BHIVA guidelines on the management of tuberculosis in adults living with HIV

Public consultation comments

Compilation of all comments received via the BHIVA website. The writing group thanks everyone who replied to the consultation. All comments were considered by the writing group and amendments have been made where appropriate.
9 February 2018

Contents

	Name	Affiliation	Comments	Writing group response (The guidelines have been revised based on the comments unless otherwise stated)
1.	Hugh Mc Gann	Leeds Teaching hospitals NHS trust	What ART to start Raltegravir is suggested as an alternative where efavirenz is contraindicated with the other option being a boosted PI with rifabutin based TB therapy. Dolutegravir is not recommended since results of the on-going randomised clinical trial are not yet available. I would suggest that dolutegravir based ART should be included as an alternative for patients where efavirenz is contra indicated. The Relate study had a relatively high rate of virological failure with both raltegravir 400 mg BD and 800 mg BD. Twice daily dolutegravir has been shown to be effective in PK studies and there is real world experience of good outcome in small patient cohorts using dolutgravir with rifampicin based ART. This includes our data presented at HIV drug therapy Glasgow 2016. P147 Use of dolutegravir in combination with rifampicin-based TB therapy in HIV/TB co-infected patients: real- world experience from Leeds, UK Cevik, M*; Vincent, R; McGann, H (Edinburgh, UK) Patients with TB/HIV co-infection frequently present with TB having disengaged from HIV care. These patients may have archived NNRTI resistance or have another contra- indication to efavirenz. Compliance is often problematic and the use of raltegravir with its low genetic barrier may increase the risk of treatment failure with drug resistance. The use of rifabutin based TB therapy with the high pill burden to facilitate TB therapy is difficult in this group and not using ART, at least for the first 2 months, as suggested is far from ideal. In these patients I believe dolutegravir provides an effective alternative.	We have included DTG as an option Reference not added as better evidence from RCT has been included
2.	Lisa Hamzah	King's College Hospital	Great guidelines but would appreciate a comment on the recommended dose of Raltegravir now we have the 1200mg OD dosing, thanks	Comment added
3.	British Infection Society	Ann Goodman, British Infection Association guidelines rep	This is an excellent guideline which the BIA fully support. Some minor points: 'Conventional microscopy and culture' is mentioned throughout the document but appears to mean Z-N stain and AFB culture rather than MC&S	Changed accordingly

			p18 bottom paragraph- 20% in HIV-infected individuals 'with TB'? Consider testing those with diabetes from low incidence areas (p23) opens testing to a large number of patients who are unlikely to have LTBI- does the evidence show that the benefits of testing this group outweigh the harms and are cost-effective? Table 10.1 needs headings on every page for ease of reading. Overall the document is comprehensive and helpful and are now more aligned with the NICE guidance. Minor comments: Rationale and evidence for waiting 2 months before starting ART in patients with TB meningitis is not stated in section 9.1. Choice of ART (section 9.2) recommends Efavirenz as third line agent, even though most clinicians would now use an integrase inhibitor and evidence from the Reflate TB trial that Raltegravir regimens were beneficial compared to Efavirenz regimens.	Changed accordingly Diabetes added Changed accordingly Wording of recommendation changed/rationale added No action required
4.	Kaveh Manavi	University Hospital Birmingham	Thank you for nicely drafted document. I would like to offer the following comments for further improvement of the guidelines if approved by the authors: 1. Rationale for latent TB infection: 6.1.1: 'In the UK, the majority of cases of TB result from reactivation of LTBI rather than recent transmission.', page 22: The guideline refers to a PHE document as the reference. I have checked the PHE document and cant how they have made such conclusion. We agree that the majority of HIV infected patients with TB are originally from African countries. A systemic review of seven studies carried out in different African countries with over 2,000 HIV infected participants, however, concluded that cases of active TB in HIV endemic settings were more likely to develop after MTB transmission [Houben RM, Crampin AC, Ndhlovu R, et al. Human immunodeficiency virus associated tuberculosis more often due to recent infection than reactivation of latent infection. Int J Tuberc Lung Dis. 2011;15(1):24-31.]. I propose the statement should be amended based on the published evidence. 2. Recommendation on use of GeneXpert assay: Cepheid, the manufacturer of geneXpert assay for TB has stopped the production of the assay and substituted it with GeneXpert Ultra assay for TB. The new assay identifies resistance to rifampicin, isoniazide and four other anti-TB medications. I think the guideline document should refer to geneXpert Ultra assay for more accuracy. On its performance, I would refer my colleagues to Dorman SE, et al. Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. The Lancet Infectious Diseases. DOI: http://dx.doi.org/10.1016/S1473-3099(17)30691-6. GeneXpert Ultra assay has an excellent performance for diagnosis of TB meningitis as well: Bahr NC, et al. Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. The Lancet Infectious Diseases. DOI: http://dx.doi.org/10.1016/S1473-	No action required GeneXpert Ultra added

			3099(17)30691-6 I also propose the guidelines should highlight the 90 minute turnaround time for the test results with geneXpert; a feature that I have found very helpful in clinical practice. 3. Prescription of vitamin D, section 7.3, page 30: The current statement on not prescribing vitamin D supplement may be in contradiction with NICE guidelines. NICE guidelines [PH56], recommend that none white individuals in the UK should take vitamin D supplements. This would be a significant proportion of patients with TB too. 4. Figure 6.1, page 23: I think the algorithm is helpful and agree with it. I think the document would benefit from further expansion on TB symptoms in HIV infected patients including fever, raised LFTs, lymphadenopathy, lung consolidation, anaemia, and weight loss. I hope the above make sense. I would be happy to provide more information if required. Kind regards Kaveh Manavi	Statement about vitamin D has been removed This is beyond the scope of these guidelines
5.	British Thoracic Society	British Thoracic Society	RECOMMENDATIONS Molecular tests (diagnosis of multidrug-resistant TB) The evolution of MDR-TB suggests that early detection of isoniazid resistance would be valuable to ensure that the dosing of rifamycin is sufficient (Manson AL et al. Nat Genet. 2017; 49(3):395-402). LTBI – diagnosis Regarding LTBI, London will count as a medium-TB-incidence area if the homeless population is included (the lower limit of incidence 40 per 100,000 should be included in the recommendation). The recommendation that an IGRA should be repeated if the first result is indeterminate or borderline, should give an indication of timing, e.g. after ART or when the CD4 count has reached >200/mm3? LTBI - treatment Delete "at risk" in the first recommendation as it is unclear whether a positive IGRA confers the risk, HIV co-infection confers the risk or there are other risk factors that need to be taken into account. As LTBI is going to be treated, the special reference to chemotherapy and steroids seems superfluous. Treatment of active drug-sensitive TB A comment should be made that fixed dose combinations should give adequate drug doses (several of the combinations give either inadequate pyrazinamide doses or more importantly inadequate isoniazid and rifampicin doses).	Wording changed to include INH Indication of timing added Changed accordingly Changed accordingly Not in agreement/no action required

			The grading regarding vitamin D seems higher than the evidence allows – anecdotal cases of hypercalcaemia when no vitamin D levels were obtained in those who had adequate or high vitamin D. This recommendation could be deleted. Management of drug-resistant TB In view of the difficulties in the use of moxifloxacin (dose required usually 600 mg to reach the required MIC and cost), the new WHO guidelines prefer levofloxacin as the fluoroquinolone of choice. DOT The recommendation against routine DOT has a grade inconsistent with the evidence. The trials indicated no difference. The clinician should decide regarding adherence risks and significance should TB develop. IRIS For IRIS, the clinical significance of the paradoxical reaction and patient distress should be the deciding factors as to whether steroids are required? Contacts Whilst recent infection is important in increasing the value of preventive treatment, limiting contact tracing to those with pulmonary or laryngeal TB and HIV co-infection is likely invalid, as those with EPTB may have acquired TB recently from an infectious case. COMMENTS ON PARTICULAR SECTIONS 5.2.2 and 5.3. The paragraphs regarding adenosine deaminase should be removed. This test has been repeatedly found to be wanting and was highlighted as one of two main serological tests (the other being the mixture termed Antigen60) that should not be used (WHO). 5.4 Lymph node TB has a distinct immunology and pathology compared to disseminated TB. The two subjects should be treated separately. This paragraph really deals with the use of urinary LAM in disseminated TB and could be entitled accordingly. 5.7.1. The figures for HIV-MDRTB co-infection should be given. 6.1.1 "A positive IGRA …. Indicates (rather than constitutes and delete "a diagnosis of") LTBI". Strictly, only 80% of LTBI will have a positive IGRA (as noted in immunocompetent patients with active disease). A "diagnosis" requires fulfilment of Koch's postulates with follow-up data indicating reactivation with the index strain. TST may help uncover the 20% who will be negative by IGRA and as such the NICE guidelines are probably valid. A positive test result defined by prior probability and BCG vaccination (HTA report on	Recommendation regarding vitamin D has been removed Changed the recommendation with levofloxacin instead of moxifloxacin as per WHO guidance Grade changed to 1B No action required We mostly followed NICE guidance but included enhanced contact tracing where feasible for PLWH Not in agreement/no action needed LAM moved to appendix Figures added Changed accordingly Approach not practical – not in agreement with

			the PREDICT study) would seem to be the way forward. The relevance for NTM exposure in the UK context has not been adequately defined compared with southeastern United States.	view of writing group
			The Dutch study indicated that backpackers in India had no increased risk of TB but rather it was travel to countries with a high incidence together with staying in family homes in these countries that is significant.	No action needed
			The risk factors for hepatotoxicity with isoniazid were not indicated in the "see below" (e.g. acetylator status, immune activation – Vinnard c, et al. Br J Pharmacol 2017; 83:801-11, CYP2E1, glutathione S- transferase, and perhaps polymorphisms in PstI, DraI, TNXRD1).	Risk factors added
			6.3 Mediastinal LN TB is often difficult to diagnose and perhaps the problems has been with preventive treatment given in these circumstances?	No action needed
			Table 7.1. The dose of pyrazinamide should be 35 mg/kg.	Drug doses checked and changed according to TB monogram
			The treatment dose for ethambutol is 25 mg/kg (Horsburgh) and the 15 mg/kg dose was only used in trials for prevention of drug resistance arising during treatment (its main use in the standard regimen). The evidence that blood levels stabilize at a therapeutic level after 1500 mg daily is uncertain, noting ethambutol's high fat solubility and potential volume of distribution.	
			7, p28. The value of steroids in TBM is for early mortality – subsequent follow-up of the Vietnam cohort showed no difference in longterm outcome.	No action needed
			7.3. The vitamin D story should be given a verdict of "unproven". On these grounds I would not mention this subject in the guidelines. The references do not support the recommendation as it stands: supplementation of vitamin D in those shown to have undetectable levels in an RCT is still awaited (perhaps soon to be completed in a study in Mongolia).	Vitamin D recommendation removed
			8.2 p32. There is a danger of treating relapse with an empirical regimen of inducing further resistance. In view of the easier access to molecular testing and whole genome sequencing within the UK, the results of these tests should be awaited before designing a further regimen.	Recommendation wording changed
			8.3.1. The sentence including "but one meta-analysis suggests prolonging the course has better outcomes" requires a reference. The mention of NICE 2016 guidelines could be deleted, as this did not note the RIAQUIN trial results, was before the meta-analysis of Stagg H et al indicating that at least 4 months of a fluoroquinolone was required and ignored the USA data where treatment with REZ for 6 months has been the standard evidence-based practice for many years. The recent draft of the WHO guidelines for isoniazid mono-resistance includes these data.	Reference added
			Rifampicin mono-resistance should make reference to the many RCTs and standard comparison arm before and during the introduction of rifampicin. The WHO guidelines are based on the absence of DST and reliance on rifampicin PCR tests and hence their advice is not applicable to standard UK microbiological practice.	Beyond scope of guidelines Recommendation on treatment of R mono-

			MDR/XDR TB treatment requires DOT throughout – delete may and add an "s" to "involve".	resistance amended
			8.3.2. The WHO guidelines are applicable to countries without routine whole genome sequencing and are therefore no longer applicable to the UK. This section should be deleted. It could be replaced with a section noting that: a) pncA mutations considered significant by PHE laboratories should preclude the use of pyrazinamide (there is a growing literature indicating that pyrazinamide resistance is associated with poorer outcomes if pyrazinamide is used, presumably due to adverse effects); b) surgical resection per se is of unproven benefit – the meta-analysis did not consider the reasons for surgery and noted that minimal resection had the best outcome.	Section has been amended and recommendation based on availability of WGS added
			Table 8.1.	
			In general, the doses of mg/kg are not used as a) the size of the tablets in adults precludes specific dosing and b) children metabolize drugs more rapidly than adults and so in general require higher doses. I would therefore put the dose ranges as in the BTS TB Monographs.	Doses amended according to BTS TB monographs
			The current adult dose of levofloxacin is recommended at 1 g per day; the minimum dose of moxifloxacin to achieve blood levels between 2-4 mg/L is about 600 mg and moxifloxacin cannot be given as a liquid formulation to children such that a mg/kg dose is inadmissible.	See above
			300 mg of linezolid has been associated with prolonged periods below the MIC.	Dose amended to 600 mg od only
			Loading doses of clofazimine of 200 mg for the first 2 months have long been used in the treatment of leprosy and this recommendation is included in TB Monographs.	Doses amended according to BTS TB monographs
			The dose of pyrazinamide is inconsistent within the document – both table 7.1 and 8.1 should recommend 35 mg/kg (evidence from a comparison of the MRC Hong Kong and Singapore trials suggests this higher dose).	
			The high dose of isoniazid (900 mg od) has not been included, noting acetylator status as more important than weight.	No action needed
			The dose of PAS is not 150 mg, but rather 8-12 g daily in divided doses in adults (150 mg/kg, but higher in children) (TB Monographs)	Amended as per BTS TB monographs
			8.4.1. Migrants are not known to be a high-risk group for poor adherence. On the other hand, a high alcohol intake is a well-known risk factor for adherence that should be included.	Changed as per suggestion
			DOT is required for MDR-TB management.	Changed
			Table 10.3 seemed unclear – was the first Dose column referring to rifampicin or to US vs EMEA guidelines? Most likely the first Dose column related to ART drug, so that ART and TB therapy should be above their two columns and the first and third columns should be "Name of drug" or similar.	No action needed
			10.2.1. Regarding common challenges:	
			Pharmacokinetic studies have shown that the dose of steroids should be doubled (The effective dose	

			is ~ half, see Bergrem & Refvem. Proc Eur Dial Transplant Assn 1983; 19: 552-7 and Acta Med Scan 1983; 213; 339-43; McAllister WA et al. BMJ 1983; 286: 923-5; Lee KH et al. Eur J Clin Parmacol 1993; 45: 287-9; and Powell-Jackson PR et al. Am Rev Respir Dis 1983; 128: 307-10 suggested that even doubling was insufficient, but with a more limited study and RCT suggesting that perhaps the standard dose of steroids had made asthma more difficult to respond to an effective dose later).	Not relevant – no action needed
			Opiates should be listed under common challenges, considering the association between injecting drug use and HIV.	Opiates added
			10.2.3. This section differs compared to the evidence noted previously (8.2.1 and 10.1 regarding P-gp ….; 11.1). A specific scenario that should be included is a positive culture after 2 months of TB treatment.	No action needed
			11.3. It is unclear whether isoniazid hepatotoxicity is increased by alcohol or Hep C or whether the latter are responsible for liver enzyme changes themselves. The effect of acetylator status and GST variants is likely more important in isoniazid hepatotoxicity.	Wording changed for clarity. Comment on acetylator/GST variants added
			11.3.1 In view of the comment about moxifloxacin, I would replace "fluoroquinolone" with "levofloxacin", as recommended by WHO.	Changed
			The sequential re-introduction of TB drugs suggested in Table 11.1 occupies too much space and suggests to the quick reader that this is the preferred method (and section 11.8). Sequential introduction was an arbitrary suggestion made without evidence and no audit of subsequent resistance. The only RCT (Sharma et al, ref 14) noted that re-introduction of all TB drugs was tolerated in 90%. A drinking binge is perhaps the commonest cause of a transient rise in AST/ALT. There are therefore no grounds for a graded introduction of TB drugs, which may of itself permit resistance to arise. The Table could be in very small print in an appendix to avoid confusion between the written advice and the prominence of the Table.	Comment added and table moved to Appendix 8
			11.4 The regimens suggested for isoniazid-induced hepatotoxicity are inconsistent with those recommended for isoniazid resistance earlier. As with the WHO recommendations levofloxacin is considered the fluoroquinolone of choice. These regimens have supporting data to which reference had been made in the preceding section (8.3).	Changed to levofloxacin
			11.5. The statement that the effect of taking medication with meals "is moderate and of clinical significance" is unsupported (see data in IJTLD to the contrary). Since rifampicin shows a 100-fold difference in serum levels with standard dosing, the drug may be ineffective in those in whom blood levels fail to peak at > 8 mg/L.	Changed (statement deleted)
			Table 11.2. This has many inconsistencies and advice from a renal physician may be the main point to make. • There is no recommendation regarding renal dialysis for ethambutol. The aim should be to	Table contents checked and amended where

			reach the required peak and AUC consistent with effective treatment and then dialyse immediately thereafter. This prevents persistently high levels, which have been associated with greater toxicity. • This would then suggest that the advice for isoniazid may not be correct, if toxicity is related to high trough levels rather than being idiosyncratic, as suggested by the genetic associations. • Evidence that pyrazinamide is against any effect of renal insufficiency (Vayre P et al. Therapie 1989; 44:1-4 and Passananti GT Pharmacology 1992; 45: 129-41 compared to the earlier study by Stamatakis G et al, Nephron 1988; 30:230-4 which was designed to investigate the effect of dialysis on drug levels). • There are no published data on rifabutin and renal impairment but a single anecdotal report on the pharmacokinetics in 2002 that is inaccessible. • Rifampicin can be tolerated at doses of up to 35 mg/kg (and perhaps even higher, see publications by Martin Boeree). Rifampicin is metabolized by the liver. Therefore the recommendation for "Caution should be taken…) is inadmissible and this sentence deleted. • Czock D et al (Int J Clin Pharmacol 2015; 37: 906-16) were concerned about doses of levofloxacin that were too low in renal impairment, as were Leroy B et al. (J Antimicorb Chemother 2012; 67: 2207-12). In view of the relative safety of this drug, I am unclear why dose reductions are suggested in renal impairment. 13.1 There are very good data on the safety of TB drugs in pregnancy due to the large cohort of patients whose oral contraceptive failed and who did not realise they were pregnant for the first 2 months of fetal development (review Bothamley G. Drug Safety 2001; 24: 553-565). Suggest delete "There are insufficient data on the safety, tolerability and efficacy of TB treatment in pregnancy". This then agrees with the subsequent paragraphs. 14.1. It would be worth estimating the period of infectiousness. Isoniazid will reduce the TB bacillary population by 99% within 5 days and rifampicin within 14 days (Mitchison and Jindani studies; hence the current guidelines of 14 days in view of isoniazid resistance being the most common form of drug resistance). For those with a CD4 count < 200/mm3, a more cautious approach of 2 months has been suggested, based on the injection of sputum into guinea pigs (Mitchison and Jindani studies). The infectious period for second-line treatment of MDR-TB is unknown – linezolid has the best early bactericidal activity followed by streptomycin and moxifloxacin at about 0.5 log for the first 5 days and 0.2 for up to 14 days (see review in Donald & Diacon, Tuberculosis 2008; 88 Suppl 1: S75-83 for most drugs and Dietze R et al. AJRCCM 2008; 178: 1180-5 for linezolid). The papers by Riley and recent duplicates in Peru have noted the importance of cough hygiene in reducing infectiousness. This should be included in 14.2. Appendix 3. As noted before, ADA should not be used in the diagnosis of pleural TB (WHO recommendation). The meta-analysis was perhaps a little uncritical of the populations studied (known	inconsistencies found Changed accordingly Wording changed with the addition of 'clinical trial data' Sentence added regarding infectious period for MDR TB Added Not in agreement – no

			diagnosis vs. pleural effusions where TB was considered in the differential diagnosis as a standard of care). Xpert MTB/RIF is more valuable.	action needed
6.	Effrossyni Gkrania-Klotsas	Cambridge University Hospitals	Thank you for very well written guidelines (draft). a. I am referring to pages 22 and 23. You are effectively making a blanket LBTI treatment recommendation, regardless of age and other possible comorbidities. Our HIV cohort is getting old and I am wondering if a statement about the risks and benefits of LBTI treatment would help the decision on complicated cases. b. I am referring to pages 38 and 39. Although you are quoting Reflate TB (phase 2), you are still recommending EFV as first line, even with raltegravir superior outcomes with rifampicin. I am unclear why this is. Many thanks	Wording changed to include sentence on risk/benefit of LTBI treatment No action needed
7.	Dr Alistair Paice	ViiV Healthcare	Thank you for the opportunity to comment on the draft BHIVA TB/HIV co-infection guidelines. In the draft guidelines, you acknowledge the drug-drug interaction between DTG and rifampicin which necessitates a doubling in the dose of DTG, citing Dooley et al (ref 19). In that publication, the authors also advise that rifabutin may be co-administered with DTG without any need for dose adjustment. We suggest that it would be appropriate to include this information, which is consistent with our Dolutegravir SmPC recommendations, as you advise that rifabutin is considered to be an appropriate alternative to rifampicin in certain circumstances. As acknowledged in the draft guidelines, we are awaiting results from the INSPIRING study (ING 117175, NCT02178592, reference 20 in your list), a Phase IIIb randomised, open-label study in which antiretroviral therapy-naïve adults starting treatment for rifampicin-sensitive TB are randomised to receive a dual NRTI backbone plus either dolutegravir (DTG) or efavirenz in combination with a TB treatment regimen. The dose of DTG in this study is 50mg twice daily, because rifampicin is included in the TB treatment regimen, but will be reduced to 50mg once daily 2 weeks after the TB regimen is completed. The 24-week results of the INSPIRING study have been accepted for oral presentation at the forthcoming CROI conference in March. The 48-week data are planned to be submitted to the IAS conference taking place in July this year. Thank you. ViiV Healthcare	DTG and rifabutin dosing included in Table 10.3 No action needed No action needed
8.	Anna Goodman	British Infection Association	This is an excellent guideline which the BIA fully support. Some minor points: 'Conventional microscopy and culture' is mentioned throughout the document but appears to mean	Already covered – see above

			Z-N stain and AFB culture rather than MC&S p18 bottom paragraph- 20% in HIV-infected individuals 'with TB'? Consider testing those with diabetes from low incidence areas (p23) opens testing to a large number of patients who are unlikely to have LTBI- does the evidence show that the benefits of testing this group outweigh the harms and are cost-effective? Table 10.1 needs headings on every page for ease of reading.	Already covered – see above
9.	Tom Wingfield	University of Liverpool	Dear BHIVA HIV/TB Guideline Writing Committee, Thank you for this comprehensive update and for your ongoing guidance. Please consider rewording "Prior to testing and providing treatment for LTBI, we recommend excluding active TB, by addressing presence of TB symptoms and signs and, where appropriate, conducting investigations (e.g. radiology)." I can't see a situation in which if you identify signs and symptoms of active TB you would not need to investigate and this seems slightly incongruent with the subsequent LTBI treatment recommendation: "We recommend treatment for LTBI for at-risk individuals with a positive IGRA in whom active TB has been excluded by clinical assessment and chest radiography. (GRADE 1B)". Apologies if I have misunderstood. I also wonder whether you want to take into consideration that many TB MDTs continue to screen close contacts of TB patients with extra-pulmonary TB due to high yield of active TB disease, despite NICE 2016 guidance to only screen contacts of patients with laryngeal/pulmonary TB (citing a lack of cost-effectiveness). Whilst a full cost-effectiveness analysis will be helpful in clarifying this issue (and is, I believe ongoing in London), please consider recent evidence from Cavany et al, Thorax 2017, doi: 10.1136/thoraxjnl-2016-209677 and Wingfield et al, Thorax 2017, doi: 10.1136/thoraxjnl-2017-210202. In addition, I note there is no reference to support of patients with social risk factors as per the End TB Strategy but I appreciate that this may be beyond the scope of these guidelines. Once again, thank you for your guidance and expertise and I am grateful for this update, which will inform practice and improve patient care and outcomes. Kind regards, Tom Wingfield	Wording changed ('at risk' removed) Already covered – see above – recommendation changed to include enhanced contact tracing for EPTB
10.	Thomas Gorsuch	Manchester Royal Infirmary	1. Section 5.3.1 Pleural tuberculosis This section mentions pleural biopsy, but there is no mention of how this should be obtained. Very few practitioners remain competent in Abram's needle biopsy and its sensitivity is not as good as	Wording changed and

			thoracoscopy. The British Thoracic Society Pleural Disease guideline from 2010 refers to six studies of thoracoscopy in patients without HIV, five of them carried out in low TB incidence settings, with a pooled sensitivity for TB on culture and histology of 93%. The sixth (Diacon, van der Wal, Wyser et al ERJ 2003) was carried out in South Africa. They reported sensitivity of 100%. In the paper you quote assessing sputum induction in suspected pleural TB (Conde, et al. AJRCCM 2003), only 14% were identified immediately by positive AFB smear on induced sputum or diagnostic pleural aspiration. Although I could not find any studies of thoracoscopy for suspected TB in people living with HIV, thoracoscopy (preferably medical/local anaesthetic as it is associated with shorter hospital stays and shorter recovery times) should surely be listed as an appropriate next step for investigation, particularly if pleural fluid and induced sputum are AFB smear (+/- Cepheid Xpert MTB/Rif) negative. In addition, medical thoracoscopy is superior to blind pleural biopsy in diagnosing malignancy, which will increasingly be seen in PLWH as the population ages. 2. Section 9.2.1 Choice of ART I'm surprised at the inclusion of nevirapine (NVP) in the guideline, for those already taking it. As the guideline goes on to state, it clearly isn't acceptable as an option in naïve patients being treated for TB (www.hiv-druginteractions.org, lists several more comparative studies (generally with pharmacological rather than clinical endpoints) in addition to the four papers listed). The evidence for continuing nevirapine is from a large cohort study from Cape Town comparing EFV with NVP (Boulle et al JAMA 2008), although only a small proportion of patients had incident TB. There were significant differences in baseline characteristics between patients receiving EFV and NVP. In view of this, and the very different setting for this study, I don't think this study supports the use of NVP in UK practice. 3. Section 15 Contact screening The guideline advocates following the NICE screening approach, which is only to screen contacts of smear-positive pulmonary or laryngeal TB cases. In North West England, we continue to screen contacts of all patients with TB (Wingfield, et al. Thorax 2017). Over a four year period, 3652 household contacts of 1026 index cases of extra-pulmonary TB were identified. The detection rate of latent TB infection was 3.6% (3,600/100,000) and active TB disease 0.44% (440/100,000) with a number needed to screen (NNS) of 28 for LTBI and 227 for active disease. The paper refers to two previous studies from the UK which were not included in the NICE analysis. This calls the strategy into question of screening contacts only of pulmonary TB.	added comment on thoracoscopy Nevirapine removed Already covered – see above – recommendation changed to include enhanced contact tracing for EPTB

11.	Penny Lewthwaite	Leeds Teaching Hospitals Trust	Suggest dolutegravir is also included as a treatment option with double dose Should latent TB be screened for retrospectively in all cohorts if not done previously. Should there be an age cut off for treatment of latent TB given the increased hepatoxicity seen with age? Presumably there is no data as yet on OD raltegravir and rifampicin?	Changed – see above Writing committee did not want to include a specific age cut-off Recommendation against use of RAL od included
12.	Robin Brittain- Long	Aberdeen Royal Infirmary	In diagnosing LTBI in HIV positive individuals IGRA tests can of course be falsley negative, due to immune suppression. If the guideline can help to guide clinicians with concrete advise on how to proceed after a negative IGRA result, in an individual with low CD4 count, that would be very useful. Do we for example repeat the IGRA test? If so how often? Repeat after CD4 count has risen above a certain level, such as >200?	Guidance added on when to repeat indeterminate IGRA
13.	Paul Collini	Sheffield Teaching Hospitals	Thanks BHIVA for these new guidelines. With respect to LTBI screening I recognise that the new guidance has simplified the criteria. Their is a clear rationale for this, both in aligning better with NICE and to improve coverage as described by White, Miller et al. Latent tuberculosis infection screening and treatment in HIV: insights from evaluation of UK practice. Thorax 2017 Locally we screen all new patients in our service (both new diagnoses and newly transferred) for LTBI and will adapt to use these new criteria. However, the implication from the new guidance is that there will be group of existing patients who have been on ART for many years who didn't meet previous criteria but now do and will need screening for LTBI. This is a more complex exercise than screening all new patients, particularly in explaining the rationale and avoid anxiety in such patients. For many of these their risk of reactivation will be similar to the background risk of those without HIV who come from high TB incidence countries but have been in the UK many years (Gupta R Lancet HIV 2015). This group is not currently screened for LTBI. It would be helpful if there was clarification whether the guidance intends for such individuals to be	Wording of section changed to include comment on how services should make local arrangement to provide screening according to new guidance

			screened as well and whether the cost benefit has been considered.	
14.	Roy Trevelion	i-Base	Thanks BHIVA for this really excellent and detailed set of guidelines. Its complexity reflects how difficult it is to treat TB/HIV co-infection. And individual circumstances - such as late diagnosis with very low CD4 count, MDRTB, XDRTB, latent TB, active TB, non-pulmonary TB, and potential DDIs between ARVs and TB drugs - can mean that person-centred care is vitally important and needs input from centres of expertise in treatment. This includes from pharmacists and clinicians with experience in recurrent IRIS. The community can produce the non-technical summaries. I suggest that these are put together from the patients' perspective. Eg: Your doctor will test for TB if: xx etc. This can written so that you know: Why you are being tested; Why you are being treated for TB that's not causing symptoms: Why your TB can be treated in the weeks before starting ART, and so on. . . . I suggest that this can follow the way the BHIVA standards of care are written. It should help explain why and how a person's diagnosis and treatment is done, and followed, in a particular way. At the moment the guidelines include a summary of recommendations at the beginning, in Section 2. But they don't explain how treatment decisions can be interrelated. However, the non-tech summaries can by inserted before this section, if agreed, and flag up these interrelations before treatment is started. Importantly, this can be read by the individual on treatment and also by the clinician so that both are aware from the start of the need for complex care and testing/monitoring. Roy	No action needed
15.	Christine Bell	Manchester Foundation Trust	Screening contact of only pulmonary/laryngeal TB cases will miss other people who have been exposed. Even if the index case is not infectious, the contacts are more likely to have been exposed to infectious TB than other people.	Already covered – see above (recommendation amended)
16.	Derek Macallan	St George's, University of London	We discussed these guidelines at our MDT / Academic meeting and would like to feed back the following comments which reflect a consensus view from our centre. We congratulate the writing group on a really well organised and well thought through set of guidelines. We feel they strike a very good balance between scientific rigour and pragmatic clinical practice. We were also pleased to see the dedication to Steve Lawn which was very appropriate. In terms of specific comments: Section 5.1: The first recommendation: "We recommend performing microscopy for acid-fast bacilli (AFB) on respiratory samples (sputum, induced sputum or bronchoalveolar lavage [BAL]), followed by molecular testing, e.g. Xpert MTB/RIF, for rapid identification of MTB, in conjunction with culture and drug-sensitivity testing. (GRADE 1B) " We felt this was ambiguous – do you mean do molecular testing if smear positive? (which we would	

			endorse). Would it read better as: "We recommend performing microscopy for acid-fast bacilli (AFB), in conjunction with culture and drug-sensitivity testing on respiratory samples (sputum, induced sputum or bronchoalveolar lavage [BAL]); if smear-positive this should be followed by molecular testing, e.g. Xpert MTB/RIF, for rapid identification of MTB," This reflects our current practice If smear negative, the recommendation is covered by the next paragraph, which currently reads: "We recommend the use of molecular tests in pulmonary smear-negative samples, always in conjunction with culture and drug-sensitivity testing. (GRADE 1B)" Reading this literally, you appear to be recommending that every respiratory sample from an HIV positive patient has a molecular test for TB. We think this will generate a large number of negative samples and mandate a large increase in workload and cost. We do not think this is what you really mean – If you do, paragraph 1 is redundant as every sample will be tested anyway. Our practice for smear negative respiratory samples is to request molecular testing on a case by case basis in selected samples. This may be more practical and we suggest rewording as: "We recommend that all pulmonary smear-negative samples be processed for culture and drug-sensitivity testing. Where there is a high index of suspicion for TB, molecular tests should also be considered (GRADE 1B)" We endorse your view that IGRA do not contribute to the diagnosis of active TB. Section 6.1 Do you need to also add somewhere that individuals who are now IGRA positive but who have received a full course of treatment for TB in the past do not need chemoprophylaxis unless there is evidence to suggest that there has been subsequent re-exposure. We suggest that you add a line to the recommendations: "We do not recommend performing IGRA testing in patients with a history of treated tuberculosis." And a sentence to the text. "Patients who have a history of treated TB will likely have a positive IGRA but do not need chemoprophylaxis unless there is evidence to suggest that there has been subsequent re-exposure." We agree with the adoption of IGRA over TST for diagnosis of LTBI. We are concerned about the practicability and resource implications of testing everyone who meets these criteria for LTBI and wonder if some acknowledgement of the work/cost required to do this. A practical approach for some clinics might be to screen all new attendees rather than catch-up with	Wording amended as per suggestion Wording amended as per suggestion Sentence added (not to test for LTBI in people with previous history of TB) Already covered – see

			patients who have been on treatment for a decade or more and never been screened. Perhaps say in the guideline that risk stratification may be appropriate in operationalising these guidelines and that those most at risk are those within the first year of therapy. Section 6.2 We do not understand the meaning of the phrase "at risk" in the sentence: "We recommend treatment for LTBI for those at-risk individuals with a positive IGRA, in whom active TB has been excluded by clinical assessment and chest radiography. (GRADE 1B)" At risk of what? Who is not at risk? We suggest rewording as: "We recommend treatment for LTBI for those individuals with a positive IGRA, in whom active TB has been excluded by clinical assessment and chest radiography. (GRADE 1B)" We felt that the fourth recommendation; "We recommend treatment of LTBI in all HIV-positive individuals with a positive IGRA who are receiving cancer chemotherapy etc …" was superfluous as all these patients are captured in recommendation 1, are they not? You might like to add a phrase emphasising that the risk-benefit effect is even greater in patients with cancer etc, but the decision to treat should already have been made because they are HIV+ IGRA+. We thought it would be useful to have a comment about the timing of LTBI treatment versus the timing of ART. As incident TB is highest in the first year of therapy, might you add the phrase: "In patients not already receiving ART, we recommend that treatment of LTBI is commenced before or at the same time as ART." Section 7 recommendations and section 7.3 We felt that you had understated the potential benefits of treating vitamin D deficiency. If someone without HIV or without TB had vitamin D deficiency we would treat and there is ample evidence that in such populations, vitamin D is helpful and deficiency is harmful. The wording of your recommendation almost says "… don't whatever you do give these people vitamin D". This surely cannot be what you intend. We suggest the recommendation reads: "We do not recommend testing for vitamin D deficiency and/or supplementation of vitamin D specifically in co-infected individuals - Where present, Vitamin D deficiency should be managed as for HIV-seronegative individuals. (GRADE 1A)"	above – sentence added Wording changed Recommendation deleted Sentence on ART included Recommendation regarding vitamin D deleted

			And the text might state that: There is an absence of clear evidence for benefit with Vitamin D testing or supplementation in HIV/TB co-infected patients. Where present, Vitamin D deficiency should be managed as for HIV-seronegative individuals." Section 9.1 – We thought that your summary of when to start was clear, evidence-based and practical. Section 9.2 – we thought you should mention that raltegravir has a relatively low barrier to resistance. We also felt that although the definitive trial with dolutegravir has not yet been published, dolutegravir deserved a more positive endorsement. It is widely used in practice as the "third agent" in co-infected patients and this should be acknowledged. Section 10.2 We agree that small dose increments for efavirenz (from 600 to 800 mg) are not meaningful or evidence-based. However, we thought that the use of TDM for Efavirenz therapy (Section 10.2) was undervalued. In our paper (Wake et al) we showed that Efavirenz levels are very variable and we found that rifampicin therapy increased EFV levels in some individuals whilst reducing them in others. We think it shoudl read "TDM may be helpful in patients with severe side-effects, where a dose reduction may be possible, or where efficacy is in doubt, where doses may be suboptimal". We clearly think that Wake et al should be cited. <Evaluation of a pro-active strategy for managing tuberculosis-HIV co-infection in a UK tertiary care setting. Wake RM, Poulikakos P, Groth J, Harrison TS, Macallan DC. Int J STD AIDS. 2013; 24(4):263-8. PMID: 23635810.> Was this reference captured in your literature search? Further general comment We felt that some reference (and a recommendation?) should be made (possibly in section 3) to the importance of an integrated and (dare I say) holistic approach to treatment of these two diseases. Wake et al described a strategic approach to treatment of co-infection and this merits inclusion. The link between the TB treatment and the HIV treatment is really important and needs to be mentioned and endorsed in this guideline. The biggest risk these patients face is a lack of joined-up care. Co- management or communication and liaison between treating teams is critical to successful and safe outcomes,. We hope these comments are helpful and reiterate our positive view of the overall document.	Already covered – see above – DTG included in recommendations Not relevant – no action needed No action needed
17.	RCP		The RCP is grateful for the opportunity to respond to the above consultation.	

			We would like to endorse the response submitted by the British Thoracic Society (BTS).	
18.	HIVPA		BHIVA TB guidelines – HIVPA response Many thanks for this comprehensive updated guideline, which will be an excellent resource for healthcare professionals What ART to start • We recommend efavirenz (standard dose) in combination with tenofovir (TDF) and emtricitabine as first-line ART. (GRADE 1B) We feel this statement is too specific. The more detailed guideline / description gives more information about pros and cons of antiretroviral regimens but for those that just look at the headline information and specially if they have less experience wrt ARVs and co-morbidities then we think it needs to give a degree of flexibility. As other BHIVA guidelines use the term preferred, we would suggest the following: We recommend efavirenz (standard dose) in combination with tenofovir (TDF) and emtricitabine as the preferred ART taking into account co-morbidities and drug interactions. (GRADE 1B) • We suggest that raltegravir can be used for individuals in whom efavirenz is contraindicated. (GRADE 2B) Although the information that that even though some studies have shown that raltegravir 400mg bd is acceptable with rifamipicin, the guidelines actually suggest 800mg bd further along, but the information is difficult to find, so we suggest the dose should be included in the above sentence. □ We recommend against the use of fixed-dose combinations containing tenofovir alafenamide (TAF), when co-administered with rifampicin or rifabutin. (GRADE 1D) We would suggest removing the words 'fixed-dose' as should TAF single agent be licensed for HIV then this sentence would still be valid. • In table 10.1 a dose rifabutin 150mg daily is recommended when co-administered with elvitegravir/cobicistat (although caution recommended), however in table 10.3 a rifabutin dose of 150mg three times per week is suggested. The SPC recommends the three times per week dose, and there are no data to support using a more frequent dose of rifabutin than this, as although this is frequently used in practice with protease inhibitors, the inductive effect of rifabutin on the integrase inhibitor needs to be considered here.	Already covered – see above (EFV has strongest trial evidence in combination with rifampicin) Raltegravir recommended at both doses as per Reflate study results – recommendation against 1200 mg od dosing added Recommendation regarding TAF use added EVG/cobicistat removed from Table 10.3 – we advise caution when cobicistat is co-administered with rifabutin

			Choice of antiretroviral treatment in individuals on established ART • We recommend that rifampicin-based TB treatment is used in individuals whose established ART consists of efavirenz (GRADE 1B), nevirapine (GRADE 2C), or raltegravir (GRADE 2C) plus two NRTIs. Liverpool website states do not co-administer and quotes several papers where there was virological failure in studies using nevirapine and rifampicin. We feel that there is not enough evidence to support use of nevirapine with rifampicin • Drug interaction tables We cannot see what the numbers (1-4) or the highlighting refer to. (Maybe the latter is an editing error.)	Already covered – see above – NVP removed No action needed