How latent is latent tuberculosis?

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Mechanisms behind chronic infections
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TB in Khayelitsha, South Africa

- Population: 391,749
- Antenatal HIV prevalence: ~ 30%
- TB incidence ~1267/100,000 (i.e. > 1 % per annum)
- ~67% TB is HIV associated
- ~ 6000 cases per year
- ~ 20% deaths due to TB

Cox *et al. PLoS One* (2010) **e13901**

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SOUTH AFRICA

Diagnosis of latent tuberculosis

T-SPOT.TB

Oxford Immunotec
Harnessing the power of T cell measurement

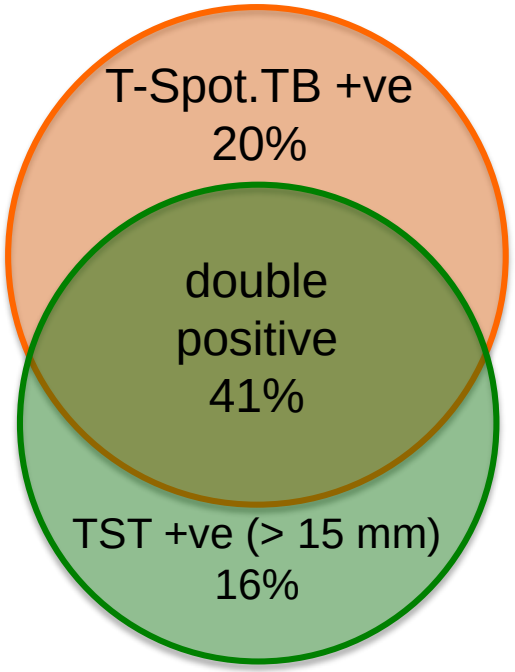
Products & Services

'A 21st Century Solution for Latent TB Detection'

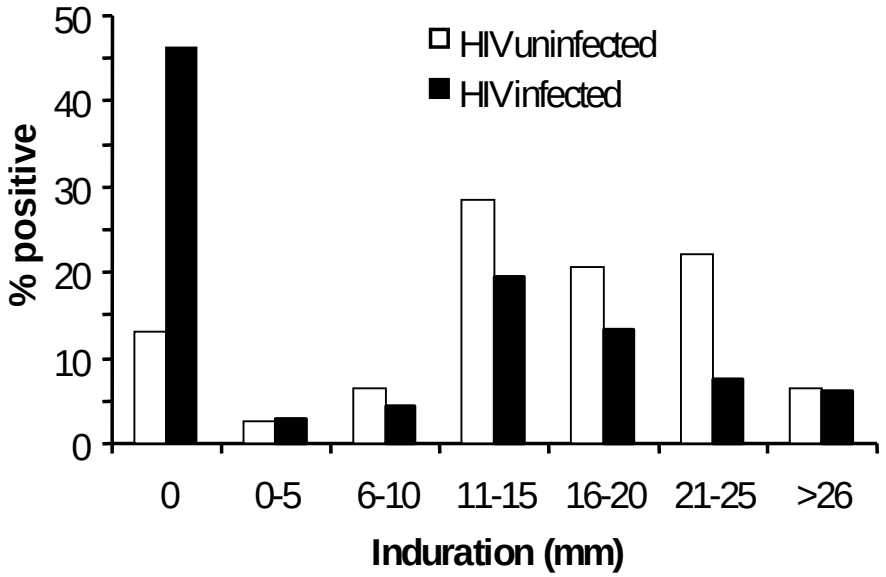
QuantiFERON®-TB Gold.
One blood test, One clear answer

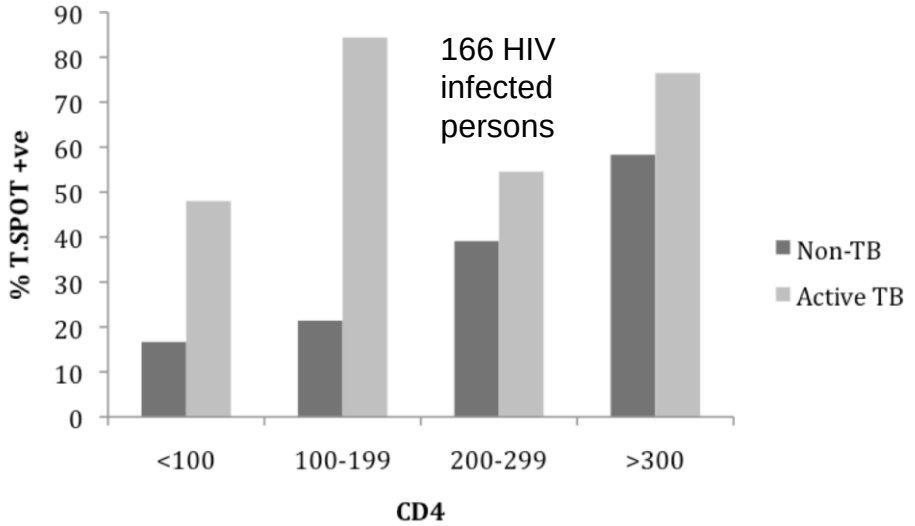
Latent TB is near universal in Khayelitsha but its ascertainment is impaired by HIV-1 infection

HIV uninfected persons



double negative 23%





Rangaka, MX, *et al.* **(**2007) *AJRCCM* **175:**514

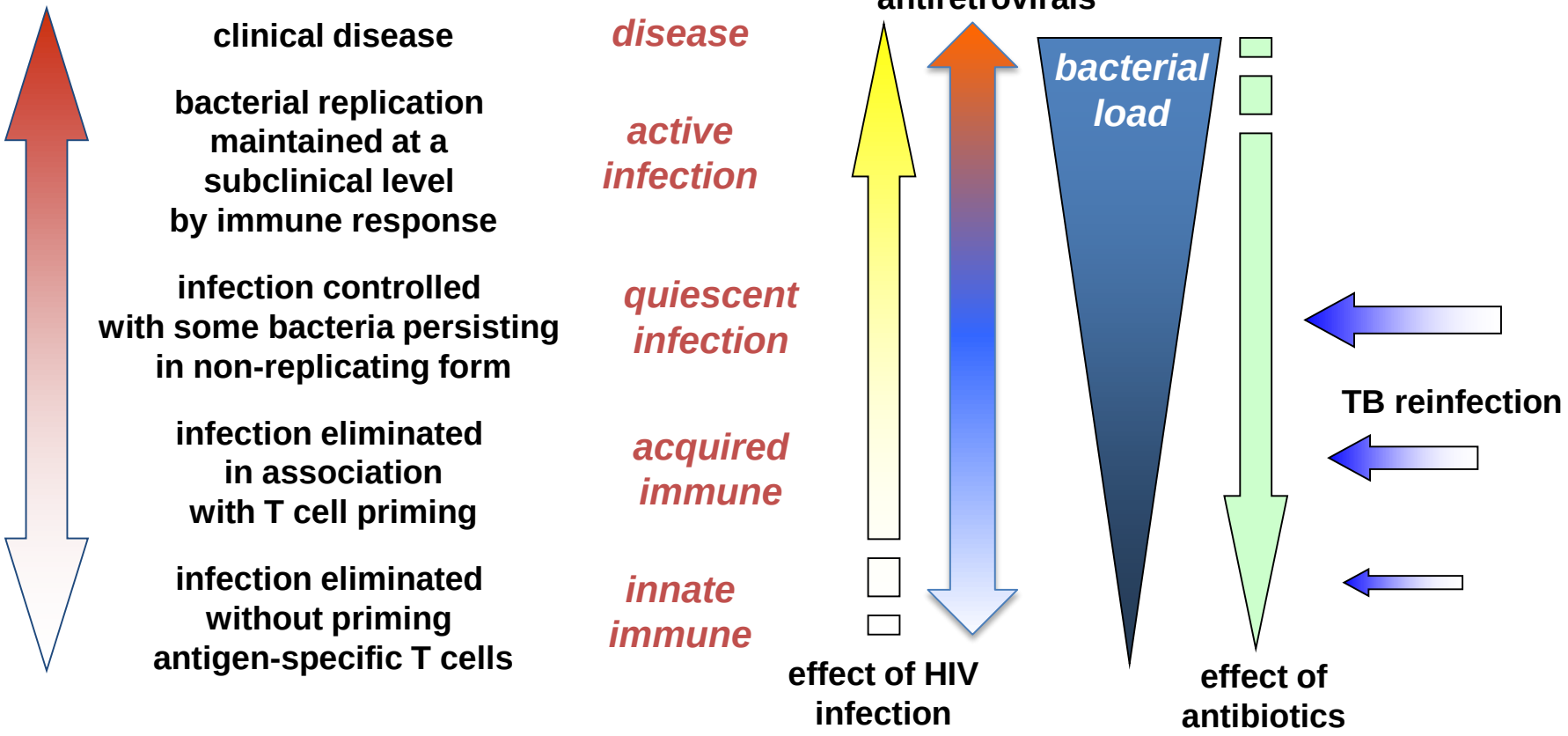
Oni, T *et al.* (2010) *Eur Resp Journal* **36**:594

When combined with antiretroviral therapy to prevent TB, isoniazid benefit greatest in TST negative

	placebo		isoniazid		HRa (95% CI)
	n	Rate/ 100 PY	n	Rate/ 100 PY	
IGRA					
Negative	261	3.3	274	1.3	0.43* (0.20 - 0.96)
Positive	205	3.9	184	3.0	0.55 (0.26 - 1.24)
TST					
Negative	283	4.1	269	1.7	0.43* (0.21 - 0.86)
Positive	202	2.8	190	2.6	0.86 (0.37 - 2.0)

Rangaka M.X. *et al. Lancet* (2014) **384**: 682

A spectrum of responses to tuberculosis infection



Young D, H Gideon, and R.J Wilkinson *Trends in Microbiology* (2009) **17**: 183-8

Barry 3rd CE, Boshoff H, Dartois V, Dick T, Ehrt S, Flynn J, Schnappinger D, Wilkinson RJ and Young DB *Nature Revs Microbio*l (2009) **7**: 845-855

Esmail H, Barry 3rd CE, Wilkinson RJ *Drug Discov Today* (2012) **17**:514-21

Esmail, HE, Barry 3rd, CE, Young, DB, Wilkinson, RJ *Philosophical Trans Roy Soc London B* (2014) 369: 20130437

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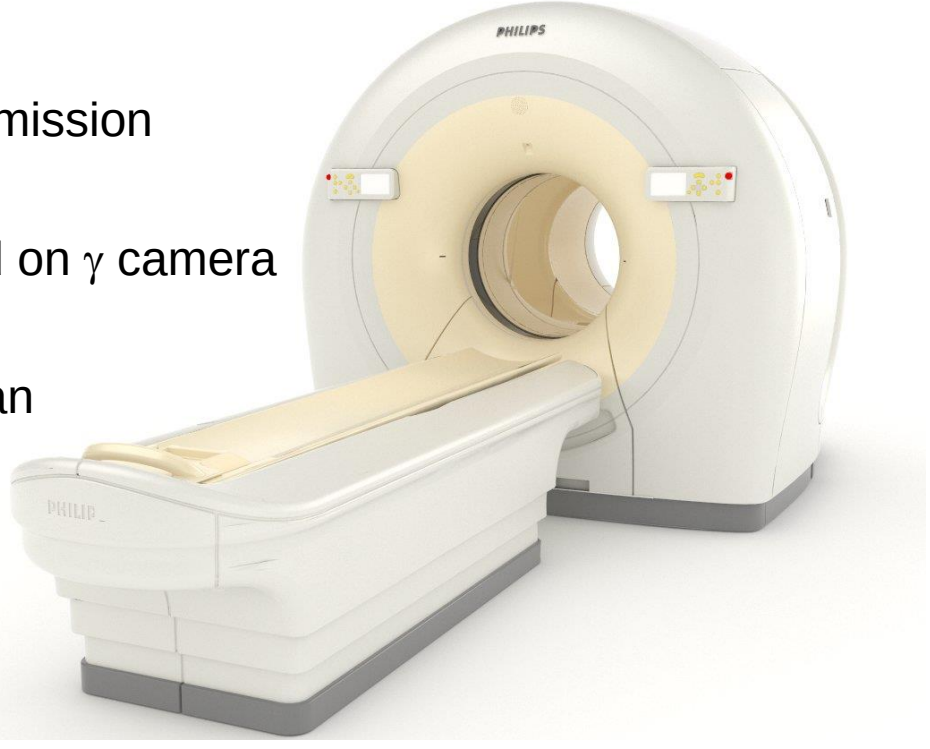
Hypotheses

A spectrum of subclinical pathologies will be observed in healthy HIV-1 infected persons with immune evidence of sensitization by *M. tuberculosis* (‘latent’ TB)

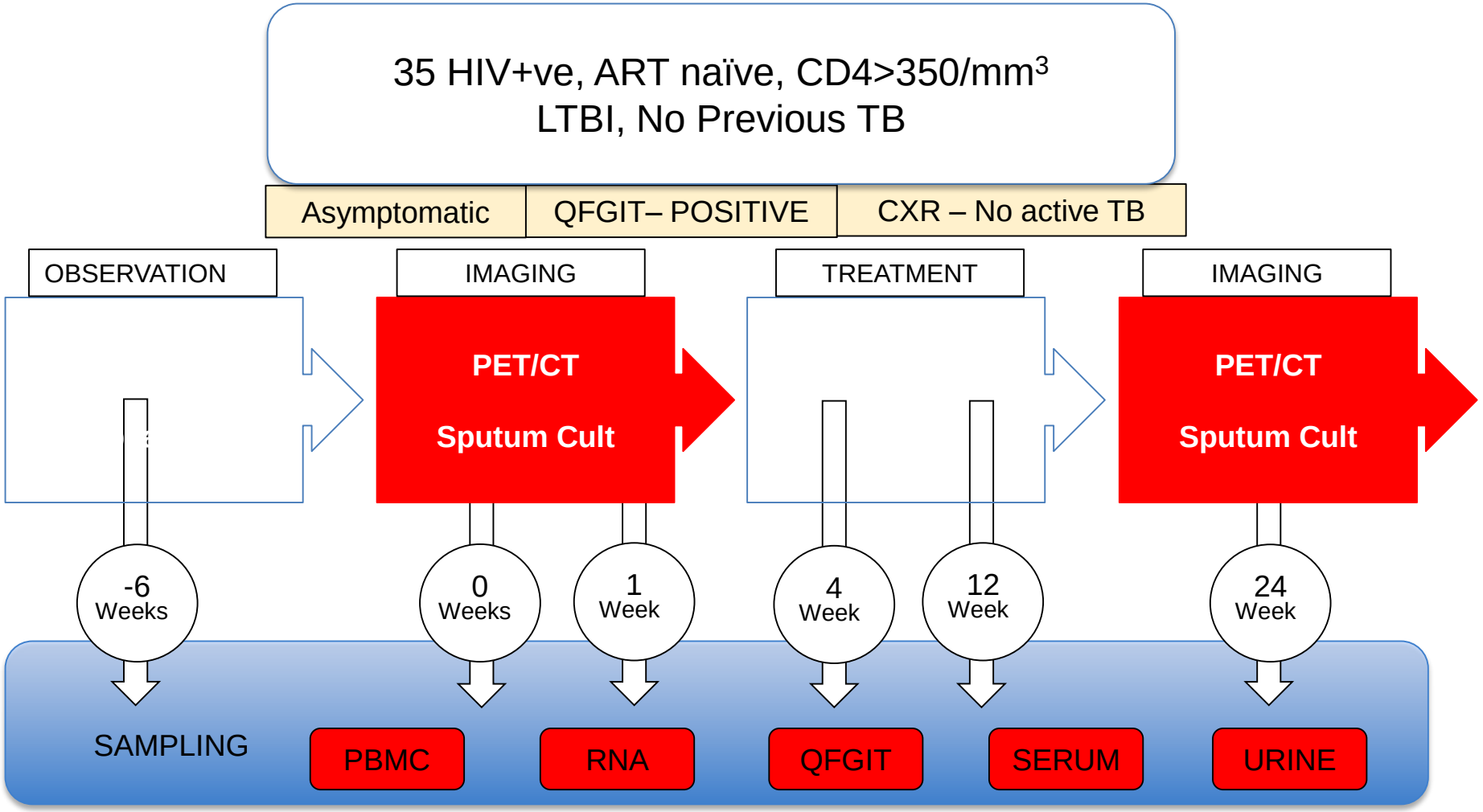
A blood transcriptional signature will characterize subclinical tuberculosis

^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography/computer tomography (FDG-PET/CT)

- PET scanner + CT scanner (hybrid with functional imaging)
- Registration of metabolic activity
  - Uptake into cells through glucose transport proteins
  - Phosphorylation within cell
- The radioisotope undergoes positron emission
- Positron-electron annihilation, recorded on γ camera
- PET images superimposed with CT scan
- 3D rendering



Study schema



CONTROLS – Age/Sex/CD4 matched active HIV-TB

Esmail, H *et al.* unpublished

PET/CT findings (n=30): Lymph nodes abnormalities

Reporting period 01 Mar-31 Oct 2015

Lymph nodes

19 (63%) HHC with lymphadenopathy

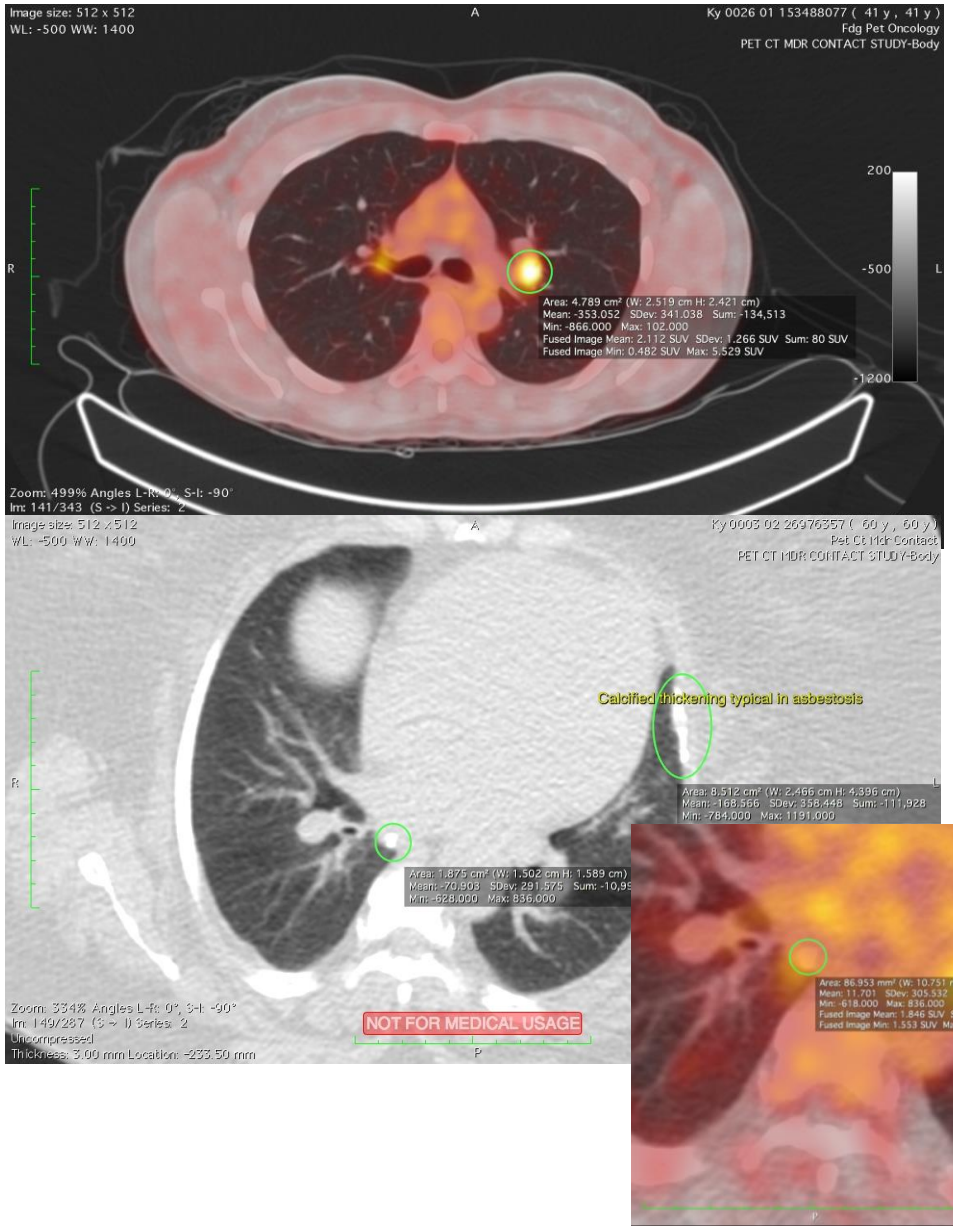
Size 2 to 21 mm
<1 cm LAD: 15/19 (79%) HHC

Calcification of LN 10/19 (52%)

SUVmax 1.0 to 6.14
SUVmax >2.5: 6/19 (32%) HHC

Other findings in LAD
SUVmax>2.5 (n=6):

None	1
Nodules	1
Infiltrate + nodules	3
Pleural thickening	1



Conclusions

- Pathology consistent with different aspects of early TB infection can be identified by PET/CT
- A transcriptional profile associates with subclinical HIV-TB: a subset of the active signature
- Network analysis predicts elevation of cytokine mediators proportional to disease extent

Translational consequences

- Transcriptomic or **protein** signature might form basis of a predictive test of latency
- Evaluation of new drug regimes to treat latent TB via PET/CT and transcriptomic profiling