British HIV Association guidelines for the management of tuberculosis in adults living with HIV 2018

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COI

- Gilead – financial support for conference
- AbbVie – development of an e-module
These guidelines update the previously published BHIVA guidelines on the treatment of TB/HIV co-infection from 2011\(^1\)

Should be used in conjunction with

- NICE: Tuberculosis guidance
- BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy;
- Current WHO guidelines for the treatment of drug-resistant tuberculosis (including INH mono-resistance);

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TB Numbers

- 10 million people fell ill with TB in 2017
- 9% were people living with HIV

72% of TB/HIV co-infection in Africa
5,664 TB cases notified in 2016\(^1\)
(5,513 in 2015)

Data from 2015:
3.8% co-infected with HIV \(\rightarrow\) 82% non-UK born
(211/5,513)

69% born in sub-Saharan African countries

PHE: Tuberculosis in England 2017 report (presenting data to end of 2016)
UKCHIC = an ongoing, UK-wide, cohort study of HIV-positive individuals attending clinic

Incidence of TB in UK HIV population

Tuberculosis among people with HIV infection in the United Kingdom: opportunities for prevention?

United Kingdom Collaborative HIV Cohort Study Group

Incidence: after >24 months on ART

BA: 530/100,000
White: 80/100,000
Other: 290/100,000

UK incidence at that time: 15/100,000

Fig. 3. Incidence of tuberculosis after starting combination antiretroviral therapy, stratified by time after starting antiretroviral therapy and ethnic group (N = 7181).
Diagnosis
Diagnosis of active pulmonary TB

- Microscopy for acid-fast bacilli, culture and drug-sensitivity testing should be performed on respiratory samples
- If smear-positive: **molecular testing** (eg. Xpert MTB/RIF Ultra) (GRADE 1B)
- All pulmonary smear-negative samples should be processed for culture and drug-sensitivity testing; molecular tests only if high suspicion for TB (GRADE 1B)

**IGRAs should not be used** to diagnose or exclude active TB

IGRA = interferon gamma release assay, eg Quantiferon, T-spot
Diagnosis of TB pleuritis

Pleural fluid +/-
Tissue analysis (pleural biopsy)

Microscopy for acid-fast bacilli, culture and drug-sensitivity testing

Even in the absence of obvious lung parenchymal involvement:

Microscopy and cultures on respiratory samples should be performed (GRADE 1B)
Diagnosis of active extra-pulmonary TB

TB meningitis

MOLECULAR TESTS on CSF samples (RULE IN not RULE OUT)

Other organs

✓ microscopy and culture for AFB
✓ histology
✓ molecular testing
Diagnosis of multidrug-resistant TB infection

Molecular techniques:
Eg Xpert, WHOLE GENOME SEQUENCING, in addition to phenotypic drug susceptibilities

If rifampicin resistance: manage as MDR TB*, in conjunction with expert centre

MDRTB definition*: resistance to at least isoniazid and rifampicin
Risk factors for possible drug-resistant TB

- Contact with MDRTB case;
- Birth, travel or work in settings with very high RR/MDR prevalence (as defined by PHE);

WHO - % of new TB cases with MDR/RR-TB, 2016
Risk factors for possible drug-resistant TB

- Previous TB treatment;
- History of poor adherence to previous TB treatment;
- No clinical improvement and/or sputum ‘smear’ positive > 2 months of TB rx or culture positive at 3 months;
- Homelessness/living in hostels, recent/current incarceration;
Latent Tuberculosis

Active TB disease: 8 million new cases per year

TB DISEASE

LATENT TB INFECTION
the “hidden epidemic”
2 billion people infected

Diagnosis of latent TB infection

**TEST for LTBI: HIV+ from high- and medium-TB-incidence countries regardless of CD4 cell count and receipt of ART**

+++ individuals newly diagnosed with HIV or recently exposed to TB (GRADE 1B)

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High TB incidence: ≥151/100,000 person years*

Medium TB incidence: 40–150/100,000 person years*

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*NICE. *Tuberculosis. NICE guideline [NG33]. 2016. [www.nice.org.uk/guidance/ng33](http://www.nice.org.uk/guidance/ng33)
High TB incidence: ≥151/100,000 person years*
Medium TB incidence: 40–150/100,000 person years*
Diagnosis of latent TB infection

HIV-positive individuals from low-incidence countries should be tested for LTBI if additional TB risk factors are present (GRADE 1B)

- Exposure to a known TB case;
- Travel to or periods of time spent consecutively in higher-incidence countries;
- CD4+ <200;
- Diabetes;
- Stage 4/5 chronic kidney disease;
- Chemotherapy for malignancy;
- Immunosuppression (organ transplantation);
- Biological disease modifiers;
- Prolonged use of corticosteroids;
- Injecting drug use;
Managing latent TB infection

Services should make local arrangements for managing the increase in numbers requiring testing (and treating) for LTBI.

It is acceptable to discuss and offer testing to those at risk at their routine follow-up appointments.
**Detection of latent TB infection**

**IGRA** rather than TST should be used when testing HIV-positive individuals for LTBI (GRADE 2C)

If result is indeterminate or borderline → repeat IGRA within 4 weeks

No testing for LTBI in individuals who have been previously treated for active tuberculosis


**IGRA** = interferon gamma release assay, eg Quantiferon, T-spot. TST = tuberculin skin test
Detection of latent TB infection

Exclude active TB

Ask for any symptoms of TB in individuals from the risk groups

Yes

IGRA

Positive

Chest radiograph

Any abnormality

No abnormality

Treat for LTBI

No

Negative

TB and other disease investigations
Treatment of latent TB infection

Recommended regimens (GRADE 1A):

- 6 months of isoniazid plus pyridoxine;
- 3 months of isoniazid plus rifampicin plus pyridoxine;

Rifapentine not yet available in UK – not currently recommended
Promising findings ACTG 5279 study 1/12 rifapentine and isoniazid non inferior to 9/12 INH
TB Treatment
Treatment of active drug-sensitive TB

- We recommend **DAILY** administration of standard TB therapy in patients with drug-sensitive TB (GRADE 1A)*

- **2RHZE/4RH**

- **CNS TB: 2RHZE(+steroids)/7-10RH**

- Fixed-dose combination tablets

Management of drug-resistant TB

Isoniazid mono-resistance (~6%): rifampicin, ethambutol, levofloxacin and pyrazinamide daily for 6 months (GRADE 1C)

All individuals with rifamycin-resistant (including MDR*) TB should be managed in conjunction with expert centre in the management of drug-resistant TB

**MDRTB definition***: resistance to at least isoniazid and rifampicin
ART & TB treatment

When to start: naïve

Start ART within 8–12 weeks of TB diagnosis (GRADE 1A)

If CD4 cell count <50 cells: ART within 2 weeks (GRADE 1A)
No early initiation of ART in individuals with TB meningitis (GRADE 1A)

ART immediately vs 2 months after starting TB rx (253 patients with HIV-related TB meningitis):

- No survival benefit
- More frequent severe adverse events
ART & TB treatment

What ART to start / continue (third agent)

- **Efavirenz**\(^1\) (standard dose) (GRADE 1B)
- **Raltegravir**\(^2\) 400 mg bd/800 mg bd or
- **Dolutegravir**\(^3\) (DTG) 50 mg bd (GRADE 2C)
- If need for a ritonavir-boosted PI: use **rifabutin** (GRADE 1C)

Do not use:
- nevirapine or cobicistat
- TAF or bictegravir - until clinical outcome data available

SCREEN FOR DRUG-DRUG INTERACTIONS

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**IRIS**

**Immune Reconstitution Inflammatory Syndrome**

‘Paradoxical’ & ‘Unmasking’

Paradoxical IRIS: *worsening or appearance of new signs, symptoms or radiographic abnormalities, occurring after the initiation of ART*

**Criteria**:  
- temporal association with initiation of ART  
- demonstration of response to ART (VL ↓, CD4+↑)  
- clinical deterioration with an inflammatory process  
- exclusion of other causes that could explain deterioration

* Meintjes et al, Lancet 2008
IRIS

Risk factors
✓ low baseline CD4+ & rapid recovery of CD4+;
✓ rapid decline in HIV viral load;
✓ dissemination of TB outside the lung;
✓ Short time between anti-TB rx and ART;

If clinically significant IRIS: use corticosteroids, tapered over 4–6 weeks (GRADE 1C)
[Prednisone or methylprednisolone at a dose of 1–1.5 mg/kg]

Recurrent IRIS and complex cases can be difficult to manage: seek advice from centre of expertise in managing TB
TB Treatment failure & relapse

- A microbiological diagnosis should **ALWAYS** be pursued
- **SEEK ADVICE** from a Centre with expertise
- New regimens should be based on results from rapid molecular testing and whole genome sequencing

If immediate treatment is needed:
use at least **two to three new drugs from different classes** while awaiting the results of drug susceptibility tests
We recommend individualised, enhanced patient-centred care plans for all patients, some of which may include DOT and video observed therapy (VOT).

We recommend the **routine** use of DOT and VOT in patients with MDRTB.
Control of transmission/ Contact tracing

All hospitals and HIV units should have a TB infection control plan

**Notification/tracing of contacts**

Do not delay contact tracing until notification

Screen close contacts of any person with pulmonary or laryngeal TB

Enhanced contact tracing for PLWH, including contacts of people with EPTB should be implemented where feasible

T Wingfield et al., Thorax, 2017
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