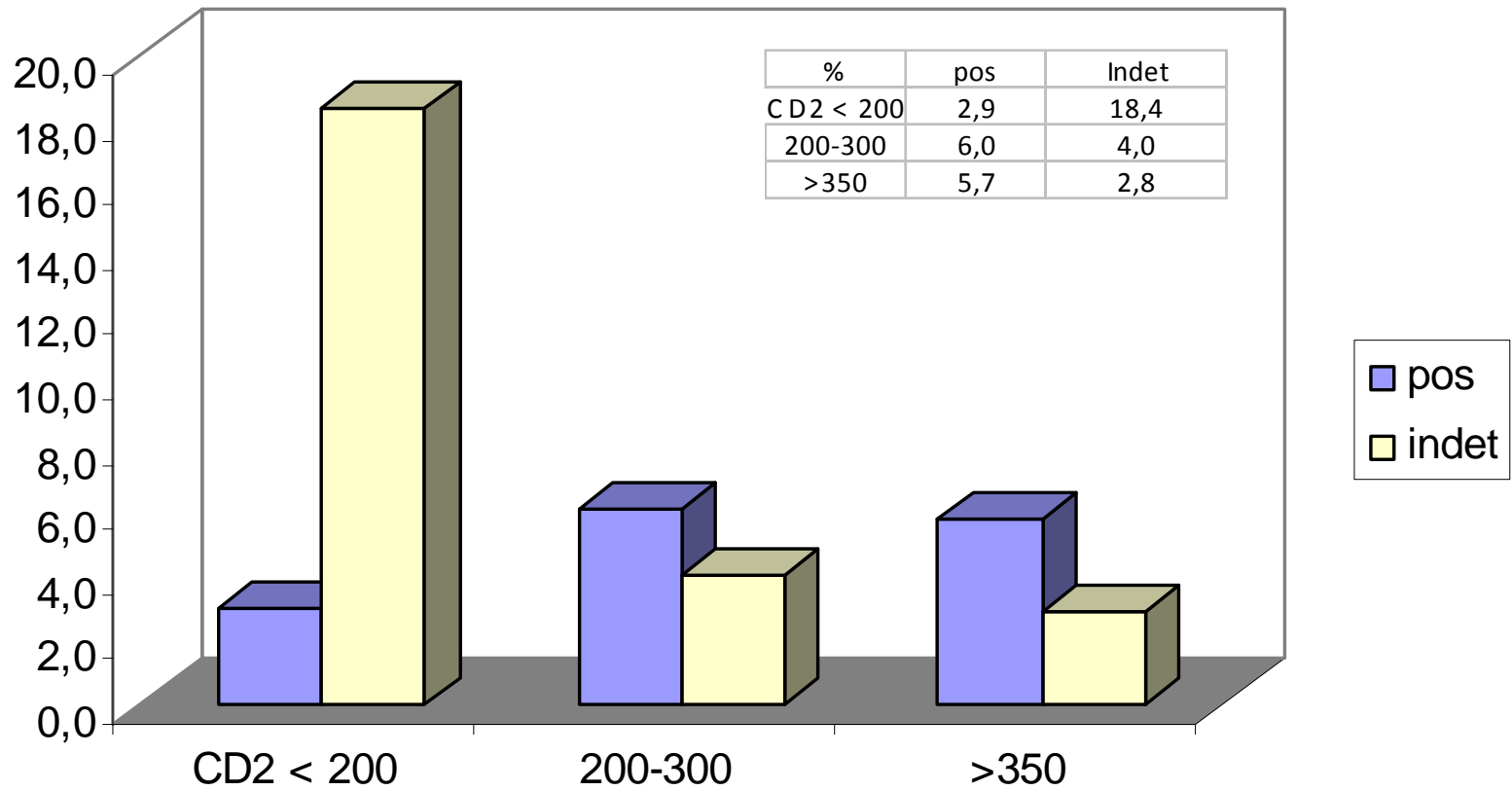


Figure 2. Percentage of positive responders to ESAT6/CFP10 ELISPOT and to TST, by CD4 cell count (n=247). doi:10.1371/journal.pone.0001441.g002

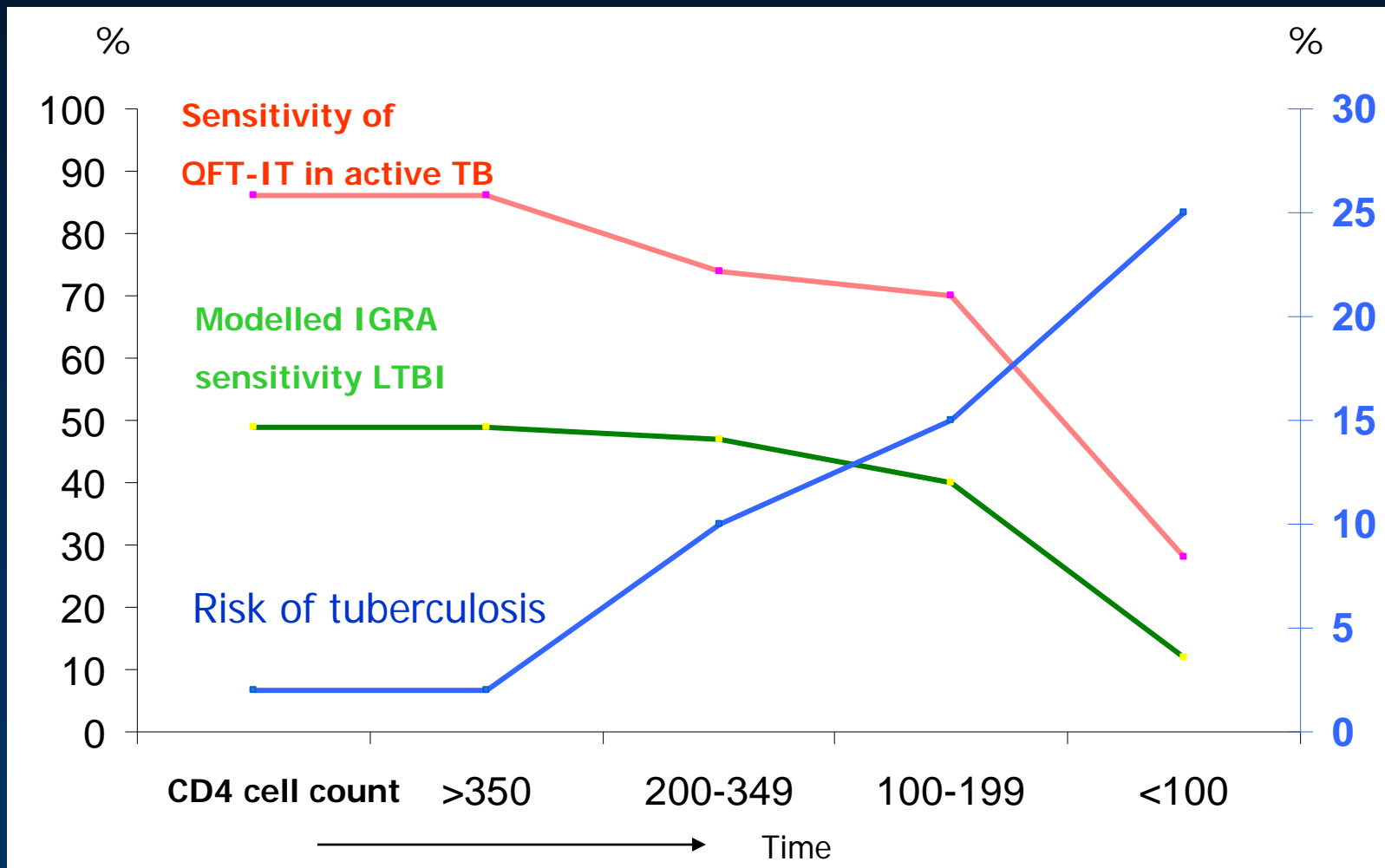
the proportion of positive responses to the EC ELISPOT assay decreased with decreasing CD4 counts (test for trend: $p = 0.0012$)

Impact of CD4 cell count on QFT-IT results in HIV positive



data from Aichelburg 2009

When to use IGRA in HIV infected

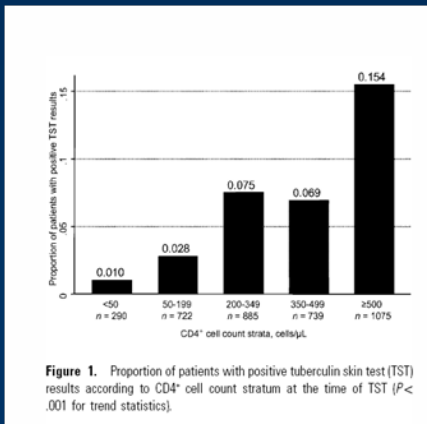


Modified from Aabye 2009, Raby 2008, Lawn 2006

Yet unsolved questions

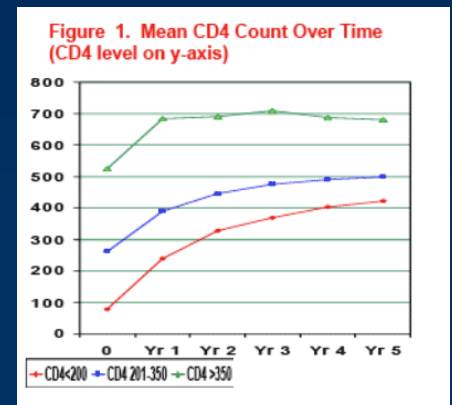
- We don't know

- If MTB specific immunity reconstitute completely during ARV ?
 - > HIV positive with low nadir CD4 cell count may have lost their antigen specific T cells
- If acute HIV is detrimental for MTB specific memory immunity

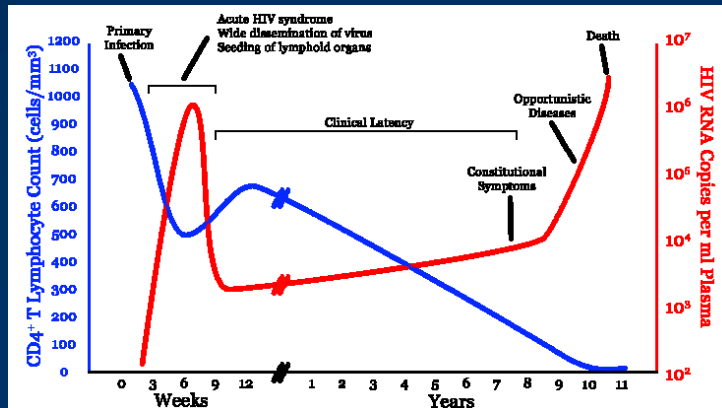
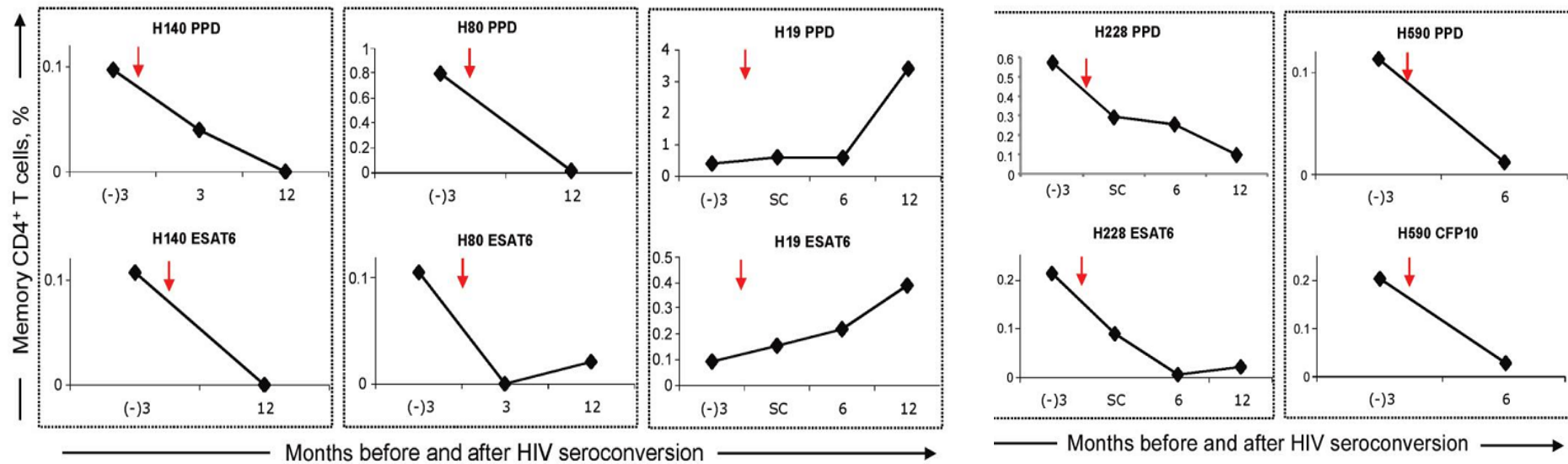


Impaired TST response in HIV pos
with low nadir CD4 cell count

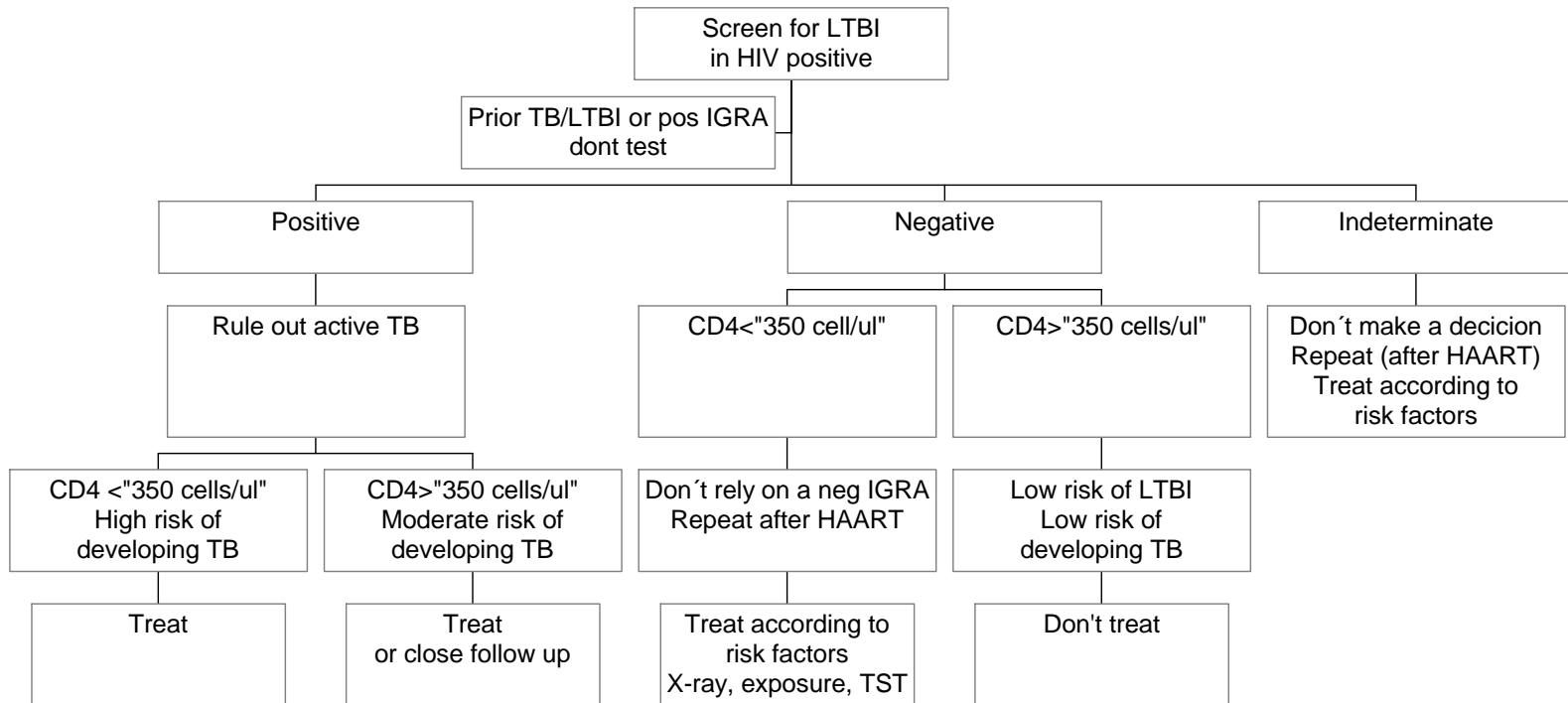
*Elzi et al, CID
2007, 44;94-102*



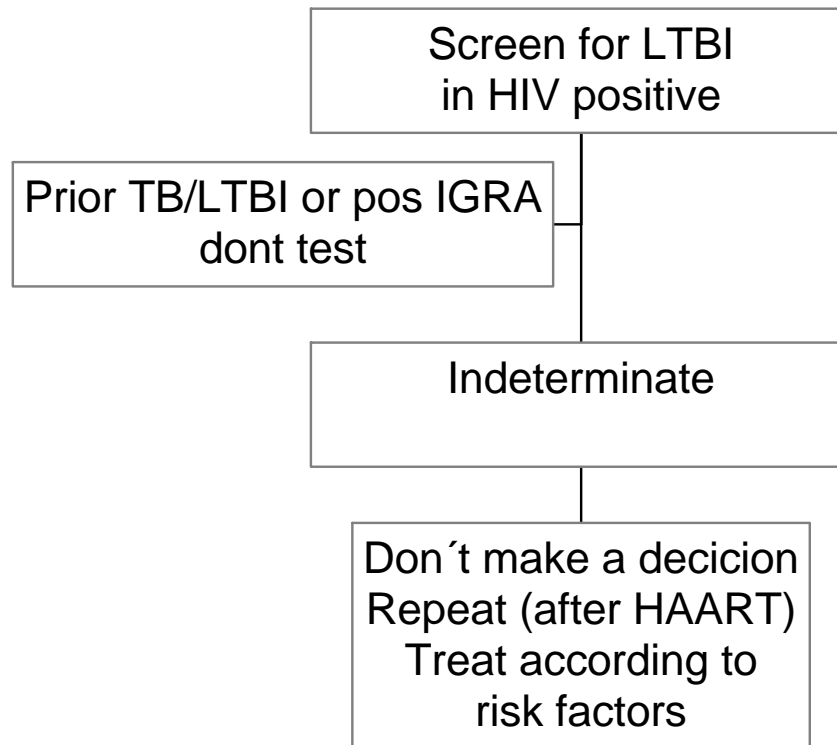
Depletion of *M. tuberculosis* specific memory CD4 cells during acute HIV infection



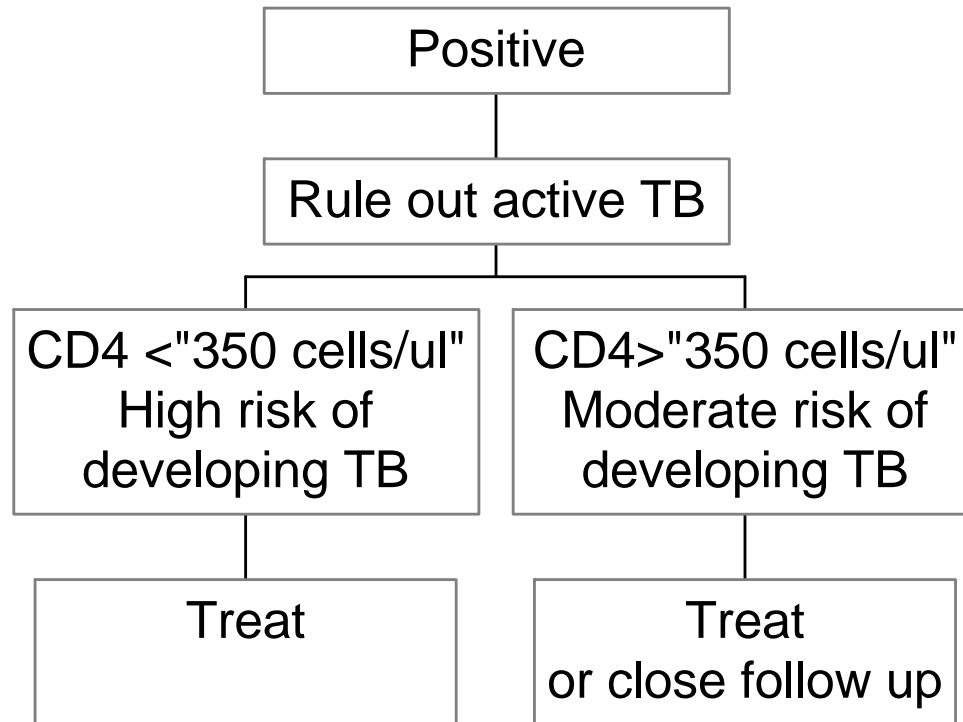
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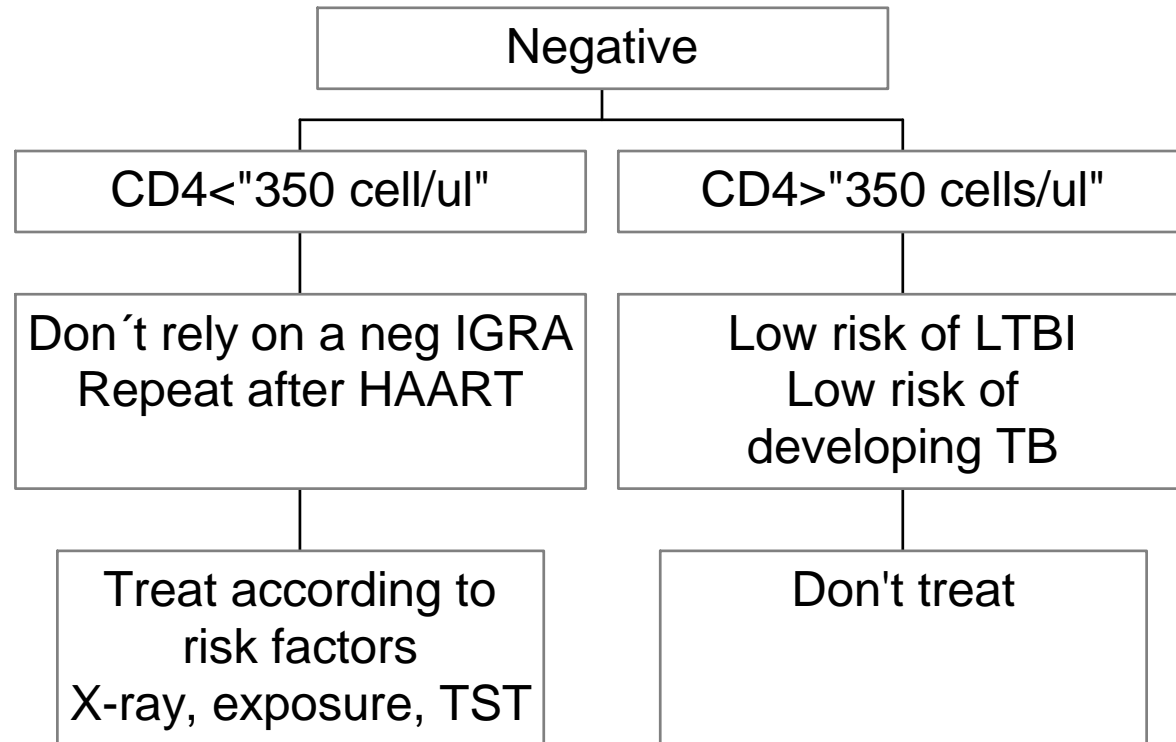
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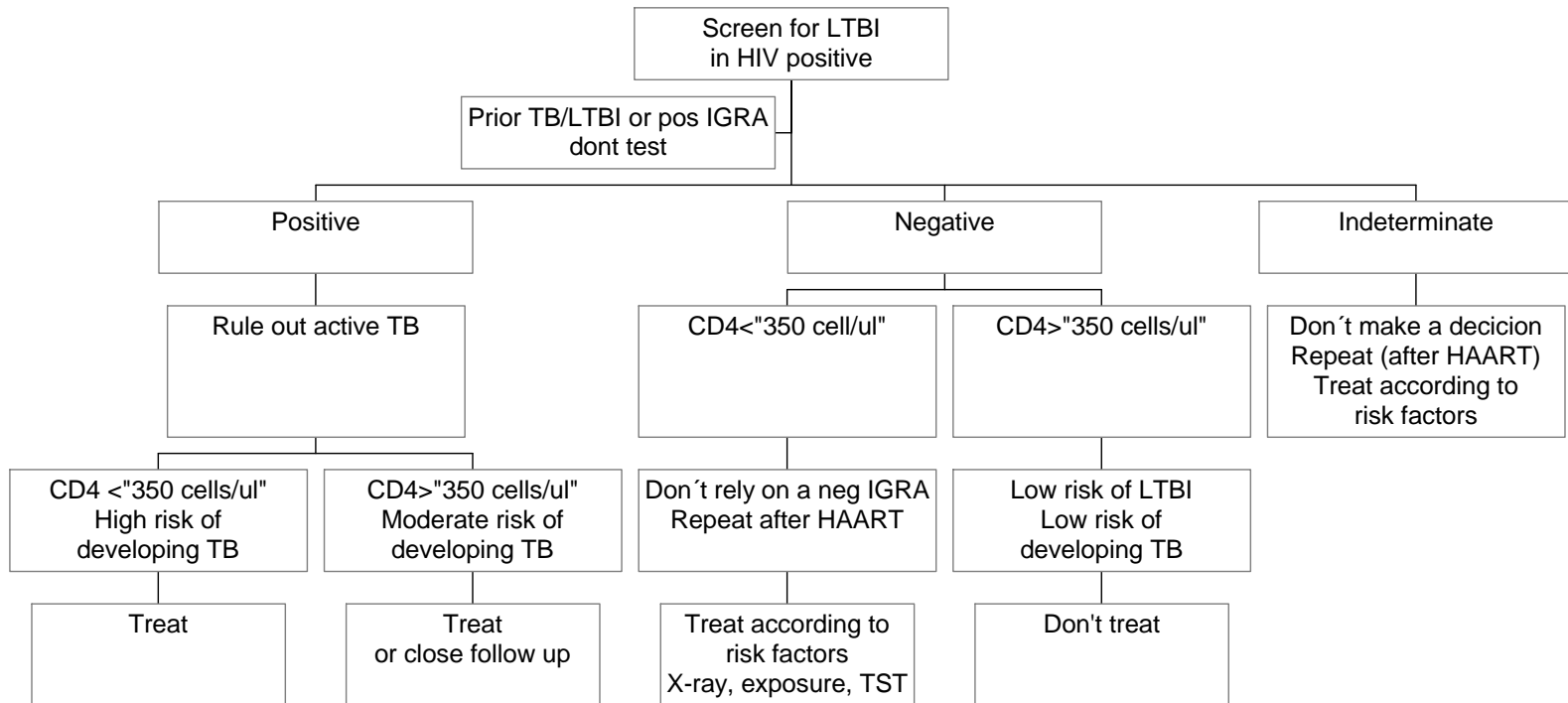
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Limitations

- Culture or AFB pos TB is easy to diagnose
- The difficult cases are AFB negative
- No marker for LTBI, thus we don't know the true sensitivity in healthy HIV +

IGRA in HIV HIV positive

Contra	Pro
<p>Reduced sensitivity in HIV+</p> <p>More indeterminate</p> <p>Inverse relation between indet/ false negative and CD4 cell count</p> <p>Not a general rule out test (35-39% false neg)</p> <p>Does not discriminate between active and LTBI</p>	<p>Superior sensitivity in HIV positive compared to TST</p> <p>Pt with CD4 >350 cells/ul have performance comparable to HIV negative</p> <p>1/3 of the severely immuno-compromised patients have a positive IGRA response</p>

Unsolved issues

What is the added value in a clinical setting ? :

correctly diagnosed patients and prevented new cases

Are the differences between QFT-IT and T-SPOT clinically relevant?

Will we ever have a test that can discriminate between active and latent TB?

Do we know enough about the impact of HIV on IGRA performance?

Will we be able to improve the sensitivity in immunocompromised: individual cut points, additional biomarkers?

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