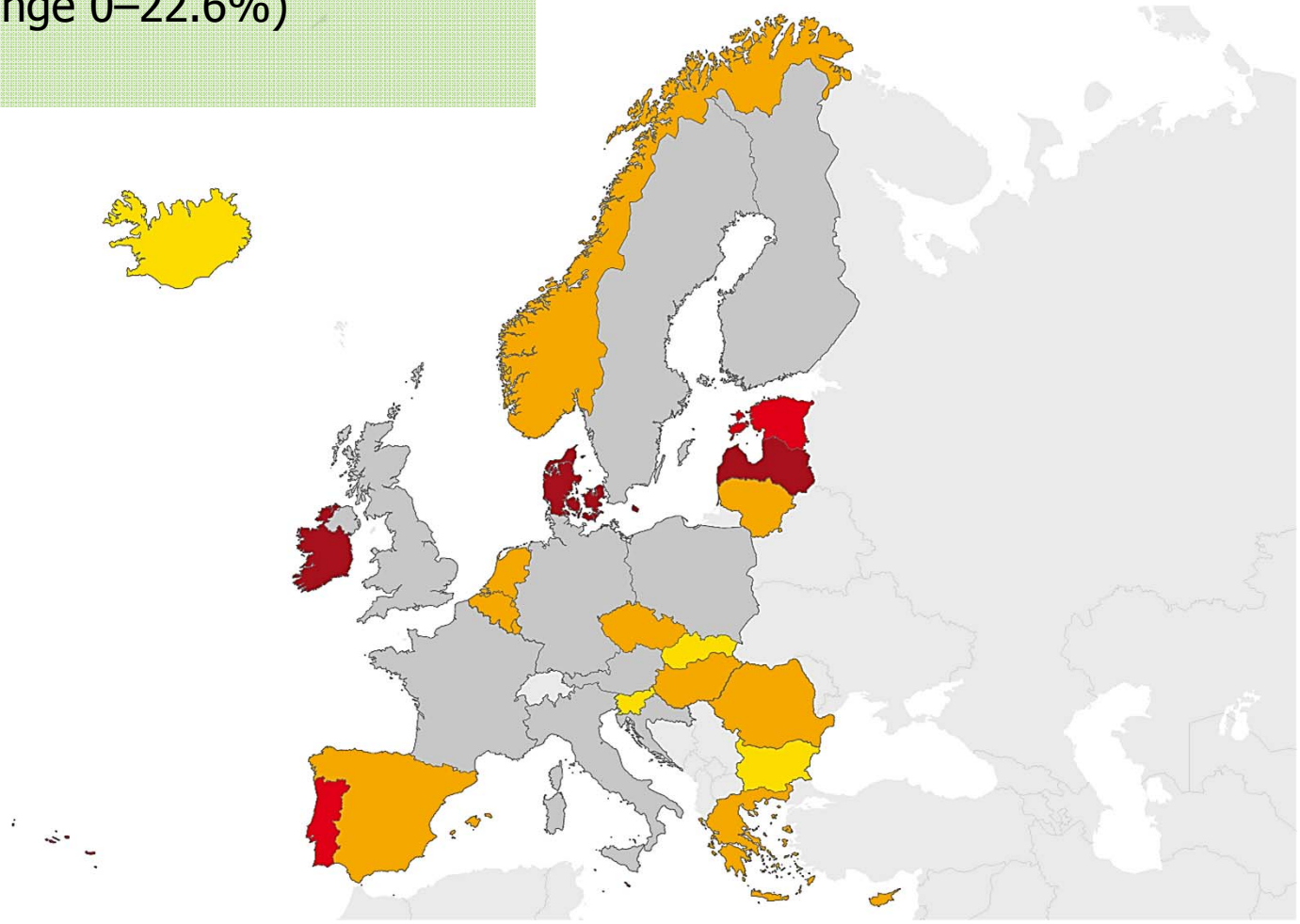
TB and immunosupression

Notified TB/HIV co-infection, EU/EEA, 2014

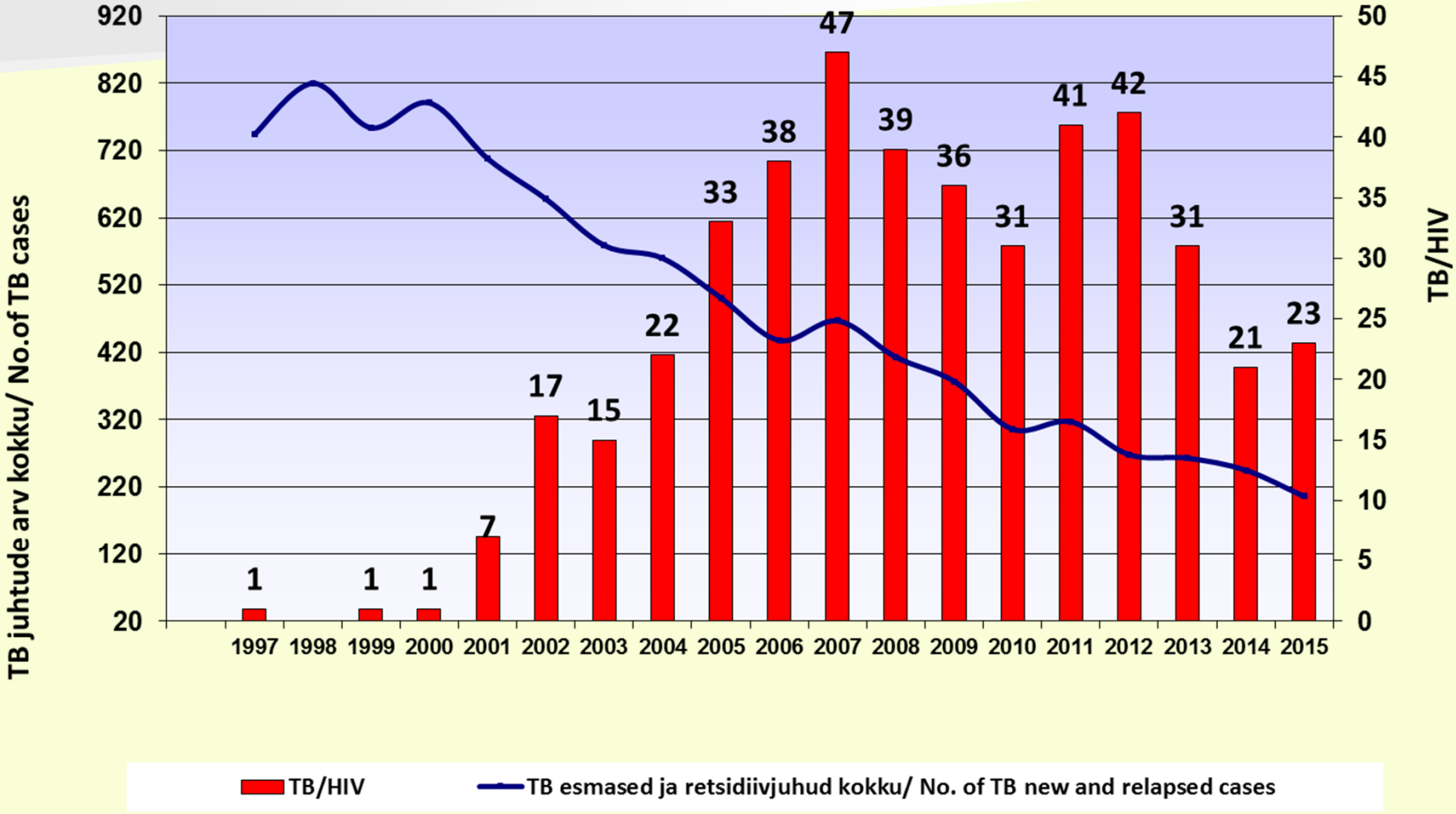
4.9% of TB cases with known HIV status* were HIV positive (range 0–22.6%)



Source: European Centre for Disease Prevention and Control. TB surveillance and monitoring in Europe, 2016.

* Among countries with at least 50% reporting completeness for HIV status

TB /HIV coinfection 1997–2015
96% TB cases were tested for HIV in 2015.
12,4% were HIV+

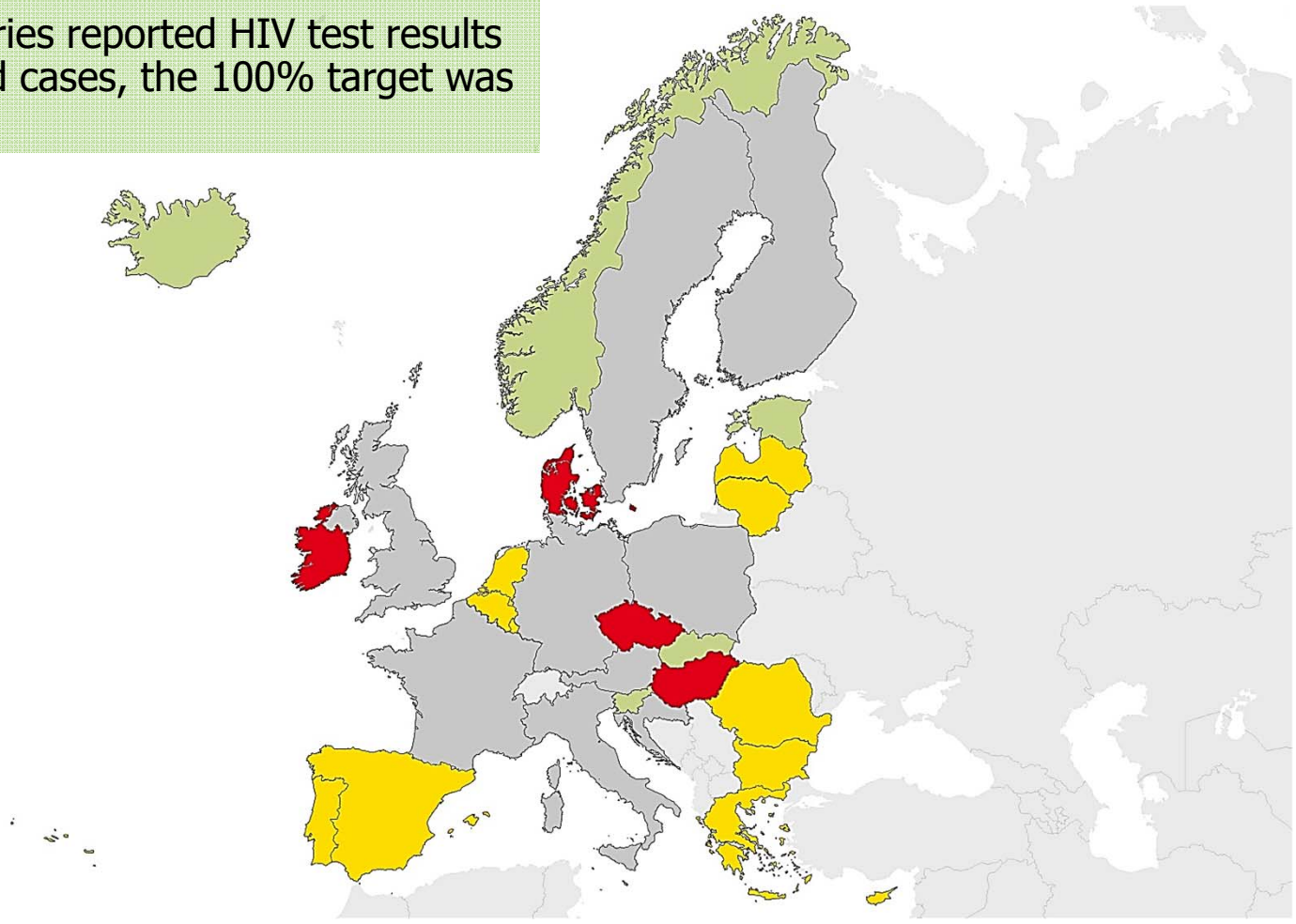


TB register 24. märts 2016

Indicator 8: Percentage of TB patients for whom HIV status is known

Target: HIV status is known for 100% of notified TB cases

Status 2014: 21 countries reported HIV test results for 36.6% of all reported cases, the 100% target was not met



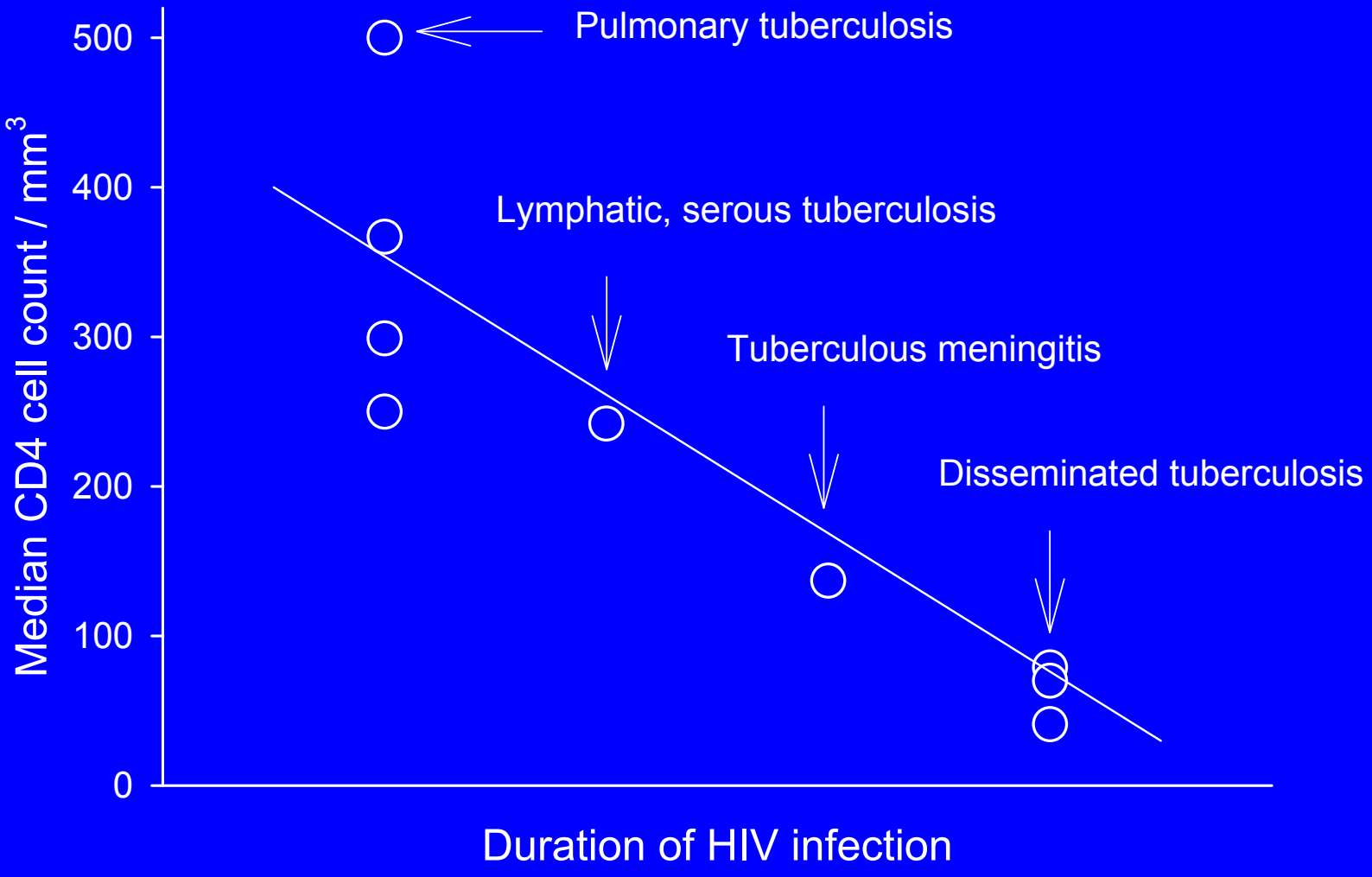
- < 50%
- 50 to 74.9%
- 75 to 99.9%
- 100%
- Not included or not reporting

Source: European Centre for Disease Prevention and Control. TB surveillance and monitoring in Europe, 2016.

* Finland and Poland reported HIV-positive cases, but not the number of tested cases for HIV, therefore excluded

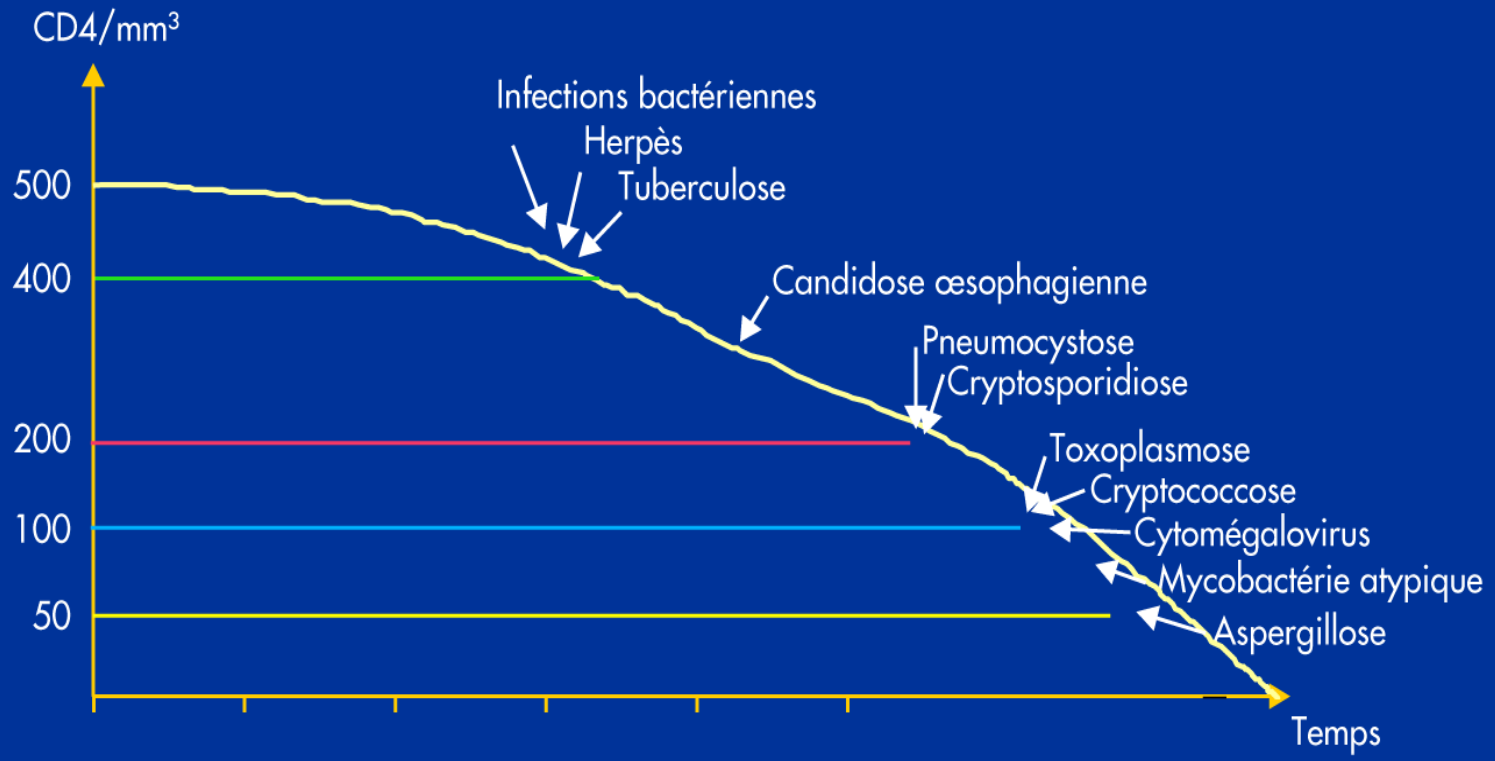
TB can occur at *any time* during the course of HIV infection

Correlation Between Extent of HIV-Induced Immuno-Suppression and Clinical Manifestation of Tuberculosis



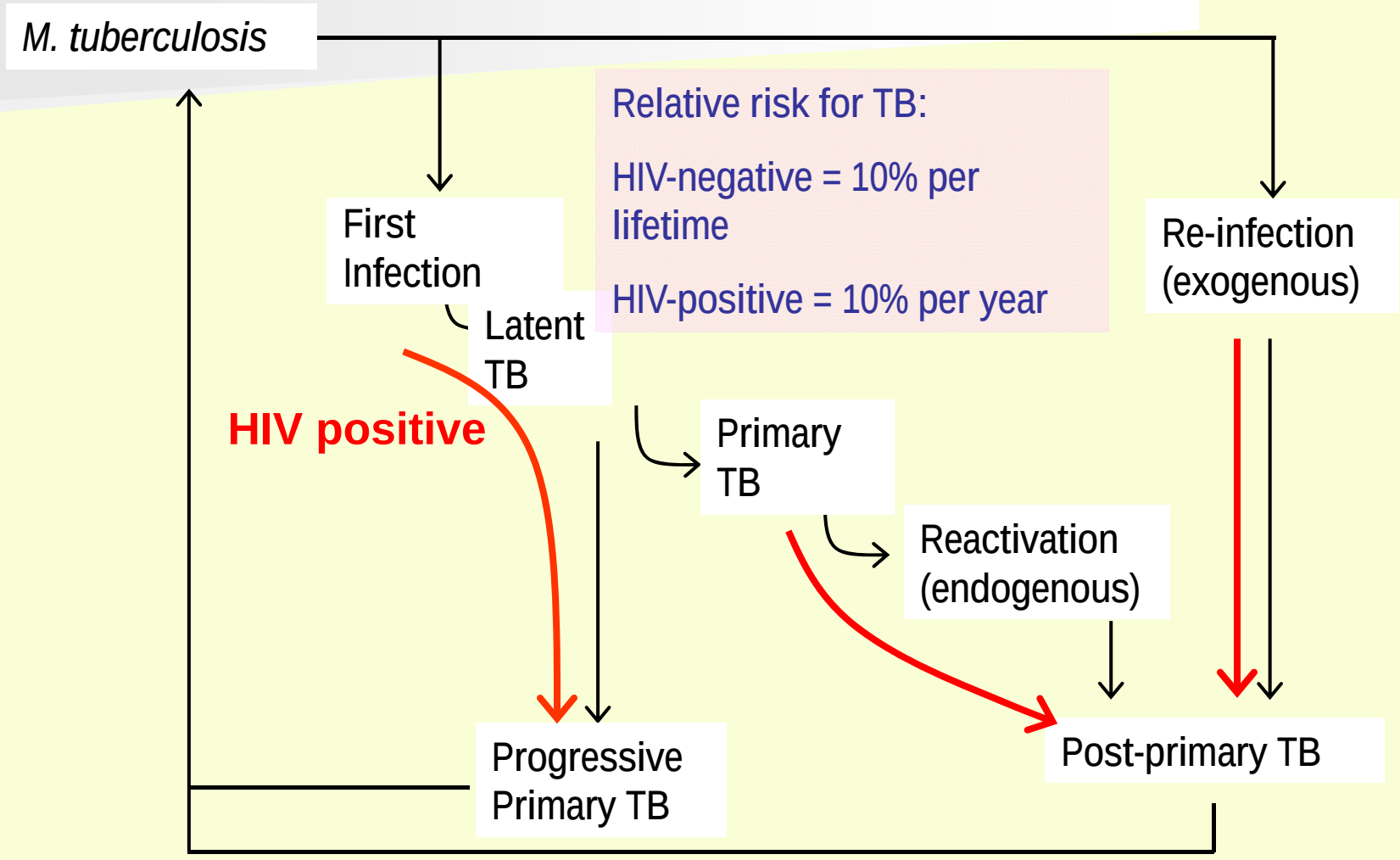
De Cock KM, et al. J Am Med Assoc 1992;268:1581-7

Risk for occurrence of opportunistic infections according to the CD4 count



In : Girard PM, Katlama CH, Pialoux G, Saimot AG. Paris : Doin SIDA 1996

HIV changing TB natural history



Slide courtesy of P Colombani, Tartu 2008

Impact of HIV on the Epidemiology of Tuberculosis

Direct:
- Reactivation of tuberculous infection acquired before HIV infection
- Progression of tuberculous infection acquired after HIV infection

Indirect:
- Transmission to the population not infected with HIV

Sutherland I. Br Comm Dis Rep 1990:10

TB/HIV coinfection (1)

- HIV-positive individuals are 26-fold more likely to develop active TB disease than HIV-negative individuals. TB is the leading cause of death among people with HIV infection

- The risk of developing active TB disease remains twofold higher in HIV-positive individuals even if their CD4+ T cell count is within normal range and they can still develop active TB disease even if they are receiving ART

- HIV-positive individuals have a very high risk of progressing to active TB disease, although they are not necessarily more-infectious to others.

- Patients with AIDS demonstrate altered patterns of infection depending on their CD4 count.
  - When CD4 count drops to below 350 cells/mm^3 appear pulmonary manifestations (post- primary infection)
  - When CD4 counts drop below 200 cells/mm^3 then the pattern of infection is more likely to resemble primary infection or miliary tuberculosis . Nodal enlargement is also common at this stage.

- All HIV-positive individuals should be regularly screened for active TB disease, particularly if they experience cough, fever, weight loss and night sweats

- Individuals who report any one of these symptoms might have active TB disease and require immediate evaluation and treatment

TB/HIV coinfection (2)

- HIV changes the presentation of active TB disease:
  it generally reduces pulmonary cavity formation and
  sputum bacillary load and
  frequently involves the lower lobe

- The most common forms of extrapulmonary TB include lymph node, pleural and disseminated TB. Pericardial and meningeal TB are less frequent but deadlier.

- The WHO recommends that all HIV-positive individuals with drug-sensitive or drug-resistant active TB disease should also begin ART within the first 2 months of TB treatment

- The management of HIV-TB is complicated-

  1) drug–drug interactions between antitubercular and antiretroviral agents make it difficult to design an effective and safe treatment regimen and can cause severe adverse effects, such as hepatotoxicity and neurotoxicity.

  2) by restoring the immune system,
  ART can trigger immune reconstitution inflammatory syndrome (IRIS),
  a condition in which the host's inflammatory response to *M. tuberculosis* infection is disproportionate and worsens the patient's status.

Tumour-necrosis factor (TNF-α) blocking medication

Tumour necrosis factor:

- key cytokine in the host immune response against *Mycobacterium tuberculosis* (granuloma integrity)
- key role in mediating immune responses in acute and chronic inflammatory diseases

- TNF-α blocking medication increasingly used for treatment of:
- rheumatoid arthritis
- inflammatory bowel disease (morbus Crohn)
- psoriasis
- morbus Bechterev)

European Advanced Course in Clinical Tuberculosis, 2013

Screening for latent TB or active disease
before initiation of therapy with THF-alpha inhibitor

Tumour-necrosis factor (TNF-α) blocking medication

- Relative risk 1.5 - 25 higher compared to patients not receiving TNF-α antagonists:
- TNF-α antagonists: - reactivation of latent TB infection / progression of *de novo* infection - close proximity with start of treatment - rapid progression - disseminated disease
- TNF-α antagonist used (infliximab (Remicade®) and adalimumab (Humira®) soluble receptor eternacept (Enbrel®)↑

European Advanced Course in Clinical Tuberculosis, 2013

- Two recent reports describe several cases of active tuberculosis occurring after treatment with the TNF-α inhibitors infliximab (Remicade) and etanercept (Enbrel), mainly in patients with rheumatoid arthritis or Crohn's disease.
- EPTB accounted 52-57% of cases, difficult to diagnose
- TB was diagnosed median 12 weeks after initiation of infliximab
- Pulmonary TB and EPTB was diagnosed after 2, 3, and 5 infliximab infusions

- All TNF-alpha treatment candidates should be screened for latent TB infection or active disease before initiation of therapy with a TNF-α inhibitor. test early (before immunosuppression; treatment completion

Keane J et al, 2001; Mohan et al, 2004 Roth S et al, 2008 Verhave JC, 2008

Screening of immunocompromised individuals

Solid organ and stem cell transplant recipients – all candidates should be screened –

- Test early (before immunosuppression; treatment completion)

Latent TB infection and TB

- TB occurs early (< 6) months after transplant (enhanced immunosuppression)
  but in renal and stem cell transplant recipients usually later
- more extrapulmonary disease

- **More difficult to test** for latent TB infection

- immune-based testing
- corticosteroids or other immunosuppressive medication

LTBI. Treatment

12 H ja 3 H+R (A). Effectiveness 90%

In most regions 6H (UK). Adherence !!

NICE 2016

Table 13. Treatment regimens for latent infection with *M. tuberculosis* [21]

Treatment regimen		Efficacy/ effectiveness	Level of evidence
12 months isoniazid [26, 211]	12H	93%/75%	A
9 months isoniazid [195, 212, 213]	9H	Approx. 90%	C
6 months isoniazid [195]	6H	69%/65%	A
4 months rifampicin [214-216]	4R	Unknown (>3HR)	C
3 months isoniazid-rifampicin [217, 218]	3HR	Equivalent to 6H	A

Erkens C, ERJ, 2010