TB and HIV

- WORLDWIDE
  - 35,500,000 people infected with HIV
  - 13% co-infected with TB
  - 25% of TB deaths HIV-related
  - 25% of AIDS deaths are TB related

- EUROPE (2014)
  - 33,000 TB, 65% HIV tested, 5% positive
  - 78% new HIV, 22% known
  - 42% injecting drug use
  - More MDR-XDR (RR 2-3)
  - Less treatment success (58% vs 84%)

vd Werf, AIDS, 2016
HIV and TB in the Netherlands

Active TB; asymptomatic HIV (screening)

Presentation with symptomatic combined TB and HIV

known HIV, duration?

HIV already known; > 5 years

HIV already known; < 5 years

Of those with known HIV 70% on ART at time of TB diagnosis

20% previous Hx of TB
CD4 and TB risk

Figure 4  Increase in relative risk of tuberculosis incidence in adults living with HIV (age ≥ 15 years) not on antiretroviral therapy by CD4-positive lymphocyte count. Thick dashed lines represent 95% credible intervals around the point estimate (thick solid line); horizontal lines represent means over depicted CD4 categories; dotted lines represent 95% credible intervals for these category means; the horizontal dashed line represents an incidence rate ratio of 1 (no change). It is assumed that individuals with a CD4 count of 1,000 cells/mm³ at the point of HIV infection.
Presentation dependent on CD4

- (classical) Pulmonary TB
- Non-cavitary PTB; extrapulmonary TB,
- Disseminated TB

CD4+ T-cells

years
Hematuria

- Dutch man, non-responsive chronic pneumonia
- BAL: PJP and *M. tuberculosis*. Lymph node: *Mtb*
- HIV, CD4 9
- Severe skin allergy (cotrim? TB-drugs?)
- Liver test dysfunction (regimen without rifampicin)

- 1,5 years later: hematuria, urologist.
- CT-scan: mass lesion 7x7 cm, suspected renal carcinoma

- Nephrectomy: granulomatous, necrotising lesion – TB!
Progressive skin lesions

62 jaar, HIV, CD4 5, Diabetes
Rapidly progressive skin lesions
Dry cough, night sweats
More multifocal or disseminated disease

- pulmonary + extrapulmonary
- miliary TB
- TB meningitis
- TB ‘sepsis

- At time of presentation
- during treatment
- After start of ART
TB diagnosis same in HIV+ and HIV-

<table>
<thead>
<tr>
<th>But</th>
<th>therefore</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary TB often atypical or paucibacillary</td>
<td>Lower threshold for CT and BAL in HIV</td>
</tr>
<tr>
<td>More extrapulmonary and disseminated TB</td>
<td>Tissue biopsies, lumbar puncture, <em>Mtb</em> Blood culture, urine LAM (especially with low CD4)</td>
</tr>
<tr>
<td>Subclinical TB may be ‘unmasked’ by ART</td>
<td>Remain vigilant for TB after start of ART; repeat diagnostics, espec. with low CD4</td>
</tr>
<tr>
<td>Broader differential (NTMs etc)</td>
<td>AFB: confirm MTB with molecular test</td>
</tr>
</tbody>
</table>
TB-HIV: treatment
ART: extremely effective

“DART”-trial in 4 African countries (Lancet 2010)
Anti-retroviral treatment (ART)

Entry blockers

Reverse transcriptase inhibitors

Integrase inhibitors

Protease inhibitors

RNA → Reverse transcriptase → DNA → Protease inhibitors

RNA → Protease inhibitors → Proteins

DNA → Integrase → Provirus
Toxicity

With permission
More TB drug-toxicity in HIV

• More (hepato)toxicity
• Especially with low CD4 counts

Recent cohort Brazil: 33% high ALAT (>3 x normal)

## TB-HIV: more and overlapping toxicity

<table>
<thead>
<tr>
<th></th>
<th>TB-drugs</th>
<th>Anti-retrovirals</th>
</tr>
</thead>
<tbody>
<tr>
<td>hepatotoxicity</td>
<td>INH, PZA, Rifampin</td>
<td>NVP, EFV, all PI’s, ..</td>
</tr>
<tr>
<td>Skin rash</td>
<td>INH, PZA, Rifampin</td>
<td>NVP, EFV, ABC, ..</td>
</tr>
<tr>
<td>Leukopenia, anemia</td>
<td>Rifampin</td>
<td>zidovudin</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>INH</td>
<td>NRTIs</td>
</tr>
<tr>
<td>Artralgia, myopathy</td>
<td>PZA, rifabutin</td>
<td>Tenofovir, integrase-remmers</td>
</tr>
<tr>
<td>fever</td>
<td>INH, rifampicine</td>
<td>ABC, ...</td>
</tr>
</tbody>
</table>

.. and PJP-prophylaxis, antifungals and HIV infection itself.
Skin lesions:

Broader differential
Interactions with rifampicin

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibacterials</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Antifungals</td>
<td>Fluconazole</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Mefloquine</td>
</tr>
<tr>
<td>HIV treatment</td>
<td>Most anti-HIV drugs, especially protease inhibitors¹</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Analgesics</td>
<td>Methadone</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>Ciclosporin</td>
</tr>
<tr>
<td>Ulcer-healing drugs</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Respiratory drugs</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Cardiac drugs</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>Digitoxin (only member of class affected)</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Disopyramide</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>Fluavastatin</td>
</tr>
<tr>
<td>CNS drugs</td>
<td></td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Tricyclic compounds</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Endocrine drugs</td>
<td></td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>All antidiabetic drugs except metformin and insulin</td>
</tr>
<tr>
<td>Estrogens and progesterones</td>
<td>Combined and progesterone only contraceptive pill</td>
</tr>
<tr>
<td>Thyroid replacement</td>
<td>Thryoxine</td>
</tr>
</tbody>
</table>

*Table 31-2: Drug Interactions with Rifampin*
Drug interactions

• 30-year old man, TB spondylitis, HIV (120 CD4 cells)
• 2 mths after HRZE: ART (truvada, efavirenz)
• HIV-genotyping: Efavirenz resistance
• Efavirenz replaced by lopinavir/ritonavir; Rifamp not to be combined with lopinavir; switch Rifamp to rifabutin (300 mg / day)

7 weeks later:
• Severe polyarthralgia, nausea
• Leucopenia, thrombocytopenia
• fever
• Painful eye, vision loss

Rifabutin toxicity
rifabutin toxicity

Efavirenz (Inducer) → Liver metabolism (cytochromes) → rifabutin → Ritonavir/lopinavir (inhibitor)

+ Concentration too low (failure / resistance formation)

- Concentration too high (toxicity)
## choice ART during TB treatment

<table>
<thead>
<tr>
<th>1st choice</th>
<th>dolutegravir or raltegravir (with NRTI backbone)</th>
<th>DTG/RTG from once to twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd choice</td>
<td>Efavirenz-based (standard dose)</td>
<td>Interaction with Rif (Cyp3A4) &amp; INH (Cyp2B6)</td>
</tr>
<tr>
<td>3rd choice</td>
<td>PI-based (double-dose lopinavir/rit)</td>
<td>Strong interactions, high toxicity</td>
</tr>
<tr>
<td></td>
<td>rifabutin instead of rifampin</td>
<td>Interactions / Toxicity</td>
</tr>
</tbody>
</table>

### New Dutch guideline:
- measure HIV- and TB-drug level at least once during combined therapy
- monitoring of HIV-RNA during TB treatment
Immune reconstitution inflammatory syndrome (IRIS)
Risk factors IRIS

- low CD4, rapid rise after start ART
- Short interval between start TB drugs and ART
- Extrapulmonary (disseminated) TB
- High load *M. tuberculosis*
- Vitamin D deficiency

- for meningitis: culture-positivity or high CSF neutrophils

Quick start of ART ~ more IRIS

N=162 ART-naive patients South Africa; CD4 < 100

Two kinds of TB-IRIS

Active TB → TB treatment → ART → Clinical worsening TB because of immune reconstitution = paradoxical IRIS

No sign of TB before ART → ART → Increased inflammation to subclinical TB because of immune reconstitution = ‘unmasking’ IRIS
Unmasking IRIS can help TB diagnosis

- Jamaican man, 28 years
- 2 years ART; treatment interruptions
- No symptoms, 80 CD4 cells
- Resistant virus. Start 2nd line ART

- 3 weeks later:
  - Fluctuating cervical mass
Also ‘unmasking’

- Young African man
- Pulmonary (MDR) TB
- Abdominal TB
- HIV, CD4 140
- Start TB treatment
- ART 4 weeks later
- Toxicity++, Evans syndrome, nephrotic syndrome ..
Steroids for IRIS

- RCT South Africa
- 110 pts; CD4 53
- Clinical definition of IRIS
- Life-threatening IRIS excluded
- Prednison 1.5 mg/kg 2 weeks, 0.75 mg/kg 2 weeks
- To open-label steroids if worse

- 6 – 8 weeks TB treatment before start ART
- IRIS 10-14 days after ART
- IRIS: mostly lymph nodes, new/larger infiltrates

Meintjes, AIDS 2010
preventive treatment IRIS

**Figure 2. Cumulative Incidence of Paradoxical TB-Associated Immune Reconstitution Inflammatory Syndrome (IRIS).**

Panel A shows the cumulative incidence of the primary end point of paradoxical TB-associated IRIS at 12 weeks. If paradoxical TB-associated IRIS had not developed before a patient died, withdrew, or was lost to follow-up, the patient was considered not to have had the syndrome. Panel B shows the cumulative incidence of TB-associated IRIS over 84 days. Diagnosis of TB-associated IRIS was determined according to the International Network for the Study of HIV-associated IRIS criteria.\textsuperscript{14} Day 0 is the day ART was initiated.

Meintjes, NEJ 2019
What if steroids don’t work?

At time of TB diagnosis  
Following start TB-drugs/ART  
After adding anti-VEGF

- 18-year old, newly diagnosed ZN-negative pulmonary TB
- HIV, CD4: 22
- ART 2 weeks after start of TB treatment
- 5 weeks later: decreased vision: IRIS
- No response to steroids
- No improvement after 2 weeks: anti-VEGF

Jain,. J Oph Inf & Inf, 2016
## IRIS

<table>
<thead>
<tr>
<th>Highest risk</th>
<th>Low CD4, disseminated TB Early start of ART</th>
<th>Timing ART after start TB drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of IRIS</td>
<td>Consider drug fever and other opportunistic infections</td>
<td></td>
</tr>
<tr>
<td>ART and TB drugs</td>
<td>Avoid treatment interruption; continue</td>
<td></td>
</tr>
<tr>
<td>Treatment IRIS</td>
<td>Corticosteroids (1 - 1.5 mg/kg)</td>
<td>Interaction with Rif</td>
</tr>
<tr>
<td>Prevention of IRIS</td>
<td>Consider steroids (30-50 mg) for high-risk pts</td>
<td>Strong interactions, high toxicity</td>
</tr>
<tr>
<td>Severe IRIS, Dx or Tx ?</td>
<td>Expert consultation</td>
<td></td>
</tr>
</tbody>
</table>
Duration TB treatment

- Old studies (no ART) worse treatment outcome with 6 mths
- No randomized trials

Current advice:
- normal-sensitive TB: **6 months**
- Large cavities, sputum + at 2 months, or patient who is not on ART: **9 mths**

- Some studies show worse outcome and some show low drug-levels:
  - Close monitoring
  - New Dutch guideline: single time-point PK for TB and HIV drugs
When to start ART?

Integration of Antiretroviral Therapy with Tuberculosis Treatment

Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis

When to start ART?
No gain of early ART with higher CD4

Mfinanga et al, Lancet Inf Di 2014; SR from 2015
## Timing ART after start of TB treatment

<table>
<thead>
<tr>
<th>Scenario</th>
<th>When to start ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated HIV, CD4&lt;50</td>
<td>after 2 weeks (balance toxicity and IRIS)</td>
</tr>
<tr>
<td>Untreated HIV, CD4&gt;50</td>
<td>within 8 weeks</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>Generally not within 4 weeks</td>
</tr>
<tr>
<td>Successfully treated HIV</td>
<td>Continue ART, consider interactions</td>
</tr>
<tr>
<td>Failing ART</td>
<td>Interrupt ART, perform HIV drug-resistance test</td>
</tr>
</tbody>
</table>
Conclusions: TB and HIV

• More TB in HIV (immunity and exposure)
• Also among ART-experienced individuals

• Often atypical, extrapulmonary, disseminated, or more rapid progressive

• Diagnosis: more aggressive

• Treatment: Toxicity, interactions and IRIS
  • timing and choice of ART
  • close monitoring (drug levels and HIV virus)
HIV and latent TB – Dutch guideline

• Have a low threshold for screening for active TB,
  • especially with low CD4 and in individuals from medium/high TB incidence
  • Also in the first months after start of ART (‘unmasking TB’)

• Do not screen for LTBI in Dutch / people from low-endemic settings, unless they have had obvious TB exposure (eg having lived in Africa)

• Screen individuals from medium / high TB incidence settings and others with significant TB exposure (estimated 250-300 people) for LTBI (using IGRA and/or TST), and provide IPT for those positive

• Consider empiric TB-prophylaxis or repeating screening if significant risk of LTBI (eg sub-Saharan Africa) and CD4s < 200